The American Journal of Medicine (2006) 119, 786-790

ELSEVIER

THE AMERICAN JOURNAL of MEDICINE®

CLINICAL RESEARCH STUDY

AJM Theme AJM Theme Issue: GI and Nutrition

Change in Lipid Profile in Celiac Disease: Beneficial Effect of Gluten-Free Diet

Pardeep Brar, MD,[a] Grace Y. Kwon, MD,[a] Steve Holleran, BA,[b] Diane Bai, MD,[a] Alan R. Tall, MD,[a] Rajasekhar Ramakrishnan, ScD,[b] Peter H. R. Green, MD[a]

Departments of [a]Medicine and [b]Pediatrics, Columbia University College of Physicians and Surgeons, New York, NY.

ABSTRACT

PURPOSE: Celiac disease is associated with hypocholesterolemia, which is thought to contribute to a favorable cardiovascular risk profile. This led to suggestions that the diagnosis of celiac disease and its treatment with a gluten-free diet may result in elevation of the serum cholesterol level and worsen this risk profile. However, no study proves this in adults. We therefore examined the effect of a gluten-free diet on the lipid profile in patients with celiac disease.

SUBJECTS AND METHODS: We identified 132 patients with celiac disease who adhered to a gluten-free diet and had lipid profiles performed before and after a median of 20.5 months on the diet. The patients lacked diseases that may affect serum lipids.

RESULTS: There were significant increases in total cholesterol and high-density lipoprotein (HDL) cholesterol ($P < .0001$) but not low-density lipoprotein (LDL) cholesterol ($P = .06$). The LDL/HDL ratio decreased by 0.36 ± 0.7 ($P < .0001$). Both men and women had a significant increase in total cholesterol and HDL and a significant decrease in the LDL/HDL ratio. Only men had increases in LDL ($P = .02$). The greatest increase in lipid values was seen in those with the lowest initial values. The largest increase in HDL was seen in subjects with more severe disease as indicated by low albumin level and presence of total villous atrophy.

CONCLUSIONS: Diagnosis of celiac disease and its treatment with a gluten-free diet resulted in improvement in the lipoprotein profile, which included an increase in HDL and a decrease in the LDL/HDL ratio.

KEYWORDS: Celiac disease; Gluten-free diet; Lipids

Celiac disease is an autoimmune disorder caused by intolerance to gluten, which is found in wheat and similar proteins in barley and rye.[1] Therapy involves a gluten-free diet in which these offending grains are eliminated. Once considered a rare disease of childhood, celiac disease is now recognized to affect approximately 1% of the population.[2,3] Those with celiac disease often have hypocholesterolemia,[2,4-8] which is more severe in men than women.[7] In addition to low cholesterol, those with untreated celiac disease have relative hypotension, which is thought to contribute to a favorable cardiovascular risk profile.[2] This raises the issue as to the wisdom of identifying and treating the vast number of people with undiagnosed celiac disease. To evaluate the impact on cardiovascular risk, we assessed the effect of a gluten-free diet on the lipid profile of a large cohort of individuals with newly diagnosed celiac disease.

METHODS

From an anonymized database of 700 patients with celiac disease (65% were females and 35% were males), we identified 132 adults with biopsy-proven celiac disease who had responded favorably to the gluten-free diet and had lipid values determined at the time of diagnosis and while on the diet for at least 6 months. Excluded were those who did not respond to or were poorly compliant with the diet; those who had dyslipidemia and were already receiving lipid-lowering medications; or those who had diabetes, malig-

Requests for reprints should be addressed to Peter H. R. Green, MD, 161 Fort Washington Avenue, New York, NY 10032.

E-mail address: pg11@columbia.edu.

0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2005.12.025

Table 1 Demographic Data on Patients

Number		132
Age (mean ± SD)		44.4 ± 16.6 y
Gender	Female	66%
	Male	34%
Duration of follow-up (median)		20.5 mo
Presentation of celiac disease	Classic (diarrhea)	39%
	Atypical/silent	61%
Villous atrophy	Partial	36%
	Total	64%

SD = standard deviation.

Table 3 Gender Differences in Changes in Lipid Parameters

Lipid Values	Male	*P* Value	Female	*P* Value
TC	27.5 ± 28.6	<.0001	15.5 ± 30.4	<.0001
HDL	10.1 ± 9.6	<.0001	9.2 ± 12.5	<.0001
LDL	9.1 ± 20.7	.03	2.4 ± 23.1	.4
Triglycerides*	8 (−22-48)	.05	−8 (−23-15)	.4
LDL/HDL ratio	−0.43 ± 0.7	.002	−0.33 ± 0.8	.002

TC = total cholesterol; LDL = low-density lipoprotein; HDL = high-density lipoprotein; SD = standard deviation.

*All lipid values are expressed as milligrams/deciliter (mean ± SD), except triglycerides as median (first quartile to third quartile).

nancy, thyroid disease, liver disease, inflammatory bowel disease, or pancreatitis at the time of celiac disease diagnosis. The variables identified were age; gender; mode of presentation of celiac disease, either classic (diarrhea) or silent/atypical; degree of villous atrophy, either partial villous atrophy (Marsh 111a) or total villous atrophy (TVA) (total/subtotal, Marsh 111b and c);[9] and time to determination of follow-up laboratory values. This study was approved by the institutional review board.

Fasting serum lipid parameters of total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and serum albumin were recorded at the time of diagnosis (before initiation of a gluten-free diet) and after maintaining a gluten-free diet for at least 6 months. Dietary compliance was assessed by a physician and dietician, as well as by assessment of celiac serologies. LDL-C values were calculated according to the Friedewald formula.[18]

Statistical Analysis

Triglyceride values were log-transformed before analysis to achieve a normal distribution. Data were analyzed by paired *t* test and multiple regression analysis.

RESULTS

In this retrospective study, the lipid values at diagnosis and on the gluten-free diet were obtained for 132 patients; their characteristics are shown in Table 1. The lipid values are shown in Table 2. There were significant increases in both TC (19.6 ± 30.2 mg/dL; $P < .0001$) and HDL-C (9.5 ± 11.6 mg/dL; $P < .0001$). The change in LDL-C of 4.6 ± 22.4 mg/dL was not significant ($P = .06$). The LDL/HDL ratio decreased by 0.36 ± 0.7 ($P < .0001$). There was no change in triglycerides. All of these patients were considered by a physician and dietitian to adhere strictly to a gluten-free diet. Follow-up serologic tests revealed a persistent positive tissue transglutaminase antibody or endomysial antibody in 12 patients, although lower in titer. The lipid changes in the subjects with positive antibodies (TC change 18.4 ± 30) were not different from subjects without positive antibodies (TC change 18.7 ± 26).

We found gender differences in the changes in lipid parameters (Table 3). Significant increases in TC and HDL were observed in both men and women, and both men and women demonstrated a significant reduction in the LDL/HDL ratio. Only men had increases in LDL ($P = .02$) and triglycerides ($P = .05$). Figure 1 shows the changes in HDL and LDL by gender. The increase in HDL resulted in the proportion of subjects who had clinically low levels of HDL (HDL < 40 mg/dL) to decrease; 32% and 21% of men had HDL greater than 40 mg/dL at diagnosis and while on the diet, respectively, and 23% and 7% of women had HDL less than 40 mg/dL before and after a gluten-free diet, respectively.

Lipid changes are graphed against the respective initial values in Figure 2. The most prominent increases are seen for those with initially low values. At higher initial values, the increases are smaller. Higher TC levels (>200 mg/dL) in patients did not further increase, and sometimes decreased; the regression lines cross zero at approximately

Table 2 Effect of Gluten-free Diet on Lipid Values

Lipid Value	At Diagnosis	On Diet	Change	*P* Value
TC	169.2 ± 35.3	188.8 ± 32.8	19.6 ± 30.2	<.0001
HDL	45.8 ± 13.3	55.1 ± 13.6	9.5 ± 11.6	<.0001
LDL	109.7 ± 26.6	114.5 ± 28.1	4.6 ± 22.4	.06
LDL/HDL ratio	2.58 ± 0.9	2.22 ± 0.8	−0.36 ± 0.7	<.0001
Triglycerides*	79 (57-120)	81 (63-118)	−0.5 (−23-34)	.47

TC = total cholesterol; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SD = standard deviation.

*All lipid values are expressed as milligrams/deciliter (mean ± SD), except triglycerides as median (first quartile to third quartile).

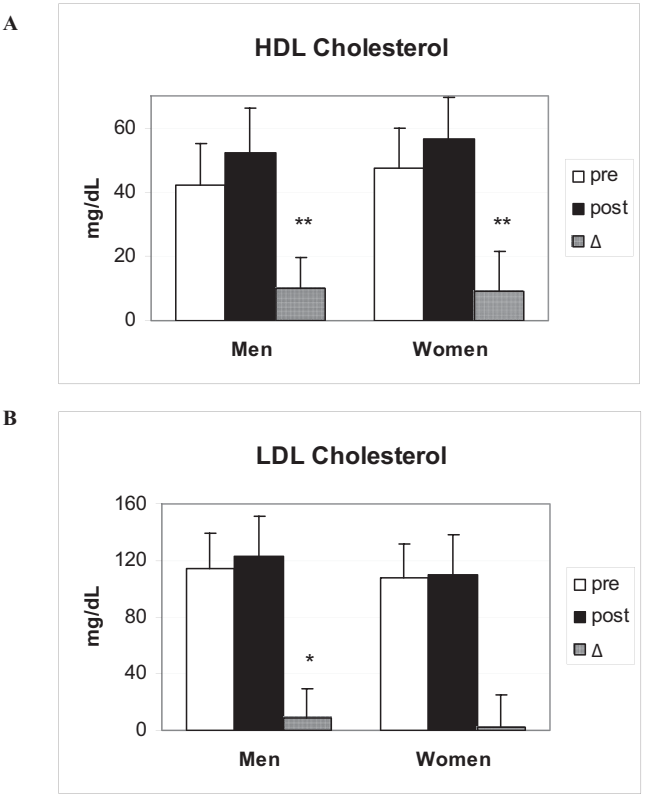

Figure 1 A. HDL cholesterol values before and after a gluten-free diet. The changes were significant in both men and women. B. LDL cholesterol values before and after a gluten-free diet. The change was significant in men, but not in women. *, $P < .05$, **, $P < .000$.

200 mg/dL for women and 230 mg/dL for men. Similarly, when one examines the individual changes in LDL levels, the increases are smaller as initial levels increase, with the lines crossing zero at approximately 120 mg/dL for women and 140 mg/dL for men.

Because the lipid changes demonstrated in Figure 2 are different for men and women and depend on initial levels, we carried out a multiple regression analysis to quantify the relationships and to explore any associations with other baseline characteristics. The associations that reached statistical significance are shown in Table 4. There was no association of the change in lipid values with the mode of clinical presentation. The change in each lipid value had a strong negative correlation with its initial value ($P = .0005$ or better), as expected from Figure 1. Men showed a higher increase in TC (13.9 mg/dL, $P = .004$), LDL-C (13.2 mg/dL, $P = .01$), and triglycerides (0.2, or ~22% higher, $P = .03$), corresponding to the different lines seen in Figure 2. There was no sex effect on the change in HDL, consistent with Figure 2. Albumin and TVA were the only baseline characteristics to show associations with lipid changes. A unit increase in baseline albumin predicted a smaller increase in TC (−13.9 mg/dL, $P = .005$), HDL (−5 mg/dL, $P = .04$), and LDL-C (−12.3 mg/dL, $P = .03$). The presence of TVA predicted an increase in HDL (4.2 mg/dL, $P = .05$) but a smaller increase, or even a decrease, in LDL (−10.4 mg/dL, $P = .02$).

DISCUSSION

Both low TC and low HDL levels are known features of active celiac disease.[6,8,10-12] Our study shows that a gluten-free diet results in a TC increase that is primarily the result of a substantial increase in HDL-C in both men and women

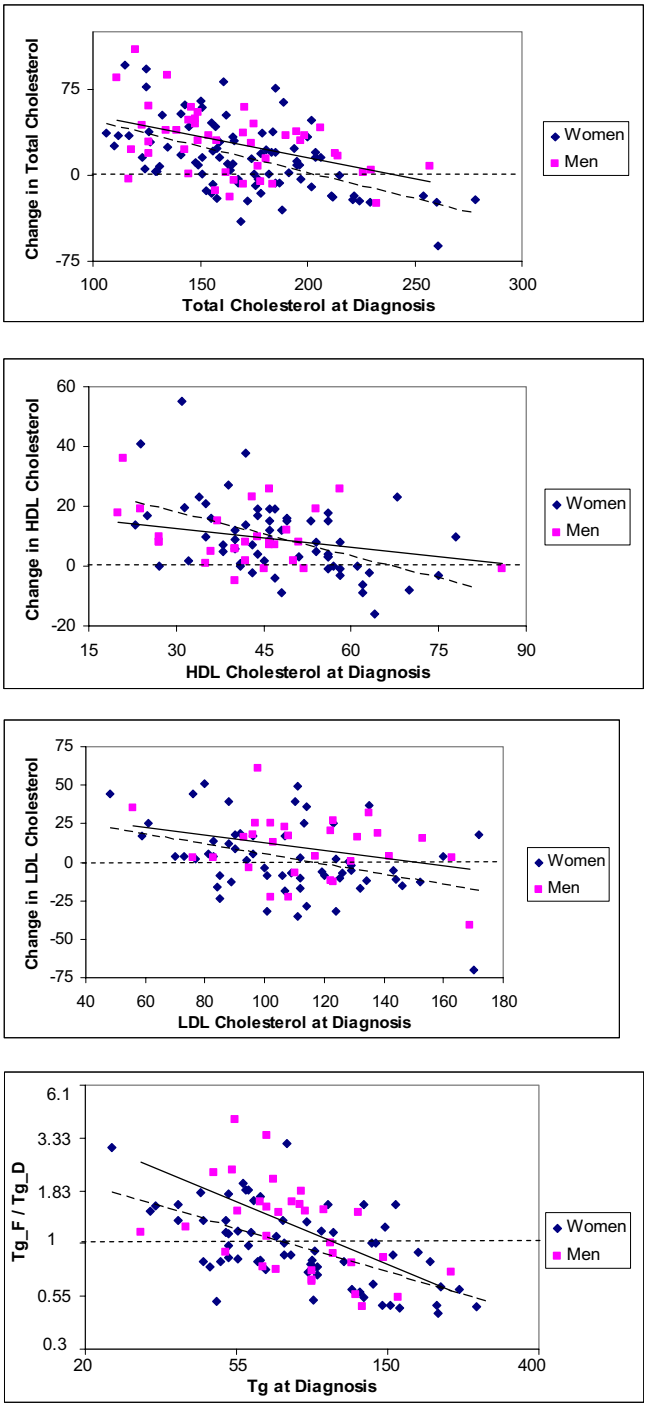

Figure 2 Change in lipid values compared to the initial value (prior to treatment with a gluten-free diet) and regression lines. Tg, triglycerides; Tg_F/Tg_D, change in triglycerides.

Table 4 Multiple Regression Analysis Showing Different Factors Affecting the Changes in Lipid Values (Slopes and *P* Values)

	Total Cholesterol	HDL Cholesterol	LDL Cholesterol	Triglycerides (log)
R^2	0.34	0.26	0.24	0.34
Intercept	141	41.5	97	0.47
Baseline level	−0.40	−0.29	−0.35	−0.005
	$P < .0001$	$P = .0005$	$P < .0001$	$P < .0001$
Male gender	13.9		13.2	0.20
	$P = .004$		$P = .01$	$P = .03$
Albumin level	−13.9	−5.0	−12.3	
	$P = .005$	$P = .04$	$P = .03$	
TVA		4.2	−10.4	
		$P = .05$	$P = .02$	

HDL = high-density lipoprotein; LDL = low-density lipoprotein; TVA = total villous atrophy.

and, to a lesser extent, the result of an increase in LDL-C in men but not in women. In both men and women, the percent increase in HDL-C is greater than that of LDL-C: 21% versus 4%. In addition, for both sexes, there is a significant decrease in the LDL/HDL ratio, indicating an improvement in the cardiovascular risk profile. These findings should allay potential concerns about an increase in cardiovascular risk being a result of the dietary treatment of celiac disease and suggest that the increased recognition and treatment of subclinical disease will not have adverse effects on cardiovascular morbidity.

The greatest increase in both TC and HDL was in subjects with the lowest initial values. Other associated factors were male gender and evidence of more severe intestinal damage as manifested by low initial albumin level and TVA found on duodenal biopsies. The increase was not related to whether the patients presented with diarrhea or had "silent" celiac disease.[1]

The low HDL levels in celiac disease can be explained by the intestine being a major source of both HDL and apo-A1, the main apo-protein of circulating HDL.[13,14] In active celiac disease intestinal apo-A1 synthesis is virtually absent.[15] This would explain the more prominent increase in serum HDL correlating with parameters of a more severe proximal intestinal lesion. The multiple regression analysis supports this, because TVA is associated with a greater increase in HDL. Specifically, TVA was associated with an additional increase in HDL of 4.2 mg/dL and a decrease in LDL of 10.4 mg/dL. The latter means that the baseline LDL-C level at which the expected change in LDL is 0 is approximately 30 mg/dL lower than without TVA; thus, in women, any baseline LDL greater than 100 mg/dL can be expected to result in no increase and possibly a decrease in LDL. These findings suggest that adherence to gluten-free diet will lead to a significant improvement in the cardiovascular profile, especially for a patient with TVA.

Another mechanism that may contribute to the changes we observed in the lipid profile is the increased absorption of dietary saturated fat after the initiation of a gluten-free diet and improvement in absorption. This may contribute to both increased LDL (by down-regulation of hepatic LDL receptors) and increased HDL, because an increased content of fat in the diet is associated with higher HDL levels. The variable response of the LDL level (Figure 2) may be a manifestation of the difference in the quantity and type of fat in the diet of the individuals.

Our study demonstrates that the treatment of celiac disease with a gluten-free diet causes an increase in TC, which may contribute to an increased cardiovascular risk.[16] However, the prominent effect was on HDL level. The HDL level has greater significance as a risk factor than TC[17] and is independent of LDL-C levels.[18]

A previous study suggested a beneficial survival effect of treated celiac disease; there was a 40% reduction in ischemic heart disease mortality among members of the Celiac Society in England and Wales compared with the general population.[19] However, a population-based study from the United Kingdom did not reveal a reduced rate of myocardial infarction when compared with the general population.[20] Population-based studies provide valuable information about celiac disease that is not available in studies from hospital-based series.[20-23] However, we are not aware of the dietary compliance of those identified by diagnostic codes in population-based studies. There is evidence of variable compliance to the gluten-free diet in the United Kingdom.[24-26] In our study, the individuals who were compliant with the gluten-free diet had a prominent increase in HDL. The increase in HDL-C levels could be protective; studies have shown that the risk of coronary heart disease decreases by 2% in men and 3% for women for each 1 mg/dL increase in HDL-C levels.[27,28] In addition, we observed that 11% of men and 16% of women who had HDL levels less than 40 mg/dL, a level considered to warrant therapeutic intervention,[29] experienced an increase in HDL to more desirable levels (>40 mg/dL).

Celiac disease is associated with low HDL-C levels that increase on a gluten-free diet. Although prospective studies would be required to demonstrate the effect of the gluten-free diet and whether this resulted in a decrease in cardiovascular risk, our findings should nonetheless mollify potential concerns that dietary treatment of celiac disease worsens cardiovascular risk.

References

1. Green PH, Jabri B. Coeliac disease. *Lancet.* 2003;362(9381):383-391.
2. West J, Logan RF, Hill PG, et al. Seroprevalence, correlates, and characteristics of undetected coeliac disease in England. *Gut.* 2003; 52(7):960-965.
3. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med.* 2003;163(3):286-292.
4. Vuoristo M, Tarpila S, Miettinen TA. Serum lipids and fecal steroids in patients with celiac disease: effects of gluten-free diet and cholestyramine. *Gastroenterology.* 1980;78(6):1518-1525.
5. Ciacci C, Cirillo M, Giorgetti G, et al. Low plasma cholesterol: a correlate of nondiagnosed celiac disease in adults with hypochromic anemia. *Am J Gastroenterol.* 1999;94(7):1888-1891.
6. Ciampolini M, Bini S. Serum lipids in celiac children. *J Pediatr Gastroenterol Nutr.* 1991;12(4):459-460.
7. Bai D, Brar P, Holleran S, et al. Effect of gender on the manifestations of celiac disease: evidence for greater malabsorption in men. *Scand J Gastroenterol.* 2005;40(2):183-187.
8. Rosenthal E, Hoffman R, Aviram M, et al. Serum lipoprotein profile in children with celiac disease. *J Pediatr Gastroenterol Nutr.* 1990;11(1): 58-62.
9. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). *Gastroenterology.* 1992;102(1): 330-354.
10. Mediene S, Hakem S, Bard JM, et al. Serum lipoprotein profile in Algerian patients with celiac disease. *Clin Chim Acta.* 1995;235(2): 189-196.
11. Capristo E, Addolorato G, Mingrone G, et al. Low-serum high-density lipoprotein-cholesterol concentration as a sign of celiac disease. *Am J Gastroenterol.* 2000;95(11):3331-3332.
12. Pillan MN, Spandrio S, Sleiman I, et al. Effects of a gluten-free diet on serum lipids and lipoprotein (a) levels in a group of patients with celiac disease. *J Pediatr Gastroenterol Nutr.* 1994;18(2):183-185.
13. Green PH, Tall AR, Glickman RM. Rat intestine secretes discoid high density lipoprotein. *J Clin Invest.* 1978;61(2):528-534.
14. Green PH, Glickman RM. Intestinal lipoprotein metabolism. *J Lipid Res.* 1981;22(8):1153-1173.
15. Floren CH, Alm P. Defective synthesis of apolipoprotein A-I in jejunal mucosa in coeliac disease. *Scand J Gastroenterol.* 1988;23(7):856-860.
16. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ.* 1994;308(6925):367-372.
17. Miller M, Seidler A, Kwiterovich PO, Pearson TA. Long-term predictors of subsequent cardiovascular events with coronary artery disease and 'desirable' levels of plasma total cholesterol. *Circulation.* 1992; 86(4):1165-1170.
18. Fonarow GC, Watson KE. High-density lipoprotein cholesterol as a therapeutic target to reduce cardiovascular events. *Am Heart J.* 2004; 147(6):939-941.
19. Whorwell PJ, Alderson MR, Foster KJ, Wright R. Death from ischaemic heart-disease and malignancy in adult patients with coeliac disease. *Lancet.* 1976;2(7977):113-114.
20. West J, Logan RF, Card TR, et al. Risk of vascular disease in adults with diagnosed coeliac disease: a population-based study. *Aliment Pharmacol Ther.* 2004;20(1):73-79.
21. West J, Logan RF, Card TR, et al. Fracture risk in people with celiac disease: a population-based cohort study. *Gastroenterology.* 2003; 125(2):429-436.
22. Tata LJ, Card TR, Logan RF, et al. Fertility and pregnancy-related events in women with celiac disease: a population-based cohort study. *Gastroenterology.* 2005;128(4):849-855.
23. Peters U, Askling J, Gridley G, et al. Causes of death in patients with celiac disease in a population-based Swedish cohort. *Arch Intern Med.* 2003;163(13):1566-1572.
24. Kumar PJ, Walker-Smith J, Milla P, et al. The teenage coeliac: follow up study of 102 patients. *Arch Dis Child.* 1988;63(8):916-920.
25. Hankey GL, Holmes GK. Coeliac disease in the elderly. *Gut.* 1994; 35(1):65-67.
26. Butterworth JR, Banfield LM, Iqbal TH, Cooper BT. Factors relating to compliance with a gluten-free diet in patients with coeliac disease: comparison of white Caucasian and South Asian patients. *Clin Nutr.* 2004;23(5):1127-1134.
27. Boden WE. High-density lipoprotein cholesterol as an independent risk factor in cardiovascular disease: assessing the data from Framingham to the Veterans Affairs High-Density Lipoprotein Intervention Trial. *Am J Cardiol.* 2000;86(12A):19L-22L.
28. Maron DJ. The epidemiology of low levels of high-density lipoprotein cholesterol in patients with and without coronary artery disease. *Am J Cardiol.* 2000;86(12A):11L-14L.
29. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106(25):3143-3421.