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Short Communication Open Access

Meal-Induced Oxidative Stress

Ngoc-Anh Le *

Biomarker Core Laboratory, Atlanta Research and Education Foundation, Atlanta Veterans Affairs Medical Center, Georgia, USA

***Corresponding author:** Ngoc-Anh Le, Biomarker Core Laboratory, Atlanta Research and Education Foundation, Atlanta Veterans Affairs Medical Center, Georgia, USA, Tel: + 404-728-7632; Email: Anh.Le@va.gov

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The target of interventions to reduce cardiovascular events has focused on total (CHOL) and low-density (LDLC) cholesterol levels. Data from the Framingham Heart Study would suggest that 50% of individuals with so-called "normal" LDLC levels (100 mg/dl or 2.6 mmol/L) would have atherosclerosis by age 50 [1]. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT), aggressive cholesterol reduction as part of a secondary trial in high-risk patients only prevented 20% of cardiac events [2]. Bayturan et al reported that, even when aggressive treatment was used to lower mean LDLC to 58.4 mg/dl (1.5 mmol/L), plaque volume could be shown to increase in 20% of the subjects [3]. Attempts to explain this residual risk have ranged from triglycerides (TG), high-density lipoprotein cholesterol (HDLC) [4] to non-HDLC [5] and biomarkers of inflammatory stress [6].

More recently, the concept of functional assays has been suggested as a novel perspective on risk factors beyond concentrations. While elevated HDL is commonly associated with lower CHD risk in both men and women [7], there is better understanding of the impact of HDL heterogeneity on its quantity, quality and function [8]. While one of the key anti-atherogenic properties of HDL is its ability to protect LDL from oxidative modification, in certain metabolic conditions, HDL may actually act as a pro-oxidant and pro-inflammatory agent [9,10]. HDL also plays a central role in cholesterol efflux, however, this functional parameter as measured ex vivo does seem to depend solely on HDLC and apoA-I levels [11].

With respect to LDL, the process is much more complicated. It is generally accepted that LDL in its native form is not atherogenic. LDL must undergo oxidative modification for the undesirable accumulation in the cells to start via the scavenger receptors [12,13]. According to the oxidation hypothesis of atherosclerosis, LDL must be trapped in the subendothelium for the oxidative modification to take place [14]. An alternative process which allows for the direct generation of oxidative epitopes in the circulation [15,16] could be proposed based on the postprandial hypothesis of atherosclerosis of Zilversmit [17]. In this scheme, as triglyceride-rich lipoproteins (TRL) interact with lipoprotein lipase anchored on the arterial wall they would be seeded with reactive oxygen species generated by an inflamed endothelium [18-20]. As the TRL are being converted to cholesterol-rich lipoproteins, either chylomicron remnants or LDL, the oxidative modification can either proceed to generate damaged lipoprotein particles or be quenched by an adequate antioxidant environment. In dyslipidemic conditions, e.g. metabolic syndrome and diabetes mellitus, the delayed clearance of triglycerides would facilitate the completion of the oxidative modification process.

In a recent double-blind, placebo-controlled, cross-over metabolic study with fenofibric acid (ABT-335), we examined the hypothesis that oxidative modification of LDL could be reduced by improving triglyceride hydrolysis in the fasting and postprandial state [21]. In this study, patients with metabolic syndrome were followed for two 8-week treatment periods separated by a 4-week washout period. During the first treatment period, participants were randomly assigned to ABT-335 or placebo and the treatment was switched for the second period. At the end of each treatment period, participants were admitted to the metabolic ward for a 6-hr meal challenge study. The meal challenge consisted of a standardized mixed meal that included only a modest amount of fat (27 g). Plasma obtained at baseline and at 4 hour postprandial were used to isolate the lipoprotein-rich fraction (d<1.21 gm/m) by ultracentrifugation within 4 hours of collection. The isolated lipoprotein-rich fraction was stored at -80oC until the completion of the second meal challenge. There was the expected 20% reduction in plasma triglycerides ($p<0.0002$) with no change in LDLC. There was a 28% reduction in incremental area under the curve for triglycerides following the meal challenge ($p<0.0005$).

Autologous LDL and HDL were obtained from the lipoprotein-rich fraction by fast protein liquid chromatography and used to examine the oxidative susceptibility of LDL in the presence of Cu++. Of the 27 patients with metabolic syndrome, fasting LDL for 15 individuals underwent spontaneous auto-oxidation without requiring the addition of Cu++ as initiator. This was observed during both the placebo and the ABT-335 periods. LDL isolated from postprandial plasma underwent auto-oxidation in 17 subjects during the placebo period and in only 10 subjects during the ABT-335 period. Mean lag time for fasting LDL was 16% longer after treatment with ABT-335 than after treatment with placebo. This modest increase in resistance to oxidation with ABT-335 was not statistically significant in this small group of subjects. Mean lag time for postprandial LDL was 28% longer with ABT-335 than with placebo ($p<0.015$). This finding suggests that ABT-335 enhanced the clearance of postprandial triglycerides resulting in greater resistance of postprandial LDL to Cu++-induced oxidative modification [21].

In the presence of Cu++, co-incubation with autologous HDL obtained either from fasting or postprandial plasma actually reduced the lag time for LDL. This is the case for both the placebo and ABT-335 period, suggesting that these patients with metabolic syndrome may have dysfunctional HDL and ABT-335 did not restore the anti-oxidant properties of HDL [21].

In summary, to fully appreciate the pro-and/or anti-atherogenic of lipid and lipoprotein biomarkers, we might need to develop clinically relevant functional assays rather than simply focusing on plasma concentrations [11,22]. With respect to oxidative modification, we need to appreciate that certain properties of plasma lipoproteins might not be conserved during postprandial lipemia especially in view of the strong evidence that meal consumption is associated with oxidative and inflammatory stress [22-25].

References

1. Jaffer FA, O'Donell CJ, Larson MG, Chan SK, Kissinger KV, et al. (2002) Age and sex distribution of subclinical aortic atherosclerosis: a magnetic resonance imaging examination of the Framingham Heart Study. Arterioscl Thromb Vasc Biol 22: 849-854.
2. Cannon CP, Braunwald E, Mc Cabe CH, Rader CJ, Rouleau JL, et al. (2004) Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 350: 1495-1504.
3. Bayturan O, Kapadia S, Nicholls SJ, Tuzcu EM, Shao M, et al. (2010) Clinical predictors of plaque progression despite very low levels of low-density lipoprotein cholesterol. J Amer Coll Cardiol 55: 2736-1742.
4. Carey VJ, Bishop L, Laranjo N, Harshfield BJ, Kwiat C, et al. (2010) Contribution of high plasma triglycerides and low high-density lipoprotein cholesterol to residual risk of coronary heart disease after establishment of low-density lipoprotein cholesterol control. Am J Cardiol 106: 757-763.
5. Arsenault BJ, Rana JS, Stroes ESG, Despres JP, Shah PK, et al. (2010) Beyond low-density lipoprotein cholesterol: Respective contribution of non-high-density lipoprotein cholesterol levels, triglycerides, and the total cholesterol/high-density lipoprotein cholesterol ratio to coronary heart disease risk in apparently healthy men and women. J Am Coll Cardiol 55: 35-41.
6. Rana JS, Arsenault BJ, Despres JP, Cote M, Talmud PJ, et al. (2011) Inflammatory biomarkers, physical activity, waist circumference, and risk of future coronary heart disease in healthy men and women. Eur Heart J 32: 336-344.
7. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, et al. (1989) High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 79: 8-15.
8. Rosenson RS, Davidson MH, Le NA, Burkle J, Pourfazib R (2015) Underappreciated opportunities for high-density lipoprotein particles in risk stratification and potential targets of therapy. Cardiovasc Drugs Ther 29: 41-50.
9. Kontush A, Chapman MJ (2006) Functionally defective high-density lipoprotein: A new therapeutic target at the crossroads of dyslipidemia, inflammation, and atherosclerosis. Pharmacol Reviews 58: 343-374.
10. Rosenson RS, Brewer HB Jr, Ansell BJ, Barter P, Chapman MJ, et al. (2016) Dysfunctional HDL and atherosclerotic cardiovascular disease. Nature Rev Cardiol 13: 48-60.
11. Khera AV, Cuchel M, de la Llera-Moya, Rodrigues A, Burke MF, et al. (2011) Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. N Engl J Med 346: 127-135.
12. Goldstein JL, Ho HK, Basu SK, Brown MS (1979) Binding site on macrophages that mediates uptake and degradation of acetylated low-density lipoproteins producing massive cholesterol deposition. Proc Natl Acad Sci USA 76: 333-337.
13. Fogelman AM, Schechter I, Seager J, Hokom M, Child JS, et al. (1980) Malondialdehyde alteration of low-density lipoproteins leads to cholesteryl ester accumulation in human monocyte-macrophages. Proc Natl Acad Sci USA 77: 2214-2218.
14. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL (1989) Beyond cholesterol: Modifications of low-density lipoproteins that increase its atherogenicity. N Engl J Med 320: 915-924.
15. Le NA, Li X, Kyung S, Brown WV (2000) Evidence for the in vivo generation of oxidatively modified epitopes in patients with atherosclerotic endothelium. Metabolism 49: 1271-1277.
16. Gradek WQ, Harris MT, Yahia N, Davis WW, Le NA, et al. (2004) Polyunsaturated fatty acids acutely suppress antibodies to malondialdehyde-modified LDL in patients with vascular disease. Am J Cardiol 93: 881- 885.
17. Zilversmit DB (1973) A proposal linking atherogenesis to the interaction of endothelial lipoprotein lipase with triglyceride-rich lipoproteins. Circ Res 33: 633-638.
18. Le NA (2009) Oxidized lipids and lipoproteins: Indices of risk or targets for management. Clin Lipidol 4: 41-54.
19. Le NA (2012) Lipoproteins as biosensors of endothelial oxidative status. Clin Lipidol 7: 49-63.
20. Le NA (2015) Lipoprotein-associated oxidative stress: A new twist to the postprandial hypothesis. Int J Mol Sci 16: 401-419.
21. Le NA, Farkas-Epperson M, Sweeney ME, Wilson PWF, Brown WV (2013) Effect of ABT-335 (fenofibric acid) on meal induced oxidative stress in patients with metabolic syndrome. Atherosclerosis 231: 268-273.
22. Hendrickson A, McKinstry LA, Lewis JK, Lum J, Louie A, et al. (2005) Ex vivo measures of LDL oxidative susceptibility predict carotid artery disease. Atherosclerosis 179: 147-153.
23. Ceriello A, Bortolotti N, Motz E, Crescentini A, Lizzio S, et al. (1998) Meal-generated oxidative stress in type 2 diabetic patients. Diabetes Care 21: 1529-1533.
24. Ceriello A, Taboga C, Tonutti L, Quagliaro L, Piconi L, et al. (2002) Evidence for an independent and cumulative effect of postprandial hypertriglyceridemia nad hyperglycemia on endothelial dysfunction and oxidative stress generation: Effects of short- and long-term simvastatin treatment. Circulation 106: 1211-1218.
25. Beisswenger PJ, Brown WV, Ceriello A, Le N-A, Goldnerg RB, et al. (2011) Meal-induced increases in C-reactive protein, interleukin-6 and tumor necrosis factor a are attenuated by prandial+basal insulin in patients with Type 2 diabetes. Diabet Med 28: 1088-1095.