A review of the evidence for alternative and complementary medical approaches in the prevention of atherosclerotic cardiovascular disease and diabetes

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The use of complementary and alternative medicine approaches has increased in the recent years. It has been utilized in both the treatment and prevention of many chronic diseases, especially in the management of hypertension, diabetes, and hyperlipidemia. Lifestyle modifications play a fundamental role in alternative and complementary medicine. Regular exercise, maintenance of optimal weight, and a healthful diet play vital roles in maintaining ideal health. Specifically, the Dietary Approaches to Stop Hypertension and Mediterranean diets have been established as having beneficial effects on blood pressure and cholesterol and even cardiovascular outcomes. Still, additional supplements including fish oil, CoQ10, and red yeast rice (among others) have shown promising beneficial effects. Unfortunately, many of the beneficial claims of natural products are not scientifically proven, lack reproducibility, and/or yield conflicting results. Until more concrete evidence can be produced, it is

important for physicians and patients alike to familiarize themselves with these natural products and increase their awareness of any potential adverse effects. *Cardiovasc Endocrinol* 6:39–43 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Cardiovascular Endocrinology 2017, 6:39–43

Keywords: alternative, cardiovascular, complementary, diabetes, natural, prevention, supplements

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Received 4 October 2016 Accepted 19 January 2017

Introduction

The use of complementary and alternative medicine approaches has increased in the recent years. Complementary medicine is used in addition to standard-of-care approaches, whereas alternative medicine is used in place of standard-of-care approaches [1]. Recent research shows a 50–80% increase in the use of complementary medicine. It has been utilized in both the treatment and the prevention of many chronic diseases [2]. Interestingly, complementary and alternative medicine accounts for ~80% of the medicine practiced in developing countries. Furthermore, of late, the use of herbal remedies has increased by an astonishing 380% [3]. This recent focus on expansion beyond the limits of traditional allopathic medicine has spawned a new field: integrative medicine. Integrative medicine focuses on natural and less invasive options for the treatment of chronic diseases. As pharmaceutical companies look for innovative ways to treat diseases, natural products are also receiving increasing attention. Unfortunately, many of the beneficial claims of natural products are not scientifically proven, lack reproducibility, and/or yield conflicting results [4].

Background

Therapeutic lifestyle modifications are the foundation of complementary and alternative medicine. Regular

exercise, maintenance of optimal weight, and a healthful diet play vital roles in maintaining ideal health. Some diets have been proven to not only assist with weight loss but also have beneficial effects for coronary artery disease (CAD), diabetes, and hypertension (HTN). The Mediterranean diet, for example, has an inverse relationship with CAD [5]. Such advantages are believed to be related to moderate alcohol consumption, low meat consumption, and high consumption of fruits, nuts, fish, and olive oil. A single dietary change has not been identified as the sole source of the benefits; rather, it appears that there is a synergistic effect among many dietary elements [6]. The PREDIMED Trial supports the Mediterranean diet as an appropriate choice for cardiovascular disease (CVD) prevention. This diet emphasizes extremely high daily intakes of nuts and olive oil [1]. Dietary Approaches to Stop Hypertension Diet focuses on fruits and vegetables, but also adds high fiber and low-fat dairy. As the name implies, it significantly lowers blood pressure in those with stage 1 HTN and high normal blood pressure [6].

Although unmeasurable, stress is postulated to play a major role in CVD risk. As such, research on techniques to reduce or eliminate stress has increased over the years. Transcendental meditation (TM) is a form of meditation that appears to have the most convincing evidence in the

reduction of CVD risk. TM has been shown to decrease catecholamine release, resulting in decreased blood pressure, oxygen consumption, and anxiety/stress. This is accomplished by having the individual, or patient, being given a mantra (consisting of a word or sound) that is repeated as he/she sits quietly for 20 min. Eventually, the individual/patient reaches a state of 'restful alertness,' resulting in the effects stated above. Many instructors encourage the use of TM twice a day before a meal. TM's ability to reduced blood pressure was recognized by the American Heart Association (AHA) and resulted in class IIb level of evidence B recommendations [7].

Metabolic syndrome is a chronic inflammatory state often related to poor dietary and exercise habits. It is associated with an increased production of proinflammatory factors that contribute toward many of the disease's manifestations. Metabolic syndrome is associated with several risk factors including, but not limited to, high blood pressure, abdominal obesity, and insulin resistance. For example, obesity exposes patients to oxidative stress, which further contributes toward macrophage infiltration into adipose tissue, thereby producing reactive oxygen species. Metabolic syndrome further alters individuals' fatty acid profiles and increases their risk for type 2 diabetes mellitus and atherosclerotic cardiovascular disease (ASCVD).

Diabetes is the most common chronic metabolic disease in nearly all countries. It currently affects more than 285 million individuals worldwide. By 2030, it is projected to impact over 430 million individuals, ~7.7% of the world's population. In the USA alone, currently between two and four million diabetic patients rely on alternative medicine to control their glucose and insulin levels [2]. Type 2 diabetes mellitus is a perfect realm for an alternative approach as it can be exceptionally responsive to lifestyle changes including diet and exercise. Supplemental alternative medicines are also increasingly being used to help control elevated glucose and insulin levels. Two frequently utilized natural supplements are cinnamon and bitter melon [8–10].

HTN is estimated to impact one in three adults. Unfortunately, only 35% of these patients eventually reach appropriate blood pressure goals. HTN is associated with increased morbidity and mortality from CVD and end-stage renal disease, and it is the most common risk factor for CAD [6]. Thus, controlling blood pressure is of the utmost importance. Some supplements that might aid in improving atherosclerotic-related diseases include magnesium (for HTN), red yeast rice (RYR) (for high cholesterol), and coenzyme Q10 [for congestive heart failure (CHF)] [6,11–22]. Alcohol and chocolate are additional – and highly favored – supplements known to have an inverse relationship with the above-mentioned diseases [23–29].

Supplements

Magnesium is a mineral nutritional supplement that has been found to have beneficial effects on blood pressure. Generally, the population in the USA is known to consume excess sodium and inadequate amounts of magnesium and potassium. As many physicians and patients alike know, a high-sodium diet increases blood pressure [6]. However, studies have shown an inverse relationship between dietary magnesium consumption and blood pressure [11]. The beneficial effects of magnesium are further amplified when combined with a high-potassium and low-sodium diet. Furthermore, studies have shown these dietary changes to be as effective as a single anti-HTN medication and that they can even potentiate an anti-HTN medication's effect if the patient is already taking one. These blood pressure-reducing effects are most notable in patients with stage 1 HTN and diabetes mellitus, and in pregnancy [12].

The dose at which magnesium becomes effective and beneficial for blood pressure has yet to be determined. However, many studies have utilized ranges between 500 and 2000 mg daily [6]. At these intakes, magnesium is believed to exert 'calcium channel blocker-like' effects. It does so by competing with sodium for binding sites on vascular smooth muscle cells, resulting in increased production of the vasodilatory substances, prostacyclin and nitric oxide [13]. In addition, magnesium suppresses Na/K/ATPase, resulting in decreased vascular tone, and therefore blood pressure [14]. It is important to recognize and even emphasize that most Americans fail to consume the bare minimum recommended daily value for magnesium: 400 mg [30].

Fish has been popularized by its omega-3 fatty acids, primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Consequently, EPA and DHA are the active ingredients in fish oil pills. Humans cannot produce adequate concentrations of EPA or DHA intrinsically, but rather require fatty fish consumption or fish oil supplements to acquire the adequate amounts [31]. Fish and fish oil supplements are recommended by the AHA as part of a healthful diet, particularly to reduce morbidity and mortality in those with CVD [32]. In 2002, the AHA recommended at least two servings of fish per week for individuals at risk of CAD. Those with established CAD were advised to consume 1 g of the omega-3 fatty acids EPA and DHA daily [33]. These recommendations stem from the results of many trials such as the DART study, which showed a 29% all-cause mortality reduction in those taking fish products after a myocardial infarction [34].

The benefits attributable to EPA and DHA are numerous. They are known to have antithrombotic effects and anti-inflammatory effects. These effects were evident in the OMEGA-PCI study, which concluded that the addition of omega-3 to aspirin and clopidogrel after

percutaneous coronary intervention resulted in potentiation of their antithrombotic effects [35]. There is additional evidence that fish oil, especially when used in conjunction with statins or fibrates, helps to further lower triglyceride levels [36]. The most common side effects of fish oil supplementation are mainly related to gastrointestinal discomfort. These side effects include burping, dyspepsia, and loose stools. However, enteric-coating fish oil pills can mitigate these side effects [32].

Coenzyme Q10, or CoQ10, exists in two forms: ubiquinol and ubiquinone. CoQ10 is found in all cells within our mitochondria, but has the highest concentration in the heart, liver, and kidneys [15]. Our bodies are typically able to maintain adequate levels naturally; nevertheless, these levels decrease with age. Some conditions, in particular, CHF, are known to decrease CoQ10 stores. Levels are also lowered by statins and β -blockers, which are often standard of care for patients with CHF [15]. This issue led to several studies evaluating the potential positive effects of repleting CoQ10. A randomized-controlled study found that patients taking CoQ10 with a New York Heart Association class III–IV achieved a 50% reduction in hospitalizations. Furthermore, supplementation resulted in improved hemodynamic parameters including ejection fraction, stroke volume, cardiac index, and cardiac output. Despite this, the study could not show a significant improvement in mortality [15].

The beneficial effects of CoQ10 are most notable at higher doses. Unfortunately, CoQ10 is fat soluble and requires intestinal absorption. This can be particularly problematic for those with advanced CHF because of intestinal edema. As a result, as much as 50% of consumed CoQ10 is excreted and lost [17]. The side effects of CoQ10 supplementation are few, with the most common one being gastrointestinal discomfort [18].

L-carnitine has been studied mostly in the context of peripheral arterial disease and intermittent claudication. L-carnitine exerts its beneficial effects by reducing lactate production and increasing the total carnitine content in muscles [37]. In a study comparing walking distance in patients with intermittent claudication from peripheral arterial disease taking L-carnitine and those taking placebo, nearly two-thirds of the patients in the L-carnitine arm experienced improved walking distance and experienced no reported adverse events [37]. It should be noted, however, that the placebo group showed a marked improvement in walking distance as well. They noted as much as a 50% increase in walking distance compared with the baseline [37]. Another study found not only increased walking distance but also an overall improved quality of life. However, this study found that the benefits were only apparent in those who were only able to walk less than 250 m at baseline. Those who were able to walk more than 250 m at baseline did not experience any

significant improvement [38]. Doses between 1 and 2 g twice daily were used in these studies.

Chocolate, for obvious reasons, is likely the most favored nutritional supplement for ASCVD prevention. Fortunately, for chocolate lovers, studies have shown an inverse relationship between chocolate consumption and CVD. The presumed mechanism of action is a decrease in both blood pressure and insulin resistance [39]. Chocolate has been shown to improve endothelial function, reduce systolic blood pressure, and reduce inflammation [40]. One study found that those with previous myocardial infarctions who consumed chocolate twice weekly showed as much as a 66% reduction in 8-year cardiac mortality compared with those who did not eat chocolate at all [23]. Flavanol is the active ingredient likely responsible for these beneficial effects. Flavanol is found at a higher concentration in dark as opposed to milk chocolate. Approximately 6 g of daily chocolate consumption has been associated with a 39% decrease in both myocardial infarction and stroke. However, those who consume this much chocolate are also reported to consume less of some other healthful dietary products, such as fruits, vegetables, and dairy [23].

Alcohol consumption has been studied extensively for its presumed benefits in decreasing CVD and mortality through the suppression of atherosclerosis. There is no particular form of alcohol that has been noted to be more beneficial than others. However, some still hypothesize that benefits are derived less from the alcohol itself, and more from resveratrol, an active ingredient found in red wine [24]. Resveratrol has two forms: *cis* and *trans*. *Trans*-resveratrol has been studied most extensively and is prevalent in red wine. This is because resveratrol is found in the skin of grapes, which is intact in red wine and removed before fermentation in white wine [25]. Resveratrol is a natural antifungal substance that protects the skins of grapes, particularly in cool, damp climates. For this reason, resveratrol is found in the highest amounts in Pinot Noirs, grapes grown in such climates [41].

It is important to keep in mind that the benefits of ASCVD are observed only with mild to moderate alcohol consumption. In one study, moderate consumption was defined as one to six alcoholic beverages per week. This amount was associated with an inverse relationship with carotid artery atherosclerosis as opposed to more than 14 drinks per week, which had a direct correlation [26]. Beyond containing resveratrol, alcohol exerts its benefits through several other putative mechanisms. It has antioxidant activity, thereby reducing reactive oxygen species. This contributes toward the reduction of hydrogen peroxidase production by oxidized low-density lipoprotein (LDL) [27]. Alcohol inhibits maturation of monocytes to macrophages, resulting in decreased foam cell formation [28]. It inhibits the activity of inflammatory enzymes, which in turn decreases the expression of CRP.

CRP levels might predict in-hospital and short-term CAD events [24]. Finally, alcohol decreases cell adhesion by suppressing the expression of E-selectin, ICAM-1, and VCAM-1 on endothelial cells [29].

Lipid-lowering agents

RYR, also known as *Monascus purpureus*, is fermented red yeast grown on rice. RYR has been used as a natural remedy to reduce lipids. Its beneficial effects are attributed to monacolin K, which is structurally identical to lovastatin [19]. In addition to the lipid-lowering effects of monacolin K, RYR has additional substances not found in statins. Some of these substances include sterols, isoflavones, and a variety of fatty acids. These substances are purported to exert beneficial effects on other chronic diseases such as diabetes and osteoporosis [20]. In addition to having these benefits, RYR has fewer side effects compared with statins. This attribute has resulted in improved patient willingness to not only try the supplement but also adhere to it. Unfortunately, commercially available RYR is not standardized [21]. This lack of 'oversight' renders RYR difficult to utilize clinically and even potentially harmful.

Xuezhi kang (XZK) is a purified form of RYR that additionally contains plant sterols and isoflavones. In a Chinese multicenter prospective double-blinded study, XZK was compared with placebo in terms of its beneficial effects on LDL and cardiovascular end points in those with previous myocardial infarction. The study concluded that XZK significantly decreased both coronary events and LDL levels compared with placebo. Furthermore, the study found the benefits of XZK to exceed those reported for statins [42].

Several studies have been carried out comparing RYR with statin therapy, all of which have yielded similar results. When comparing RYR with pravastatin, there is no difference in the amount of LDL reduction [22]. Another study compared RYR with fish oil and simvastatin. Again, there was no significant difference in the amount of lowered LDL [19]. On the basis of the results of these and many other small studies, it has been implied that RYR can be used as a substitute for statin therapy in patients who wish to avoid high costs, doctor visits, and potential side effects. However, at this time, RYR should only be considered in those who are intolerant to statin therapy.

In a manner similar to RYR, pomegranate has been used for many years for its positive impact on triglycerides and LDL. It also exerts favorable effects on lipid peroxidation and inflammation [43]. These benefits have been attributed to the phenolic compounds found in pomegranate, especially the flavonoids. One study was able to document long-term effects after 12 months of pomegranate consumption. It showed a significant decrease in the production of lipid peroxides. However, contrary to

popular belief, there have been no documented effects of pomegranate on BMI or waist circumference [44]. Pomegranate has also been known to be a potential mediator of inflammation, vasoconstriction, and platelet aggregation [45].

Hypoglycemic agents

A limited number of supplements have been shown to exert beneficial effects on glucose and insulin levels. Two widely studied supplements with hypoglycemic effects include bitter melon and cinnamon. It is hypothesized that charatin, vicine, and polypeptide p are all active ingredients in bitter melon. They have structures similar to that of insulin, and exert their purported hypoglycemic effects through an insulin-like mechanism. Unlike cinnamon, the evidence for the benefit of bitter melon on serum glucose is more limited and at this time inconclusive [8]. Cinnamon, however, has been recognized for its medicinal use for centuries. Its primary uses have been for diabetes, hyperlipidemia, and arthritis. In one study, compared with standard therapy, cinnamon was noted to produce an additional 0.83% decrease in glycated hemoglobin [9].

Doses in cinnamon studies have varied between 0.5 and 6 g/day. However, it should be noted that its effects do not appear to be dose dependent [4]. Although the mechanism by which cinnamon affects glucose levels is not clearly understood, several areas of the insulin-signaling pathways are believed to be affected. Cinnamon produces effects similar to those of many pharmaceutical agents available today. For instance, cinnamon increases PPAR- γ , GLUT-1, and GLUT-4 expression. These effects result in increased insulin sensitivity and glucose uptake by skeletal and adipose tissue [10].

Conclusion

Lifestyle modifications (diet, optimal weight maintenance, and exercise) play a fundamental role in alternative and complementary medicine. Specifically, the Dietary Approaches to Stop Hypertension and Mediterranean diets have been established as having beneficial effects on blood pressure and cholesterol and even cardiovascular outcomes. However, the favorable effects of supplements utilized as part of nonallopathic forms of medicine are still under considerable scrutiny, and their use has yet to be firmly established. Future research will hopefully bring clarity to many of the questions and concerns physicians have. However, better data are required. In particular, larger sample sizes and reproducibility of many of the studies are needed. Until then, it is important for physicians and patients alike to familiarize themselves with these natural products and increase their awareness of any potential adverse effects.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

- Wong ND, Amsterdam EA, Blumenthal RS. Physical activity. In: Ahmed HM, Ndumele CE, editors. *ASPC manual of preventive cardiology*. New York, NY: Demos Medical Publishing LLC; 2015. pp. 142–155.
- Ranasinghe P, Jayawardena R, Galappathy P, Constantine GR, de Vas gunawardena N, Katulanda P. Efficacy and safety of 'true' cinnamon (*Cinnamomum zeylanicum*) as a pharmaceutical agent in diabetes: a systematic review and meta-analysis. *Diabet Med* 2012; **29**:1480–1492.
- Medagama AB, Bandara R. The use of complementary and alternative medicines (CAMs) in the treatment of diabetes mellitus: is continued use safe and effective? *Nutr J* 2014; **13**:102.
- Medagama AB. The glycaemic outcomes of cinnamon, a review of the experimental evidence and clinical trials. *Nutr J* 2015; **14**:1.
- Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med* 2009; **169**:659–669.
- Houston M. The role of magnesium in hypertension and cardiovascular disease. *J Clin Hypertens* 2011; **13**:843–847.
- Brook RD, Appel LJ, Rubenfire M, Ogedegbe G, Bisognano JD, Elliott WJ, et al. Beyond medications and diet: alternative approaches to lowering blood pressure. A scientific statement from the American Heart Association. *Hypertension* 2013; **61**:1360–1383.
- Yin RV, Lee NC, Hirpara H, Phung OJ. The effect of bitter melon (*Mormodica charantia*) in patients with diabetes mellitus: a systematic review and meta-analysis. *Nutr Diabetes* 2014; **4**:e145.
- Crawford P. Effectiveness of cinnamon for lowering hemoglobin A1C in patients with type 2 diabetes: a randomized, controlled trial. *J Am Board Fam Med* 2009; **22**:507–512.
- Liong E, Kong SK, Au KK, Li JY, Xu GY, Lee YL, et al. Inhibition of glucose uptake and suppression of glucose transporter 1 mRNA expression in L929 cells by tumor necrosis factor- α . *Life Sci* 1999; **65**:PL215–PL220.
- Jee SH, Miller ER, Guallar E. The effect of magnesium supplementation on blood pressure: a meta-analysis of randomized clinical trials. *Am J Hypertens* 2002; **15**:691–696.
- Resnick LM. Magnesium in the pathophysiology and treatment of hypertension and diabetes mellitus. Where are we in 1997? *Am J Hypertens* 1997; **10**:368–370.
- McCarty MF. Complementary vascular-protective actions of magnesium and taurine: a rationale for magnesium taurate. *Med Hypotheses* 1996; **46**:89–100.
- Das UN. Essential fatty acids: biochemistry, physiology and pathology. *Biotechnol J* 2006; **1**:420–439.
- Oleck S, Ventura HO. Coenzyme Q10 and utility in heart failure: just another supplement? *Curr Heart Fail Rep* 2016; **13**:190–195.
- Morisco C, Trimarco B, Condorelli M. Effect of coenzyme Q10 therapy in patients with congestive heart failure: a long-term multi-center randomized study. *Clin Invest* 1993; **71**:S134–S136.
- Langsjoen PH, Langsjoen AM. Supplemental ubiquinol in patients with advanced congestive heart failure. *Biofactors* 2008; **32**:119–128.
- Mortensen SA. Coenzyme Q10: will this natural substance become a guideline-directed adjunctive therapy in heart failure? *JACC Heart Fail* 2015; **3**:270–271.
- Yang CW, Mousa SA. The effect of red yeast rice (*Monascus purpureus*) in dyslipidemia and other disorders. *Complement Ther Med* 2012; **20**:466–474.
- Erdogru O, Azirak S. A review on the red yeast rice (*Monascus purpureus*). *KSU J Sci Eng* 2005; **8**:10–15.
- Hansen KE, Hildebrand JP, Ferguson EE, Stein JH. Outcomes in 45 patients with statin-associated myopathy. *Arch Intern Med* 2005; **165**:2671–2676.
- Halbert SC, French B, Gordon RY, Farrar JT, Schmitz K, Morris PB, et al. Tolerability of red yeast rice (2400 mg twice daily) versus pravastatin (20 mg twice daily) in patients with previous statin intolerance. *Am J Cardiol* 2010; **105**:198–204.
- Janszky I, Mukamal KJ, Ljung R, Ahnve S, Ahlborn A, Hallqvist J. Chocolate consumption and mortality following a first acute myocardial infarction: the Stockholm Heart Epidemiology Program. *J Intern Med* 2009; **266**:248–257.
- Prasad K. Resveratrol, wine, and atherosclerosis. *Int J Angiol* 2012; **21**:007–018.
- Orallo F, Álvarez E, Camiña M, Leiro JM, Gómez E, Fernández P. The possible implication of *trans*-Resveratrol in the cardioprotective effects of long-term moderate wine consumption. *Mol Pharmacol* 2002; **61**:294–302.
- Mukamal KJ, Kronmal RA, Mittleman MA, O'Leary DH, Polak JF, Cushman M, Siscovick DS. Alcohol consumption and carotid atherosclerosis in older adults: the Cardiovascular Health Study. *Arterioscler Thromb Vasc Biol* 2003; **23**:2252–2259.
- Vivancos M, Moreno JJ. Effect of resveratrol, tyrosol and β -sitosterol on oxidized low-density lipoprotein-stimulated oxidative stress, arachidonic acid release and prostaglandin E2 synthesis by RAW 264.7 macrophages. *Br J Nutr* 2008; **99**:1199–1207.
- Leiro J, Arranz JA, Fraiz N, Sanmartín ML, Quezada E, Orallo F. Effect of *cis*-resveratrol on genes involved in nuclear factor kappa B signaling. *Int Immunopharmacol* 2005; **5**:393–406.
- Ferrero ME, Bertelli AE, Fulgenzi A, Pellegatta F, Corsi MM, Bonfrate M, et al. Activity in vitro of resveratrol on granulocyte and monocyte adhesion to endothelium. *Am J Clin Nutr* 1998; **68**:1208–1214.
- Morgan KJ, Stampely GL, Zabik ME, Fischer DR. Magnesium and calcium dietary intakes of the US population. *J Am Coll Nutr* 1985; **4**:195–206.
- Barringer TA, Harris W. Omega-3 fatty acid deficiency and cardiovascular disease. In: McNamara RK, editor. *The omega-3 fatty acid deficiency syndrome: opportunities for disease prevention*. New York, NY: InNova Science Publishers Inc.; 2013. pp. 213–232.
- Brinson BE, Miller S. Fish oil what is the role in cardiovascular health? *J Pharm Pract* 2012; **25**:69–74.
- Burr ML, Fehily AM, Gilbert JF. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989; **2**:757–761.
- Gajos G, Rostoff P, Undas A, Piwowarska W. Effects of polyunsaturated omega-3 fatty acids on responsiveness to dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: the OMEGA-PCI (OMEGA-3 fatty acids after PCI to modify responsiveness to dual antiplatelet therapy) study. *J Am Coll Cardiol* 2010; **55**:1671–1678.
- Roth EM, Bays HE, Forker AD, Maki KC, Carter R, Doyle RT, Stein EA. Prescription omega-3 fatty acid as an adjunct to fenofibrate therapy in hypertriglyceridemic subjects. *J Cardiovasc Pharmacol* 2009; **54**:196–203.
- Bays HE, Maki KC, McKenney J, Snipes R, Meadowcroft A, Schroyer R, et al. Long term up to 24 month efficacy and safety of concomitant prescription omega-3 acid ethyl esters and simvastatin in hypertriglyceridemic patients. *Curr Med Res Opin* 2010; **26**:907–915.
- Brevetti G, Perna S, Sabbà C, Martone VD, Condorelli M. Propionyl-L-carnitine in intermittent claudication: double-blind, placebo-controlled, dose titration, multicenter study. *J Am Coll Cardiol* 1995; **26**:1411–1416.
- Brevetti G, Diehm C, Lambert D. European multicenter study on propionyl-L-carnitine in intermittent claudication. *J Am Coll Cardiol* 1999; **34**:1618–1624.
- Buijsse B, Weikert C, Drogan D, Bergmann M, Boeing H. Chocolate consumption in relation to blood pressure and risk of cardiovascular disease in German adults. *Eur Heart J* 2010; **31**:1616–1623.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in metaanalysis detected by a simple, graphical test. *BMJ* 1997; **315**:629–634.
- Jeandet P, Bessis R, Gautheron B. The production of resveratrol (3, 5, 4'-trihydroxystilbene) by grape berries in different developmental stages. *Am J Enol Vitic* 1991; **42**:41–46.
- Lu Z, Kou W, Du B, Wu Y, Zhao S, Brusco OA, et al. Chinese Coronary Secondary Prevention Study Group. Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. *Am J Cardiol* 2008; **101**:1689–1693.
- Berkemeyer S. The straight line hypothesis elaborated: case reference obesity, an argument for acidosis, oxidative stress, and disease conglomeration? *Med Hypotheses* 2010; **75**:59–64.
- Kojadinovic MI, Arsic AC, Debeljak-Martacic JD, Konic-Ristic AI, Kardum ND, Popovic TB, Glibetic MD. Consumption of pomegranate juice decreases blood lipid peroxidation and levels of arachidonic acid in women with metabolic syndrome. *J Sci Food Agric* 2016; doi:10.1002/jsfa.7977.
- Kawakami Y, Murakami Y, Kawakami T, Muroyama N, Takiue T, Moritani Y, et al. Abnormal fatty acid profile of blood cell phospholipids and dietary fatty acid intake in patients with ulcerative colitis. *J Clin Biochem Nutr* 2005; **37**:95–102.