

An Integrative Medical Approach To Reversing Cardiovascular Disease: Practicing Beyond the Standard of Care  
by Gary Huber, DO, AOBEM, and Brittany Bankemper, PharmD

## Notes

1. Heart disease facts [Web page]. CDC. Aug. 1, 2015. <http://www.cdc.gov/heartdisease/facts.htm>.
2. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. Nov. 12, 2013.
3. Johnston N, Jernberg T, Lagerqvist B, et al. Improved identification of patients with coronary artery disease by the use of new lipid and lipoprotein biomarkers. *Am J Cardiol*. 2006;97:640–645.
4. Huang H, Mai W, Liu D, et al. The oxidation ratio of LDL: A predictor for coronary artery disease. *Dis Markers*. 2008;24341–24349.
5. Kraft JR. *Diabetes Epidemic & You*. Trafford Publishing; 2008
6. Huber G. Metabolic syndrome and cardiovascular disease: a look at the mechanism that drives this inflammatory process: part 1 understanding the metabolic problem. *Townsend Lett*. May 2013.
7. Huber G. Metabolic syndrome and cardiovascular disease: testing and treatment part 2: quantifying risk and review of treatment options. *Townsend Lett*. June 2013.
8. Vital statistics of the United States [Web page]. Feb. 27, 2013. CDC. <http://www.cdc.gov/nchs/products/vsus.htm>.
9. Taubes G. *Good Calories, Bad Calories*. Anchor; 2008.
10. Health and medical history of President Dwight Eisenhower [Web page]. DoctorZebra.com. July 9, 2003. <http://www.doctorzebra.com/prez/g34.htm>.
11. Davis W. *Wheat Belly*. Rodale; 2014.
12. Perlmutter D. *Grain Brain*. Little, Brown; 2013.
13. Nilsson S, Mölsted S, Karlberg C, et al. No connection between the level of exposition to statins in the population and the incidence/ mortality of acute myocardial infarction: An ecological study based on Sweden's municipalities. *J Negat Results Biomed*. 2011;10:6.
14. Culver AL, Ockene IS, Balasubramanian R, et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. *Arch Intern Med*. 2012;172(2):144–152.
15. Nakata M, Nagasaka S, Kusaka I, et al. Effects of statins on the adipocyte maturation and expression of glucose transporter 4 (SLC2A4): implications in glycaemic control. *Diabetologia*. 2006;49:1881–189.
16. Grover HS, Luthra S, Maroo S. Are statins really wonder drugs? *J Formos Med Assoc*. 2013;1–7.
17. Shepherd J, Blauw GJ, Murphy N=MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 23 November 2002;360(9346):1623–1630.
18. Jain MK, Ridker PM. Anti-inflammatory effects of statins: clinical evidence and basic mechanisms. *Nat Rev Drug Discov*. December 2005;4.
19. Tchernof A, Nolan A, Sites CK, Ades PA, Poehlman ET. Weight loss reduces c-reactive protein levels in obese postmenopausal women. *Circulation*. 2002;105:564–569
20. Heilbronn LK, Noakes M, Clifton PM. Energy restriction and weight loss on very-low-fat diets reduce C-reactive protein concentrations in obese, healthy women. *Arterioscler Thromb Vasc Biol*. 2001;21:968–970.
21. Okita K, Nishijima H, Nagai T, et al. Can exercise training with weight loss lower serum c-reactive protein levels? *Arterioscler Thromb Vasc Biol*. 2004;24:1868–1873.
22. Zhang Y, Gao Y, Tan A, et al. Endogenous sex hormones and C-reactive protein in healthy Chinese men. *Clin Endocrinol*. 2013;78:60–66.
23. Rappaport SM. Implications of the exposome for exposure science. *J Expo Sci Environ Epidemiol*. 2011;21:5–9.
24. Houston MC. Nutrition and nutraceutical supplements in the treatment of hypertension. *Exp Rev Cardiovasc Dis*. 2010;8:821.
25. Libby, Peter. Inflammation and cardiovascular disease mechanisms.

26. Mah E, Bruno RS. Postprandial hyperglycemia on vascular endothelial function: mechanisms and consequences. *Nutr Res.* 2012 Oct;32(10):727–740. doi:10.1016/j.nutres.2012.08.002. Epub 2012 Sep 7.
27. Wang L, Lim EJ, Toborek M, Hennig B. The role of fatty acids and caveolin-1 in tumor necrosis factor alpha-induced endothelial cell activation. *Metabolism.* 2008;57:1328–1239.
28. Zakkar M, Van der Heiden K, Luong le A, et al. Activation of Nrf2 in endothelial cells protects arteries from exhibiting a proinflammatory state. *Arterioscler Thromb Vasc Biol.* 2009;29:1851–1857.
29. Li Q, Zhang Q, Wang M, et al. Docosahexaenoic acid affects endothelial nitric oxide synthase in caveolae. *Arch Biochem Biophys.* 2007;466:250–259.
30. Li Y, Ying C, Zuo X, et al. Green tea polyphenols down-regulate caveolin-1 expression via ERK1/2 and p38MAPK in endothelial cells. *J Nutr Biochem.* 2009;20:1021–1027.
31. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364:937.
32. Ornish D, Brown SE, Billings JH, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. *Lancet.* 1990;336:129–133.
33. Piya MK, Harte AL, McTernan PG. Metabolic endotoxaemia: is it more than just a gut feeling? *Curr Opin Lipidol.* 2013 Feb;24(1):78–85.
34. Wong JMW. Gut microbiota and cardiometabolic outcomes: influence of dietary patterns and their associated components. *Am J Clin Nutr.* 2014;100(suppl):369S–377S.
35. Becker DJ, Gordon RY, Morris PB, et al. Simvastatin vs therapeutic lifestyle changes and supplements: randomized primary prevention trial. *Mayo Clin Proc.* 2008 Jul;83(7):758–764.
36. Johnston N, Jernberg T, Lagerqvist B, et al. Improved identification of patients with coronary artery disease by the use of new lipid and lipoprotein biomarkers. *Am J Cardiol.* 2006 Mar 1;97(5):640–645.
37. Rautiainen S, Levitan EB, Orsini N, et al. Total antioxidant capacity from diet and risk of myocardial infarction: a prospective cohort of women. *Am J Med.* 2012 Oct;125(10):974–980. doi:10.1016/j.amjmed.2012.03.008.
38. Sharp CD, Hines I, Houghton J, et al. Glutamate causes a loss in human cerebral endothelial barrier integrity through activation of NMDA receptor. *Am J Physiol Heart Circ Physiol.* 2003;285:H2592–H2598.
39. Li DP, Averill DB, Pan HL. Differential roles for glutamate receptor subtypes within commissural NTS in cardiac-sympathetic reflex. *Am J Physiol Regul Integr Comp Physiol.* 2001 Sep;281(3):R935–R943.
40. Fragala MS, Kraemer WJ, Denegar CR, et al. Neuroendocrine-immune interactions and responses to exercise. *Sports Med.* 2011;41(8):621–639.
41. Naci H, Ioannidis JPA. Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. *BMJ.* 2013;347:f5577.
42. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002 February 7;346(6):393–403.
43. Smith GD, Ben-Shlomo Y, Beswick A, et al. Cortisol, testosterone, and coronary heart disease: prospective evidence from the Caerphilly study. *Circulation.* 2005;112:332–340.
44. Alabdulgader AA. Coherence: a novel nonpharmacological modality for lowering blood pressure in hypertensive patients. *Glob Adv Health Med.* 2012 May;1(2):56–64. doi:10.7453/gahmj.2012.1.2.011.
45. Vandana B, Vaidyanathan K, Saraswathy LA, et al. Impact of integrated amrita meditation technique on adrenaline and cortisol levels in healthy volunteers. *Evid Based Complement Alternat Med.* 2011. Article ID 379645.
46. Rääkkönen K, Keltikangas-Järvinen L, Adlercreutz H, Hautanen A. Psychosocial stress and the insulin resistance syndrome. *Metabolism.* 1996;45:1533–1538.
47. Morgentaler A, Miner MM, Caliber M, et al. Testosterone therapy and cardiovascular risk: advances and controversies. *Mayo Clin Proc.* February 2015;90(2):224–251.
48. Tibblin G, Adlerberth A, Lindstedt G, Bjorntorp P. The pituitary-gonadal axis and health in elderly men: a study of men born in 1913. *Diabetes.* 1996;45:1605–1609.
49. Haffner SM, Shaten J, Stern MP, Smith GD, Kuller L. Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. *Am J Epidemiol.* 1996;143:889–897.

50. Stellato RK, Feldman HA, Hamdy O, Horton ES, McKinlay JB. Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men. *Diabetes Care*. 2000;23:490–494.
51. Oh J-Y, Barrett-Connor E, Wedick NM, Wingard DL. Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo Study. *Diabetes Care*. 2002;25:55–60.
52. Svartberg J, Jenssen T, Sundsfjord J, Jorde R. The associations of endogenous testosterone and sex hormone-binding globulin with glycosylated hemoglobin levels, in community dwelling men: the Tromsø study. *Diabetes Metab*. 2004;30:29–34.
53. Laaksonen DE, Niskanen L, Punnonen K, et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care*. 2004;27:1036–1041.
54. Zhang Y, Gao, Y, Tan A,. Endogenous sex hormones and C-reactive protein in healthy Chinese men. *Clin Endocrinol*. 2013;78:60–66.
55. Pitteloud N, Mootha VK, Dwyer AA, et al. Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. *Diabetes Care*. 2005; Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. *J Clin Endocrinol Metab*. 2006 Apr;91(4):1305–1308. Epub 2006 Jan 24.
56. Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. *Science*. January 21, 2005;307(5708):384–387.
57. Mootha VK, Lindgren CM, Eriksson KF, et al. PGC-1 -responsive genes involved in oxidative phosphorylation are coordinately down-regulated in human diabetes *Nat Genet*. 2003;34:267–273.
58. Philips GB, Pinkernell BH, Jing TY. The association of hypotestosteronemia with coronary artery disease in men. *Arterioscler Thromb*. 1994;14:701–706.
59. Chou TM, Sudhir K, Hutchison SJ, et al. Testosterone induces dilation of canine coronary conductance and resistance arteries in vivo. *Circulation*. 1996;94:2614 –2619.
60. Hak AE, Wittteman JC, de Jong FH, Geerlings MI, Hofman A, Pols HA. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. *J Clin Endocrinol Metab*. 2002;87:3632–3639
61. Muller M, van den Beld AW, Bots ML, Grobbee DE, Lamberts SW, van der Schouw YT. Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. *Circulation*. 2004;109:2074–2079.
62. Taheri S, Lin L, Austin D, et al. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med*. December 2004;1(3).
63. Hursel R, Rutters F, Gonnissen HK, et al. Effects of sleep fragmentation in healthy men on energy expenditure, substrate oxidation, physical activity, and exhaustion measured over 48 h in a respiratory chamber. *Am J Clin Nutr*. 2011;94:804–808.
64. Stamatakis KA, Punjabi NM. Effects of sleep fragmentation on glucose metabolism in normal subjects. *Chest*. 2010;137:95–101.
65. Trakada G, Chrousos G, Pejovic S, et al. Sleep apnea and its association with the stress system, inflammation, insulin resistance and visceral obesity. *Sleep Med Clin*. 2007 June;2(2): 251–261. doi:10.1016/j.jsmc.2007.04.003.