

# Circulation Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart  
Association®   
*Learn and Live*<sup>SM</sup>

## **Polyphenols and Cholesterol Efflux: Is Coffee the Next Red Wine?**

Megan F. Burke, Amit V. Khera and Daniel J. Rader

*Circ. Res.* 2010;106;627-629

DOI: 10.1161/CIRCRESAHA.109.215855

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2010 American Heart Association. All rights reserved. Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circres.ahajournals.org/cgi/content/full/106/4/627>

Subscriptions: Information about subscribing to Circulation Research is online at  
<http://circres.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:  
[journalpermissions@lww.com](mailto:journalpermissions@lww.com)

Reprints: Information about reprints can be found online at  
<http://www.lww.com/reprints>

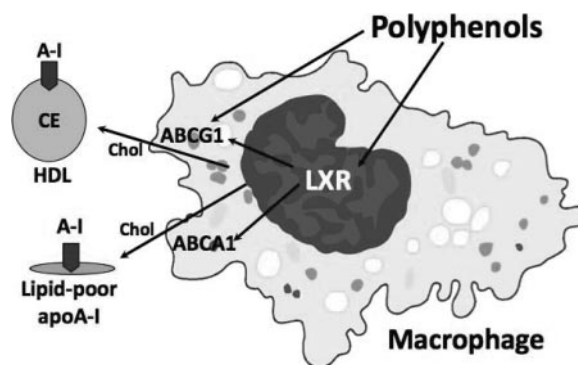
## Polyphenols and Cholesterol Efflux Is Coffee the Next Red Wine?

Megan F. Burke, Amit V. Khera, Daniel J. Rader

Despite strong evidence for an inverse association between high-density lipoprotein cholesterol (HDL-C) levels and cardiovascular risk,<sup>1</sup> successful therapeutic strategies to target HDL have remained elusive. A recent Phase III clinical trial failed to show clinical benefit with the cholesteryl ester transfer protein inhibitor torcetrapib despite markedly increased HDL-C levels.<sup>2,3</sup> This outcome reinforced a growing consensus that measurement of HDL-C alone may be an incomplete surrogate for the *in vivo* functionality of HDL and the clinical efficacy of targeting HDL. The careful mechanistic assessment of HDL function has thus emerged as a potential way forward.<sup>4</sup>

Macrophage reverse cholesterol transport (RCT), the process by which cholesterol is transported from macrophage “foam” cells to the liver for ultimate fecal excretion, has been postulated to play a major role in HDL-mediated atheroprotection.<sup>5</sup> Indeed, quantitative measures of macrophage RCT are more strongly associated with atherosclerosis than plasma HDL-C concentrations in mice.<sup>6</sup> The first critical step of macrophage RCT involves efflux of cellular cholesterol to circulating HDL particles. Research in recent years has documented a specific role for the macrophage transporters ATP-binding cassette subfamilies A1 and G1 (ABCA1 and ABCG1) in cholesterol efflux (see the Figure). These findings have stimulated efforts to target the macrophage at the cellular level as a means of enhancing overall RCT. For example, pharmacological agonism of the liver X receptor (LXR) upregulates both ABCA1 and ABCG1 expression,<sup>7,8</sup> promotes macrophage cholesterol efflux *ex vivo* and RCT *in vivo*,<sup>9</sup> and recently entered early phases of clinical testing.<sup>10</sup>

Coffee is one of the most widely consumed beverages in the world.<sup>11</sup> Chronic coffee consumption has been extensively studied in relation to cardiovascular disease, although the results of these studies have been inconclusive.<sup>12–15</sup> Many of these inconsistencies likely reflect inherent limitations of observational epidemiology; residual confounding from other lifestyle variables that vary according to coffee intake, including cigarette smoking, almost assuredly complicates these analyses. Furthermore, the physiological effects of



**Figure.** Postulated mechanisms for effects of polyphenols on macrophage cholesterol efflux. Cholesterol is effluxed out of macrophage foam cells in the first step of RCT. Efflux to lipid-free or lipid-poor apolipoprotein A1 (apoA-I) particles (which then become mature HDL) occurs via the ABCA1 transporter, whereas efflux directly to mature HDL particles occurs via the ABCG1 transporter.<sup>27</sup> Resveratrol and anthocyanins promote the efflux pathway via upregulation of liver X receptor (LXR).<sup>21,23</sup> Uto-Kondo et al demonstrated that two phenolic acids, as well as whole coffee, increased both mRNA and protein levels of ABCG1 and SR-BI, but not ABCA1, by enhancing mRNA stability.<sup>24</sup>

coffee likely vary according to precise formulation and across individuals. An interesting case-control analysis reinforced this point: caffeinated coffee consumption was associated with an increased risk of myocardial infarction only in those with slow caffeine metabolism.<sup>16</sup> Limited data are available with regard to the impact of coffee on lipid metabolism, although one randomized controlled trial noted modest increases in both HDL-C and low-density lipoprotein cholesterol levels after daily consumption of filtered coffee for 8 weeks.<sup>17</sup>

Although the relationship between coffee and coronary disease has not been conclusively determined, it remains plausible that some individual components may be atheroprotective and worthy of further study. Specifically, coffee is a major source of polyphenols,<sup>18</sup> a group of compounds that has received substantial interest in recent years. The term polyphenol represents a wide variety of compounds derived from plants, and polyphenols are present in many components of the human diet.<sup>19</sup> It is widely believed that polyphenols have protective properties, and there is increasing evidence to support their beneficial relationship to various diseases. Although there are limited data on specific polyphenols, polyphenol-rich foods have previously been associated with decreased risk of cardiovascular disease in multiple studies.<sup>20</sup> Interestingly, certain polyphenols, such as resveratrol and anthocyanins (both found in red wine among other sources), have been shown to increase macrophage cholesterol efflux *ex vivo* (Table).<sup>21–23</sup>

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Institute for Translational Medicine and Therapeutics and Cardiovascular Institute, University of Pennsylvania School of Medicine, Philadelphia.

Correspondence to Daniel J. Rader, 654 BRB II/III, University of Pennsylvania School of Medicine, 421 Curie Blvd, Philadelphia, PA 19104. E-mail rader@mail.med.upenn.edu

(*Circ Res.* 2010;106:627–629.)

© 2010 American Heart Association, Inc.

*Circulation Research* is available at <http://circres.ahajournals.org>  
DOI: 10.1161/CIRCRESAHA.109.215855

**Table. Selected Polyphenols and Their Dietary Sources**

Polyphenol	Dietary Source	Effect on Cholesterol Efflux	Mechanism	Reference
Resveratrol	Red wine, berries, peanuts	Positive	Increased expression of LXR	21, 22
Anthocyanins	Red wine, berries	Positive	Increased expression of ABCA1	23
Phenolic acids (caffeic and ferulic)	Coffee, wheat	Positive	Increased expression of ABCG1 and SR-BI	24
Isoflavones	Soy	Unknown	NA	NA
Quercetin	Onions, apples	Unknown	NA	NA
Catechins	Tea, red wine chocolate	Unknown	NA	NA

In this issue of *Circulation Research*, Uto-Kondo et al, describe a careful series of experiments that tested the hypothesis that polyphenols found in coffee may promote macrophage cholesterol efflux.<sup>24</sup> The authors focused their study on caffeic and ferulic acids, phenolic acids (a subclass of polyphenols) known to be present in coffee and increased in plasma by coffee consumption.<sup>25</sup> Importantly, both compounds increased HDL-mediated cholesterol efflux in vitro in a dose-dependent fashion via enhanced expression of the ABCG1 (and SR-BI) transporters. Ferulic acid, but not coffee itself, was additionally shown to modestly enhance macrophage RCT in vivo in mice. Finally, the authors elegantly extended these findings to humans using a placebo-controlled crossover study design. As expected, plasma isolated 30 minutes after consumption of 1 cup of caffeinated coffee was substantially enriched in phenolic acids. Intriguingly, “post-coffee serum” displayed a 40 percent increase in its ability to promote cholesterol efflux from human monocyte-derived macrophages, together with upregulation of ABCG1 and SR-BI. This study thus provides compelling evidence that phenolic acids, with coffee as a delivery mechanism, can increase macrophage-specific cholesterol efflux via upregulation of known cholesterol transporters.

The authors are to be commended for their creative combination of in vitro, mouse in vivo, and human ex vivo approaches in answering questions regarding the complex RCT pathway. However, several limitations should be noted. Although intuitive, an association between enhanced macrophage cholesterol efflux capacity of serum and cardiovascular disease in humans has not been definitively demonstrated. Secondly, the quantitative importance of ABCG1- and SR-BI-mediated cholesterol efflux in the overall human macrophage RCT pathway remains unclear. The authors did not prove that consumption of phenolic acids in isolation, rather than via coffee, is linked to similar results. Finally, because plasma phenolic acid levels decline rapidly after a bolus of

coffee, the findings of the authors may not be generalizable to a longer and more relevant time frame of coffee consumption.

Despite these limitations, this study lays the foundation for multiple avenues of additional research. Ongoing optimization of assays to assess macrophage RCT in humans may permit definitive studies to show that coffee (or polyphenols in general) promote RCT in vivo.<sup>26</sup> Future efforts may systematically characterize the many polyphenols, particularly with regard to their impact on cholesterol efflux and RCT. If indeed the constituent phenolic acids, rather than coffee as a whole, enhance HDL metabolism and RCT, it may ultimately be possible to deliver them more reliably and efficiently in pill form. This approach would not be without precedent in the field of lipid biology; the beneficial effects of omega-3 fatty acids, traditionally delivered via a high-fish diet, have been recapitulated for the treatment of dyslipidemia as the prescription drug Lovaza (GlaxoSmithKline).

In summary, Uto-Kondo et al provide a useful methodologic framework for studies that explore the association between various compounds and cholesterol efflux. Their work adds to a growing body of evidence that suggests a role for polyphenols in cellular cholesterol efflux. If confirmed, this conceptual approach to enhancement of macrophage RCT flux could prove valuable in the prevention and treatment of cardiovascular disease in humans.

### Sources of Funding

Supported by National Heart, Lung, and Blood Institute grant P01-HL22633 (to D.J.R.).

### Disclosures

None.

### References

- Ashen MD, Blumenthal RS. Clinical practice. Low HDL cholesterol levels. *N Engl J Med*. 2005;353:1252–1260.
- Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B, ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med*. 2007;357:2109–2122.
- Rader DJ. Illuminating HDL—is it still a viable therapeutic target? *N Engl J Med*. 2007;357:2180–2183.
- deGoma EM, deGoma RL, Rader DJ. Beyond high-density lipoprotein cholesterol levels evaluating high-density lipoprotein function as influenced by novel therapeutic approaches. *J Am Coll Cardiol*. 2008;51:2199–2211.
- Cuchel M, Rader DJ. Macrophage RCT: key to the regression of atherosclerosis? *Circulation*. 2006;113:2548–2555.
- Rader DJ, Alexander ET, Weibel GL, Billheimer J, Rothblat GH. The role of RCT in animals and humans and relationship to atherosclerosis. *J Lipid Res*. 2009;50(suppl):S189–S194.

#### Non-standard Abbreviations and Acronyms

<b>ABCA1</b>	ATP-binding cassette subfamily A1
<b>ABCG1</b>	ATP-binding cassette subfamily G1
<b>HDL-C</b>	high-density lipoprotein cholesterol
<b>RCT</b>	reverse cholesterol transport
<b>SR-BI</b>	scavenger receptor class B type I

7. Costet P, Luo Y, Wang N, Tall AR. Sterol-dependent transactivation of the ABC1 promoter by the liver X receptor/retinoid X receptor. *J Biol Chem*. 2000;275:28240–28245.
8. Wang N, Lan D, Chen W, Matsuura F, Tall AR. ATP-binding cassette transporters G1 and G4 mediate cellular cholesterol efflux to high-density lipoproteins. *Proc Natl Acad Sci U S A*. 2004;10:9774–9779.
9. Naik SU, Wang X, Da Silva JS, Jaye M, Macphee CH, Reilly MP, Billheimer JT, Rothblat GH, Rader DJ. Pharmacological activation of liver X receptors promotes RCT in vivo. *Circulation*. 2006;113:90–97.
10. Katz A, Udata C, Ott E, Hickey L, Burczynski ME, Burghart P, Vestergvist O, Meng X. Safety, pharmacokinetics, and pharmacodynamics of single doses of LXR-623, a novel liver X-receptor agonist, in healthy participants. *J Clin Pharmacol*. 2009;49:643–649.
11. Barone JJ, Roberts HR. Caffeine consumption. *Food Chem Toxicol*. 1996;34:119–129.
12. Grobbee DE, Rimm EB, Giovannucci E, Colditz G, Stampfer M, Willett W. Coffee, caffeine, and cardiovascular disease in men. *N Engl J Med*. 1990;323:1026–1032.
13. Willett WC, Stampfer MJ, Manson JE, Colditz GA, Rosner BA, Speizer FE, Hennekens CH. Coffee consumption and coronary heart disease in women. A ten-year follow-up. *JAMA*. 1996;275:458–462.
14. Lopez-Garcia E, van Dam RM, Willett WC, Rimm EB, Manson JE, Stampfer MJ, Rexrode KM, Hu FB. Coffee consumption and coronary heart disease in men and women: a prospective cohort study. *Circulation*. 2006;113:2045–2053.
15. Greenberg JA, Chow G, Ziegelstein RC. Caffeinated coffee consumption, cardiovascular disease, and heart valve disease in the elderly (from the framingham study). *Am J Cardiol*. 2008;102:1502–1508.
16. Cornelis MC, El-Sohemy A, Kabagambe EK, Campos H. Coffee, CYP1A2 genotype, and risk of myocardial infarction. *JAMA*. 2006;295:1135–1141.
17. Fried RE, Levine DM, Kwiterovich PO, Diamond EL, Wilder LB, Moy TF, Pearson TA. The effect of filtered-coffee consumption on plasma lipid levels. Results of a randomized clinical trial. *JAMA*. 1992;267:811–815.
18. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. *J Nutr*. 2000;8S(suppl):2073S–2085S.
19. Manach C, Williamson G, Morand C, Scalbert A, Rémésy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am J Clin Nutr*. 2005;1(suppl):230S–242S.
20. Manach C, Mazur A, Scalbert A. Polyphenols and prevention of cardiovascular diseases. *Curr Opin Lipidol*. 2005;16:77–84.
21. Sevov M, Elfineh L, Cavelier LB. Resveratrol regulates the expression of LXR-alpha in human macrophages. *Biochem Biophys Res Commun*. 2006;348:1047–1054.
22. Berrougui H, Grenier G, Loued S, Drouin G, Khalil A. A new insight into resveratrol as an atheroprotective compound: inhibition of lipid peroxidation and enhancement of cholesterol efflux. *Atherosclerosis*. 2009;207:420–427.
23. Xia M, Hou M, Zhu H, Ma J, Tang Z, Wang Q, Li Y, Chi D, Yu X, Zhao T, Han P, Xia X, Ling W. Anthocyanins induce cholesterol efflux from mouse peritoneal macrophages: the role of the peroxisome proliferator-activated receptor [gamma]-liver X receptor [alpha]-ABCA1 pathway. *J Biol Chem*. 2005;280:36792–36801.
24. Uto-Kondo H, Ayaori M, Ogura M, Nakaya K, Ito M, Suzuki A, Takiguchi SI, Yakushiji E, Terao Y, Ozasa H, Hisada T, Sasaki M, Ohsuzu F, Ikewaki K. Coffee consumption enhances high-density lipoprotein-mediated cholesterol efflux in macrophages. *Circ Res*. 2010;106:779–787.
25. Monteiro M, Farah A, Perrone D, Trugo LC, Donangelo C. Chlorogenic acid compounds from coffee are differentially absorbed and metabolized in humans. *J Nutr*. 2007;137:2196–2201.
26. Murphy EJ. Stable isotope methods for the in vivo measurement of lipogenesis and triglyceride metabolism. *J Anim Sci*. 2006;84(suppl):E94–E104.
27. Adorni MP, Zimetti F, Billheimer JT, Wang N, Rader DJ, Phillips MC, Rothblat GH. The roles of different pathways in the release of cholesterol from macrophages. *J Lipid Res*. 2007;48:2453–2462.

---

KEY WORDS: macrophage cholesterol efflux ■ polyphenols ■ phenolic acids ■ coffee ■ cardiovascular disease