Association of dyslipidemia with chronic non-malignant pain in elderly patients with femoral neck fractures treated by primary total hip arthroplasty: a retrospective study

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Abstract
Objective: The association of chronic non-malignant pain (CNP) with dyslipidemia is unclear. This retrospective study was performed to evaluate the association between CNP and...
dyslipidemia in elderly patients with femoral neck fractures (FNFs) treated by primary unilateral total hip arthroplasty (THA).

**Methods:** We retrospectively identified 521 consecutive patients with FNFs (AO/OTA type 31B) who underwent primary unilateral THA from 2009 to 2021. The study population was divided into patients with and without CNP. Serum lipids were measured for each patient. The association between CNP and dyslipidemia was assessed using a multivariate binary logistic regression model.

**Results:** In total, 436 patients (220 with CNP, 216 without CNP) were eligible for analysis. In the quantile regression, the adverse effect of CNP was significantly attenuated by resilience in patients with a high high-density lipoprotein (HDL) concentration and low low-density lipoprotein (LDL) concentration. The multivariate binary logistic regression model showed that the HDL and LDL concentrations were the only variables significantly associated with the development of CNP.

**Conclusion:** Both a low HDL and high LDL concentration may result in the occurrence of CNP in elderly patients with FNFs treated by primary unilateral THA.

**Keywords**
Dyslipidemia, association, chronic pain, low-density lipoprotein, high-density lipoprotein, femoral neck fracture, total hip arthroplasty

**Introduction**

Chronic non-malignant pain (CNP), which has a high prevalence and refractory nature, is typically characterized by hyperalgesia and has been linked to restrictions in daily activities, emotions, and quality of life. Moreover, severe CNP can shorten patients’ life expectancy. Population-based estimates of CNP among Chinese elderly individuals range from 10% to 39% with significant subgroup differences. The increasing prevalence of CNP is attributable to demographic and lifestyle changes and is predicted to lead to a pronounced increase in the prescription of opioid analgesics for CNP, which has initiated escalating concern regarding the potential harms of these drugs. However, no clear consensus on population-wide CNP prevention or interventions has been established. Although the high prevalence of CNP has led to increased interest in underlying CNP-related risk factors, no clear risk factors for CNP appear to have been identified to date. Epidemiological studies have demonstrated that dyslipidemia may be a risk factor for the occurrence and development of CNP. Additionally, CNP might be highly comorbid with dyslipidemia. The lipid–pain relationship may be bidirectional: dyslipidemia may lead to gain (sensitization) or loss (desensitization) of function relative to the incoming CNP signals, whereas CNP may conversely have a feedback effect on serum lipid levels.

Whether CNP and dyslipidemia have a positive correlation has been debated. Increases in serum lipids may be paralleled by an increase in the duration of CNP. Furthermore, the focus on normal serum
lipid levels may underestimate the harms of CNP. Notably, dyslipidemia may instigate or exacerbate CNP, potentially increasing the risk of CNP-related events. No lipid-related assessment of the risk of CNP in elderly patients with femoral neck fractures (FNFs) treated by primary unilateral total hip arthroplasty (THA) has been performed to date. We therefore performed a retrospective study to evaluate the association between CNP and dyslipidemia in such patients.

**Materials and methods**

**Study population**

This study was approved by the Investigational Ethics Review Board of Pu’ai Hospital, Tongji Medical College, Huazhong University of Science and Technology (IRB-07214), and the board granted an exemption from the requirement for informed consent because of the retrospective nature of the study. The reporting of this study conforms to the STROBE guidelines, and all patient details have been de-identified.

Data for 521 consecutive patients with FNFs (AO/OTA type 31B) who had been treated by primary unilateral THA (cemented femoral component and standard-device acetabular component; Stryker Orthopaedics, Mahwah, NJ, USA) from March 2009 to January 2021 were retrospectively identified from the East China Hip Arthroplasty Database. CNP was defined as chronic pain that had developed or increased in intensity after the surgical procedure and persisted for 3 months after the surgery in accordance with the International Association for the Study of Pain guidelines. THA was performed using a direct anterior approach. The key exclusion criteria were deficient baseline data, hypoesthesia (decreased response to a stimulus that is normally painful), hyperalgesia, allodynia, cancer pain, nerve trauma, joint damage, gastric ulcers, endometriosis, diseases related to cholesterol metabolism, thyroid dysfunction, polytrauma, Paget’s disease, rheumatoid arthritis, and consumption of lipid-lowering medications.

**Study endpoints**

The primary endpoint was the association between CNP and dyslipidemia in elderly patients with FNFs treated by primary unilateral THA. Pain measurement was performed using a visual analog scale on the first day after surgery. Assessment of serum lipids was performed for each patient in both groups. Serum lipids included total cholesterol (TC), triglycerides (TGs), low-density lipoprotein (LDL), high-density lipoprotein (HDL), apolipoprotein A1 (apoA1), apolipoprotein B (apoB), apolipoprotein E4 (apoE4), leptin, and adiponectin. The blood samples were processed in accordance with the method described in previous reports. Dyslipidemia was defined as a TG concentration of ≥8.3 mmol/L, HDL concentration of ≤2.2 mmol/L, and LDL concentration of ≥8.9 mmol/L.

**Statistical analysis**

The serum lipid variables are expressed as mean ± standard deviation. Categorical variables were compared using the chi-square test or Fisher’s exact test, and continuous variables were compared using Student’s t-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data. The primary analysis of the association between CNP and dyslipidemia was performed using a multivariate binary logistic regression model. All analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). The
level of significance was set at $p < 0.05$ for all statistical analyses.

**Results**

In total, 521 elderly individuals with FNFs who had been treated by primary unilateral THA and had available baseline data were included in the study. Eighty-five patients did not meet the study criteria, and the remaining 436 patients were analyzed as shown in Figure 1. The study population was divided into patients with CNP (Group CP, $n=220$) and patients without CNP (Group NC, $n=216$). The median age was 67.74 years (range, 61–73 years) in the CP group and 67.65 years (range, 61–74 years) in the NC group with no significant difference. In the baseline data on serum lipids, we found significant differences in leptin, adiponectin, TC, HDL, LDL, TGs, apoE4, and apoE genotype ($p < 0.001$). The mean leptin, adiponectin, LDL, TG, and apoE4 carrier values were considerably higher in the CP group than in the NC group ($p < 0.001$), and the mean TC and HDL values were significantly lower in the CP group than in the NC group ($p < 0.001$). A significant difference was also detected in the apoE genotype ($p < 0.001$). No significant differences were detected in the remaining baseline data, as shown in Table 1.

Table 2 shows the results of the multivariate binary logistic analysis of factors associated with CNP in this cohort of elderly patients with FNFs treated by primary unilateral THA. Age, education, smoking, and body mass index were not involved in this analysis. In the quantile regression, the adverse effect of CNP was significantly attenuated by resilience in patients with a high HDL concentration ($p = 0.003$) and low LDL concentration ($p = 0.001$). This effect appeared to be mainly driven by the high HDL and low LDL. The multivariate binary logistic regression model showed that the HDL and LDL concentrations were the only variables associated with the development of CNP (odds ratio, 7.08; 95% confidence interval, 4.30–8.72; $p < 0.001$ and odds ratio, 6.51; 95% confidence interval, 3.93–7.48; $p < 0.001$, respectively). Other variables (leptin, adiponectin, TC, apoA1, apoB, TGs, apoE4, and apoE genotype) were not associated with CNP in the present analysis.

**Discussion**

This retrospective study may provide evidence that both a high LDL and low HDL concentration are strongly associated with the occurrence of CNP in elderly patients with FNFs treated by primary unilateral THA. Both a high LDL and low HDL concentration may be the primary risk factors for CNP in most patients. Measurement of serum lipids may be particularly important for elderly patients with CNP. Both a low LDL and high HDL concentration may have a favorable benefit-risk profile for the prevention of CNP, but the consumption of lipid-lowering drugs may be increased in patients with both a high LDL and low HDL concentration.

A series of clinical aggravations attributed to high-impact CNP have been frequently mentioned in published reports. These aggravations have indisputably become important factors restricting patients’ daily activities. In the present study, both a high LDL and low HDL concentration tended to be robust predictors of CNP. However, we detected little evidence of a temporal relationship between the occurrence of CNP and the presence of dyslipidemia, and we found no evidence that the occurrence of CNP can further aggravate dyslipidemia. CNP is usually recognized to arise from altered neuronal activity that is associated with a heightened perception of pain (peripheral and/or central sensitization). An elevated cholesterol level or hyperlipidemia (a high LDL level in
particular) may be an important risk factor for the occurrence of CNP. Dyslipidemia is associated with an increased risk of the development of atherosclerosis. Several studies have demonstrated that atherosclerosis promotes neuronal degeneration or neurotransmitter synthesis disorder, which leads to a disorderly increase in lipid metabolites (such as oxidized lipids). The accumulation of oxidized lipids in the microvasculature stimulates the local release of inflammatory mediators, which can directly initiate and accelerate sensitization of pain-sensing nociceptors located at functional afferent neurons. 

Previous studies of CNP tended to underestimate serum lipids among elderly individuals, focusing instead on the management of high-impact CNP. Recent studies have shown that dyslipidemia may be one of the most important contributors to CNP, and even more recent studies have revealed that the plasma lipidomic profile is associated with CNP. However, the role of dyslipidemia in the occurrence and development of CNP remains controversial. A few studies regarding the effect of dyslipidemia on CNP have shown that hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (such as atorvastatin) can competitively

Figure 1. Flow diagram demonstrating selection of patients for evaluation of the association between chronic non-malignant pain and dyslipidemia in a cohort of elderly individuals with femoral neck fractures treated by primary unilateral total hip arthroplasty, and reasons for exclusion. THA, total hip arthroplasty; Group CP, chronic non-malignant pain group; Group NC, normal controls.
inhibit the conversion of HMG-CoA to mevalonic acid.\textsuperscript{34,35} Although HMG-CoA reductase inhibitors represent an encouraging opportunity to improve the management of CNP,\textsuperscript{34} clinical application is limited and few products appear to be in use for CNP.\textsuperscript{10} In 2013, Pathak et al.\textsuperscript{36} assessed the antihyperalgesic and anti-inflammatory effects of atorvastatin in a chronic constriction injury model of neuropathic pain in rats. The results showed that atorvastatin tends to be a supplementary therapeutic option in treating neuropathic pain. In 2014, Pathak et al.\textsuperscript{37} further evaluated the effect of atorvastatin on oxidative stress and hyperalgesia in a chronic constriction injury model of neuropathic pain in rats. The results demonstrated that atorvastatin attenuates neuropathic pain by down-regulating oxidative damage at peripheral levels. Analogously, Ala et al.\textsuperscript{14} investigated the efficacy of atorvastatin in reducing postoperative pain in 66 patients who underwent open hemorrhoidectomy in a randomized, placebo-controlled trial. The results demonstrated that atorvastatin reduces postoperative pain and decreased opioid requirements compared with placebo. Based on comparable scenarios, several other studies have revealed that dyslipidemia is apt to instigate the occurrence of CNP and that the onset of dyslipidemia is significantly associated with the duration and extent of CNP.\textsuperscript{13,16,38}

Table 1. Patient demographics

| Variable            | CP (n = 220) | NC (n = 216) | p-value* |
|---------------------|-------------|--------------|----------|
| Age, years          | 67.74 ± 6.22| 67.65 ± 6.48 | 0.125    |
| Sex, male/female    | 88/132      | 94/122       | 0.457    |
| Education, years    | 15.43 ± 8.16| 15.61 ± 8.49 | 0.181    |
| Smoking, years      | 8.57 ± 5.48 | 8.61 ± 6.13  | 0.296    |
| BMI, kg/m\textsuperscript{2} | 25.47 ± 7.96 | 25.52 ± 8.05 | 0.157    |
| Leptin, ng/mL       | 13.11 ± 8.69| 8.83 ± 5.42  | <0.001*  |
| Adiponectin, μg/mL  | 16.73 ± 9.26| 8.65 ± 6.97  | <0.001*  |
| TC, mmol/L          | 4.35 ± 1.84 | 4.91 ± 1.43  | <0.001*  |
| HDL, mmol/L         | 1.69 ± 0.49 | 3.64 ± 0.81  | <0.001*  |
| LDL, mmol/L         | 13.72 ± 4.46| 6.76 ± 1.96  | <0.001*  |
| TGs, mmol/L         | 11.41 ± 2.28| 6.47 ± 1.76  | <0.001*  |
| apoA1, mg/dL        | 100.22 ± 17.08| 101.27 ± 19.26 | 0.201    |
| apoB, mg/dL         | 56.34 ± 14.29| 56.78 ± 15.37 | 0.363    |
| apoE4 carrier, %    | 55.7        | 38.6         | <0.001*  |
| apoE genotype, %    |             |              | <0.001*  |

E2/2 4.1 5.4
E2/3 8.3 14.7
E2/4 2.4 7.3
E3/3 41.3 38.2
E3/4 39.7 34.6
E4/4 4.3 3.6

Data are presented as mean ± standard deviation or n (%).
*Significant difference (p < 0.05).
Dyslipidemia is involved in the evolution of CNP. In this process, oxidized lipids frequently inhibit or interrupt the normal nerve signal transmission pathway, triggering the enhancement of neuronal feedback and promoting the excessive release of neurotransmitters; this eventually leads to the establishment of abnormal signal transmission pathways and the occurrence of CNP. However, CNP further induces the release of inflammatory mediators, which further aggravates or worsens dyslipidemia and finally leads to breakdown of the lipid metabolic balance. Dyslipidemia plays a key role in this vicious circle. This is primarily because dyslipidemia can not only directly trigger the release of neurotransmitters but also promote the explosive release of inflammatory factors through the immune response.

The results of this retrospective study should be interpreted in light of several key limitations. First, the retrospective nature of the study and the exclusion criteria somewhat limit our ability to draw reliable conclusions. Second, the sample size was relatively small, restricting the estimation of consistent conclusions. Replication of the study with a larger sample size appears to be necessary. Furthermore, several subjective outcome measures (such as age, education, and smoking) were included in the study, and subjective self-assessment could result in potential reporting bias. Third, some comorbidities were not involved when evaluating the baseline data. Fourth, stratification of dyslipidemia was not performed in this study, which may have introduced a deviation. Fifth, the lack of generalizability is inevitable because our study population comprised elderly patients, the direct anterior approach was used for THA in all patients, and strict exclusion criteria were applied. Finally, although our study followed the general principles of research and the factors influencing CNP were multifaceted, involving both laboratory and non-laboratory parameters (i.e., duration of the operation, surgical approach), these

Table 2. Multivariate binary logistic regression analysis of factors associated with chronic non-malignant in the present cohort of elderly patients with femoral neck fractures treated by primary unilateral total hip arthroplasty

| Factors               | Regression coefficient (β) | Standard error | Odds ratio | 95% CI         | χ²   | p-value |
|-----------------------|-----------------------------|----------------|------------|----------------|------|---------|
| Leptin                | 0.46                        | 0.127          | 2.23       | 0.54–3.76      | 3.26 | 0.374   |
| Adiponectin           | 0.31                        | 0.264          | 2.18       | 0.65–2.71      | 3.79 | 0.216   |
| TC                    | 0.75                        | 0.375          | 1.90       | 0.22–3.16      | 4.15 | 0.154   |
| TGs                   | 0.58                        | 0.213          | 2.03       | 0.51–3.01      | 3.25 | 0.243   |
| LDL                   | 1.27                        | 0.325          | 6.51       | 3.93–7.48      | 3.09 | <0.001* |
| HDL                   | 0.56                        | 0.129          | 7.08       | 4.30–8.72      | 2.31 | <0.001* |
| apoA1                 | 0.35                        | 1.942          | 1.49       | 0.87–5.35      | 4.79 | 0.361   |
| apoB                  | 1.74                        | 3.251          | 1.18       | 0.43–2.42      | 4.12 | 0.284   |
| apoE4 carrier         | 2.35                        | 2.130          | 2.74       | 0.81–3.68      | 2.56 | 0.178   |
| apoE genotype         | 2.43                        | 1.482          | 4.36       | 0.30–5.71      | 1.43 | 0.191   |

CI, confidence interval; TC, total cholesterol; TGs, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; apoA1, apolipoprotein A1; apoB, apolipoprotein B; apoE, apolipoprotein E

*Significant association (p < 0.05).
factors are relatively fixed, and interventions for dyslipidemia may have a certain impact on the outcome of CNP.

In conclusion, the results of this retrospective study reveal that both a low HDL and high LDL concentration tend to be associated with the occurrence of CNP in elderly patients with FNFs treated by primary unilateral THA. This implies that dyslipidemia may be involved in the occurrence of CNP in these elderly patients. Given the retrospective nature of this study and the small sample size, future large-sample randomized controlled studies are needed to determine whether such a relationship exists.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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References
1. Treede RD, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: The IASP classification of chronic pain for the International Classification of Diseases (ICD-11). Pain 2019; 160: 19–27.
2. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of chronic pain and high-impact chronic pain among adults - United States, 2016. MMWR Morb Mortal Wkly Rep 2018; 67: 1001–1006.
3. Campbell G, Hall WD, Peacock A, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: Findings from a 4-year prospective cohort study. Lancet Public Health 2018; 3: e341–e350.
4. Ji RR, Xu ZZ and Gao YJ. Emerging targets in neuroinflammation-driven chronic pain. Nat Rev Drug Discov 2014; 13: 533–548.
5. Tsang A, Von Korff M, Lee S, et al. Common chronic pain conditions in developed and developing countries: Gender and age differences and comorbidity with depression-anxiety disorders. J Pain 2008; 9: 883–891.
6. Busse JW, Wang L, Kamaleldin M, et al. Opioids for chronic noncancer pain: A systematic review and meta-analysis. JAMA 2018; 320: 2448–2460.
7. Sheng JY, Liu S, Wang YC, et al. The link between depression and chronic pain: Neural mechanisms in the brain. Neural Plast 2017; 2017: 9724371.
8. Dowell D, Haegerich TM and Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA 2016; 315: 1624–1645.
9. Hoffmann H, Walther D, Bittner R, et al. Smaller inguinal hernias are independent risk factors for developing chronic postoperative inguinal pain (CPIP): A registry-based multivariable analysis of 57,999 patients. Ann Surg 2020; 271: 756–764.
10. Donnelly TJ, Palermo TM and Newton-John TRO. Parent cognitive, behavioural, and affective factors and their relation to child pain and functioning in pediatric chronic pain: A systematic review and meta-analysis. Pain 2020; 161: 1401–1419.
11. Vieira G, Cavalli J, Goncalves ECD, et al. Effects of simvastatin beyond dyslipidemia: Exploring its antinociceptive action in an animal model of complex regional pain syndrome-type I. Front Pharmacol 2017; 8: 584.
12. Stensson N, Ghafori B, Gerdle B, et al. Alterations of anti-inflammatory lipids in plasma from women with chronic widespread pain - a case control study. Lipids Health Dis 2017; 16: 112.
13. Heuch I, Heuch I, Hagen K, et al. Associations between serum lipid levels and chronic low back pain. Epidemiology 2010; 21: 837–841.
14. Ala S, Alvandipour M, Saeedi M, et al. Effects of topical atorvastatin (2%) on post-hemorrhoidectomy pain and wound healing: A randomized double-blind placebo-controlled clinical trial. *World J Surg* 2017; 41: 596–602.

15. Piomelli D and Sasso O. Peripheral gating of pain signals by endogenous lipid mediators. *Nat Neurosci* 2014; 17: 164–174.

16. Hassler SN, Johnson KM and Hulsebosch CE. Reactive oxygen species and lipid peroxidation inhibitors reduce mechanical sensitivity in a chronic neuropathic pain model of spinal cord injury in rats. *J Neurochem* 2014; 131: 413–417.

17. Bazan NG and Flower RJ. Medicine: Lipid signals in pain control. *Nature* 2002; 420: 135–138.

18. Eriksen J, Sjögren P, Bruera E, et al. Critical issues on opioids in chronic non-cancer pain: An epidemiological study. *Pain* 2006; 125: 172–179.

19. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.

20. Cabrera D, Kruger M, Wolber FM, et al. Association of plasma lipids and polar metabolites with low bone mineral density in Singaporean-Chinese menopausal women: A pilot study. *Int J Environ Res Public Health* 2018; 15: 1045.

21. Brown EE, Sturm AC, Cuchel M, et al. Genetic testing in dyslipidemia: A scientific statement from the national lipid association. *J Clin Lipidol* 2020; 14: 398–413.

22. Grundy SM, Cleeman JI, Merz CNB, et al. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. *Circulation* 2004; 110: 227–239.

23. Jacobson TA, Maki KC, Orringer CE, et al. National lipid association recommendations for patient-centered management of dyslipidemia: Part 2. *J Clin Lipidol* 2015; 9: S1–S122.e1.

24. VanDenKerkhof EG, Peters ML and Bruce J. Chronic pain after surgery time for standardization? A framework to establish core risk factor and outcome domains for epidemiological studies. *Clin J Pain* 2013; 29: 2–8.

25. Barahman M, Zhang W, Harris HY, et al. Radiation-primed hepatocyte transplantation in murine monogeneic dyslipidemia normalizes cholesterol and prevents atherosclerosis. *J Hepatol* 2019; 70: 1170–1179.

26. Gottesman RF, Albert MS, Alonso A, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the atherosclerosis risk in communities (ARIC) cohort. *JAMA Neurology* 2017; 74: 1246–1254.

27. Zysset D, Weber B, Rihs S, et al. TREM-1 links dyslipidemia to inflammation and lipid deposition in atherosclerosis. *Eur J Clin Invest* 2016; 7: 13151.

28. Gong KW, Zhao W, Li N, et al. Air-pollutant chemicals and oxidized lipids exhibit genome-wide synergistic effects on endothelial cells. *Genome Biol* 2007; 8: R149.

29. Osthues T and Sisignano M. Oxidized lipids in persistent pain states. *Front Pharmacol* 2019; 10: 1147.

30. Hill RZ, Hoffman BU, Morita T, et al. The signaling lipid sphingosine 1-phosphate regulates mechanical pain. *Elife* 2018; 7: e33285.

31. Piomelli D, Hohmann AG, Seybold V, et al. A lipid gate for the peripheral control of pain. *Nature* 2002; 420: 78–84.

32. Pousin P, Gowler PRW, Burston JJ, et al. Lipidomic identification of plasma lipids associated with pain behaviour and pathology in a mouse model of osteoarthritis. *Metabolomics* 2020; 16: 32.

33. Loo L, Wright BD and Zylka MJ. Lipid kinases as therapeutic targets for chronic pain. *Nature* 2014; 34: 15184–15191.

34. Youssef S, Stuve O, Patarroyo JC, et al. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. *Nature* 2002; 420: 78–84.
36. Pathak NN, Balaganur V, Lingaraju MC, et al. Antihyperalgesic and anti-inflammatory effects of atorvastatin in chronic constriction injury-induced neuropathic pain in rats. *Inflammation* 2013; 36: 1468–1478.

37. Pathak NN, Balaganur V, Lingaraju MC, et al. Atorvastatin attenuates neuropathic pain in rat neuropathy model by down-regulating oxidative damage at peripheral, spinal and supraspinal levels. *Neurochem Int* 2014; 68: 1–9.

38. Marra S, Ferru-Clement R, Breuil V, et al. Non-acidic activation of pain-related acid-sensing ion channel 3 by lipids. *EMBO J* 2016; 35: 414–428.

39. Kummerow FA, Olinescu RM, Fleischer L, et al. The relationship of oxidized lipids to coronary artery stenosis. *Atherosclerosis* 2000; 149: 181–190.