REVIEW

Obesity and cardiovascular dysfunction: A role for resveratrol?

Ebrahim K. Naderali*

Obesity Biology Unit, School of Clinical Science, University of Liverpool, Daulby Street, Liverpool L69 3GA, UK

Summary   Obesity, characterized by excess adipose tissue is now becoming a worldwide epidemic. Various studies have suggested that obesity *per se* is an independent cardiovascular risk factor, as well as predisposing to type 2 diabetes, hypertension and dyslipidaemia. Furthermore, obesity induces insulin resistance, which is associated with development of cardiovascular diseases that include hypertension, and reduced endothelial function.

A variety of pharmacological and physiological as well as surgical interventions have been used to counteract deleterious effects of obesity with some degree of success. A number of new medicinal agents are being considered as a candidate for managing obesity and its associated cardiovascular abnormalities. Resveratrol, a naturally occurring phenolic trihydroxystilbene substance, which is present in a variety of plants have been shown to reverse detrimental effects of diet-induced obesity. This review examines role of resveratrol as a future anti-obesity agent.
© 2008 Asian Oceanian Association for the Study of Obesity. Published by Elsevier Ltd. All rights reserved.

Contents

* Tel.: +44 151 7064108; fax: +44 151 7066579.
  E-mail address: naderali@liv.ac.uk.

Obesity: a cardiovascular hazard factor

Obesity is a major risk factor for important illnesses including hypertension, diabetes, degenerative arthritis and myocardial infarction as well as psychological factors that include anger, anxiety, and depression [1,2]. It is a cause of significant morbidity and mortality and generates great social and financial costs. In fact obesity is now being considered as a worldwide health problem such that in 1997 the World Health Organization (WHO) stated that ''*obesity should now be regarded as one of the greatest neglected public health problems of our time*....'' This public health problem does not recognize race, sex or age boundaries, affecting virtually anyone in any walks of life. A study of the effects of obesity on echocardiograph parameters has identified obesity-induced changes in cardiac parameters in children as young as 6 years of age [3—5]. A 22-year longitudinal study in 346 British men and women suggested that children who have higher body mass index (BMI) are more likely to become obese as adults [6]. The same study reported that men and women who gained the most weight during early childhood had highest blood pressure.

Numerous elements have been shown to be associated with developing the risk of obesity, with age and male sex being the most important factors [7,8]. Many obese patients accomplish weight loss with diet, exercise and lifestyle modification, achieving substantial reductions in central obesity and associated disturbances corresponding to a significant decrease in cardiac events and mortality [9—11]. However, long-term results of weight loss programs are disappointing with people often regaining most of the weight initially lost. To date, a number of anti-obesity drugs have been developed by major pharmaceutical industries with a degree of success in number of patients. Other extreme measures used in accelerating weight loss have proven to be of major benefit to severely obese patients. For example, weight reduction induced by gastric operation in severely obese patients is associated with attenuation of obesity-induced cardiac hypertrophy and cardiac malfunction [12]. Therefore, the search for alternative approaches in tackling obesity-induced cardiovascular disorders becomes more important.

Clinical manifestations of obesity-induced cardiovascular disorders

Although certain proportions of cardiovascular disorders are attributed to the secondary complications of obesity (hypertension, atherosclerosis, type 2 diabetes and aging), a direct deleterious effect of obesity on the cardiovascular system is becoming more and more evident. Patients with morbid obesity have higher rates of sudden unexpected cardiac-related death [13]. The exact mechanism(s) of death in these patients is not yet fully understood. Nevertheless, the importance of obesity as an independent factor for cardiovascular dysfunction, both at arterial and cardiac myocyte levels is becoming more apparent.

Both obesity and abdominal fat distribution are closely related to coronary heart disease. Weight variability, even a moderate weight gain from age 20, is strongly associated with an increased risk of coronary death and non-fatal myocardial infarction [14,15]. The risk of coronary heart disease is high in those with central fat distribution and even higher in those with an android pattern [16,17] with abdominal obesity being as an independent risk factor for acute coronary events [18]. Epidemiological studies have shown a significant variation of lean/obese ratio in populations of normotensive and hypertensive subjects with a strong association between obesity and hypertension (Fig. 1) [19,20].
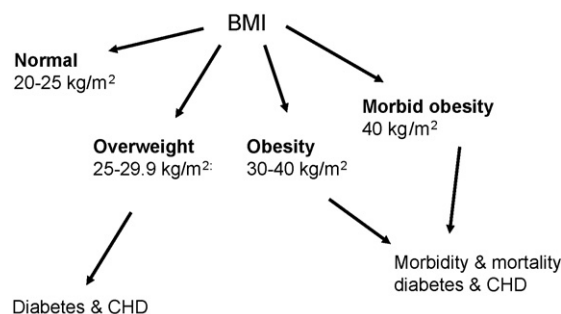

Figure 1 Characterization of obesity and health problems associated with it according to body mass index (BMI). Even a small rise in BMI, increases the chances of diabetes, coronary hear disease (CHD) which ultimately leads to severe morbidity and mortality.
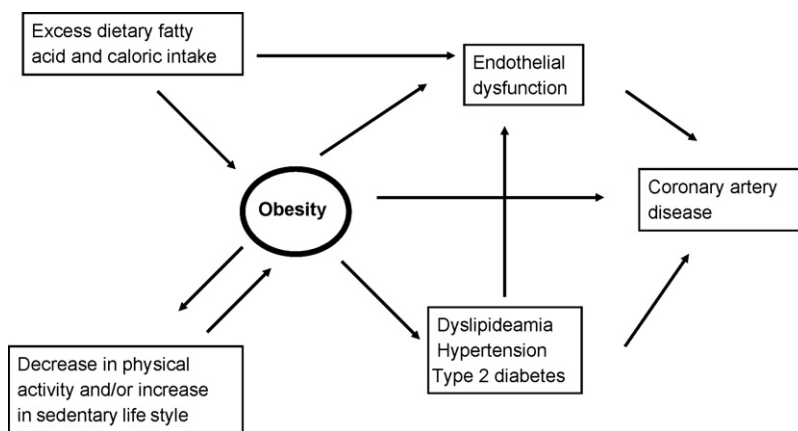
Figure 2 Schematic diagram of factors associated with the development of obesity and secondary disorders associated with obesity.

Effects of obesity on vasculature

There is no comprehensive information on the role of obesity on vascular morphology and function. The vast majority of studies on the effects of obesity on vascular function have been carried out on either animal models which are genetically prone to obesity or subjects which present with secondary complications such as type 2 diabetes, dyslipidaemia and hypertension. Nonetheless, they all have shown a degree of vascular abnormalities that occur at both endothelial and smooth muscle levels.

Obesity induces specific abnormalities of endothelial function (Fig. 2). The endothelium is crucial to key arterial functions, including the regulation of vascular tone. Endothelial cells produce various vasoactive mediators, notably

the vasodilator nitric oxide (NO) which acts on the underlying vascular smooth muscle [21]. NO reduces vessel tone, interferes with myocyte and leukocyte adhesion to vascular endothelium, decreases platelet aggregation and adhesion and inhibits smooth muscle proliferation and migration. NO production is regulated by the endothelial form of NO synthase (eNOS), which is stimulated by mediators and hormones that include acetylcholine (ACh), bradykinin and insulin [21—23] (Fig. 3). The integrity of the NO axis can be tested by measuring arterial relaxation in response to stimuli such as acetylcholine (ACh), which acts *via* endothelial muscarinic receptors to induce NO generation [21—23]. An impaired NO-mediated vasorelaxation has been demonstrated in obese and subjects with abnormal lipid profiles [24,25] with the most striking abnormality being a blunted vasodilatation
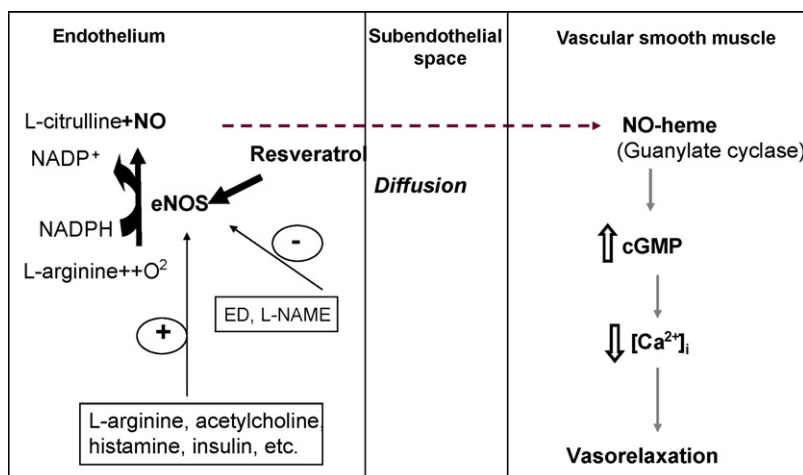

Figure 3 Schematic representation of the role of intact endothelium in the synthesis and release of nitric oxide (NO). NO production can be augmented by agonists and NO precursor while endothelial denudation (ED) and inhibitors of NOS activity would severely attenuate NO synthesis.

in response to cholinergic receptor stimulation. In human, body fat >28% represents approximately 50% reduction in endothelium-dependent vasodilatation [25,20]. This impaired endothelium-mediated vasorelaxation could contribute to hypertension [23] and its presence in subjects at high risk of atherogenesis suggests that it may predict atheroma formation and ultimately coronary and peripheral arterial disease [23,26]. In fact, endothelial vasomotor dysfunction (e.g. impaired ACh-induced relaxation) has been demonstrated in several conditions of increased cardiovascular risk, including hypertension, type 2 diabetes, hypercholesterolaemia, hypertriglyceridaemia and obesity [25,27−31].

The endothelial dysfunction is now considered as a robust predictor of coronary atheroma and myocardial infarction. In human, severe endothelial dysfunction increases cardiac events that include myocardial infarction, percutaneous or surgical coronary revascularization, and/or cardiac death [32,33]. These observations strongly point to the notion of association between increased cardiac events and severe endothelial dysfunction highlighting the concept of the importance of coronary endothelial dysfunction in the progression of coronary atherosclerosis. Moreover, obesity increases endothelium-dependent vasoconstriction in the absence of endothelial NO [25,31,32,33], while pharmacological interventions to increase NO leads to beneficial outcomes in patients with heart disease [34], hypercholesterolaemia [35], hypertension [36], and peripheral arterial occlusive disease [37,38].

Resveratrol

Resveratrol a naturally occurring phenolic trihydroxystilbene substance, present in variety of plants. A wide range of beneficial effects has been attributed to resveratrol which includes anti-inflammatory, anti-cancer, anti-lipid, anti-aging and vasoprotective effects [39−41]. The vasorelaxant property of resveratrol has attracted a considerable interest amongst numerous research groups with a number of studies reporting direct and indirect vasorelaxant effects for resveratrol.

Tissue distribution and excretion of resveratrol

In rats, following a single oral administration, resveratrol was found mainly to be distributed in stomach, duodenum, liver and kidney with detectable metabolites, resveratrol monoglucuronide and resveratrol monosulfate in plasma. The majority of the resveratrol was excreted as metabolites only 0.59% and 0.027% of the dosage were excreted in urine and bile, respectively as unchanged drug within 24 h [42]. In vitro studies of the hepatic metabolism and transport system for resveratrol in Wistar and Mrp2-deficient TR(−) rats showed extensive dose-dependent metabolism of resveratrol to six glucuronides and sulfates (M1−M6), with a high-hepatic extraction ratio and clearance whereby the canalicular transporter Mrp2 selectively mediated the biliary excretion of glucuronides [43]. A small-scale phase I study of oral resveratrol (single doses of 0.5, 1, 2.5, or 5 g) on healthy volunteers reported recovery of resveratrol and six metabolites from plasma and urine samples. Peak plasma levels of resveratrol at the highest dose (5 g) occurred at 1.5 h post-dose. Peak levels of two monoglucuronides and resveratrol-3-sulfate were three- to eightfold higher than resveratrol itself indicating extensive metabolism of resveratrol. Urinary excretion of resveratrol and its metabolites was rapid, with 77% of all urinary agent-derived species excreted within 4 h after the lowest dose [44]. These data indicate a rapid absorption, distribution and metabolism and excretion of resveratrol.

Effects of resveratrol on obesity

Animal studies have reported caloric restriction mimetic effects for resveratrol resulting in weight reduction and improvement of life span of animals fed with high-caloric diet [45,46]. The weight reducing effects of resveratrol may, at least in part, be due to its effects on adipocytes. Resveratrol therapy decreases cell viability of maturing pre-adipocytes and mature adipocytes by increasing apoptosis in vitro, probably by down-regulating expression of PPARgamma, C/EBPalpha, SREBP-1c, FAS, HSL, LPL and up-regulating expression of genes regulating mitochondrial activity (SIRT3, UCP1 and Mfn2) [45−48]. Diminished mitochondrial oxidative phosphorylation and aerobic capacity are associated with reduced longevity. Animal studies have shown that resveratrol treatment increases aerobic capacity. This phenomenon was associated with an induction of genes for oxidative phosphorylation and mitochondrial biogenesis [49,50], thereby improving animal survival time. Hence, it is plausible that a similar mechanism may help to improve survival time and reduce effects of aging in human subjects.

In high-fat diet fed rats, resveratrol prevents abdominal obesity and triglyceride accumulation in hepatic cells (HepG2 cells) [51,52]. Moreover, both *in vivo* and *in vitro* studies have shown that resveratrol promotes the phosphorylation of AMPK [45—49]. The AMP-activated kinase (AMPK) is a sensor of cellular energy levels. It is activated by increases in the cellular AMP:ATP ratio and acts as a barometer for preserving cellular energy levels. Activation of AMPK by resveratrol, may act to regulate intracellular energy levels and ultimately control intracellular metabolism ultimately regulating body weight. More recent studies have also suggested inhibition of TNF-α production and suppression of two lipogenesis gene expressions as alternative mechanisms by which resveratrol inhibits lipid accumulation [51,52], thereby protecting against diet-induced obesity and insulin resistance [45—51].

Resveratrol and anti-inflammatory effects

In adipose tissue, resveratrol inhibits TNF-α-induced monocyte chemo-attractant protein (MCP-1) secretion and gene transcription, promoter activity, *via* down-regulation of TNF-α-induced MCP-1 transcription [53]. Moreover, resveratrol reverses the secretion and mRNA expression of the atherogenic adipokines, PAI-1 and IL-6, induced by TNF-α [54]. Resveratrol ameliorates glycerol-induced renal injury by suppressing the inflammatory process and by inhibiting lipid peroxidation [55]. Similarly, treatment with resveratrol significantly attenuated renal dysfunction and oxidative stress in diabetic rats [56] and increased GFR and renal blood flow in gentamicin-induced nephrotoxic rats [57] probably due to its effect on renal lipid peroxidation. Therefore, it is plausible to assume a significant anti-inflammatory role for resveratrol.

Effects of resveratrol on vasculature

High-fat diet and refined carbohydrate diet induces endothelial dysfunction by altering oxidant/antioxidant imbalance and depressing NOS protein expression [58] and enhancing ROS-mediated inactivation and sequestration of NO leading to development of hypertension [59]. Resveratrol therapy prevents diet-induced rise in blood pressure together with improvement on acetylcholine-dependent vasorelaxation of the aorta [20], uterine and mesenteric resistance arteries [60], possibly by improving endothelial function. A similar direct vasorelaxant effect of resveratrol on resistance arteries from lean and dietary-obese suggested two distinct mechanism of action namely an endothelium-dependent effect in lean animals and non-endothelium-dependent response in obese animals. The endothelium-dependent effect of resveratrol is mediated by activation of NO production while endothelium-independent effect appears to be a direct vasodilatory response [61], which may be partly due to activation of rapid oestrogen receptors [62]. Administration of streptozotocin (STZ) induces diabetes manifested as weight loss and hyperglycaemia. In arteries from STZ-induced rats, contractile responses to noradrenalin generally tend to be augmented while vasorelaxation to ACh almost always attenuated. Resveratrol treatment reverses all metabolic and contractile abnormalities associated with STZ-induced diabetes [63] through a nitric oxide pathway [64] indicating improvement of endothelial function. Similarly, histological studies have reported that resveratrol reduces the size, density, and mean area of atherosclerotic plaques, and thickness of the intima layer in atherosclerotic lesions [65] further underlining cardiovascular protective effects of resveratrol.

Resveratrol effects on heart

Numerous reports suggest a remarkable role of resveratrol as a pharmacological agent for preconditioning the heart in a nitric oxide (NO)-dependent manner. Resveratrol has direct protective effects on the heart. It improves post-ischemic cardiac function in the presence or absence of glucose intake and reduces incidence of ventricular fibrillation and infarct size [46]. Furthermore, resveratrol increases GLUT-4 expression while reducing endothelin expression and cardiac apoptosis in ischemic-reperfused hearts in the presence or absence of glucose intake suggesting direct protective effects on the heart [46]. Hypercholestrolaemia causes down regulation of vascular endothelial growth factor and hemeoxygenase-1 and increased association of caveolin-1 eNOS, decreasing the availability of eNOS. The deleterious effects of hypercholestrolaemia in rat myocardium are reversed by resveratrol, improving neovascularization [66] of the myocardial infarcted zone leading to less ventricular remodeling [67]. Similarly, resveratrol-treatment decreases infarct size and cardiomyocyte apoptosis in STZ-induced diabetic rats following ischemic injury. The

mechanism(s) responsible for the cardioprotective effect of resveratrol in the diabetic myocardium may include up-regulation of Trx-1, NO/HO-1, and VEGF in addition to increased MnSOD activity and reduced blood glucose level [68]. In ApoE-deficient mice, resveratrol exposure is associated with increased activation of Akt/eNOS together with a restoration of nitric oxide production in human umbilical vein endothelial cells exposed to oxLDL, thereby improving ischemia-induced neo-vascularization in high-cholesterol conditions by increasing the number and the functional activities of endothelial progenitor cells and by restoring the Akt-eNOS-NO pathway [69]. Interestingly, over expression of iNOS and VEGF occur within 24 h while the inductions of KDR and eNOS take more than 3 and 5 days of post-resvertarol treatment, respectively [69] suggesting a biphasic NO production in response to resveratrol, with inducible NOS being more sensitive than constitutive NOS. Thus, resveratrol provides cardioprotection by reducing myocardial infarct size and decreasing number of apoptotic cardiomyocytes by up-regulating expression for iNOS, eNOS and VEGF and KDR from hearts at the end of reperfusion.

Summary

Obesity is now considered a major health concern in many developed and developing countries. It results in development of type II diabetes, hypertension, cardiovascular morbidity and premature mortality. Initial studies have reported a remarkable ability of resveratrol to inhibit weight gain, improve endothelial function, reduced inflammatory responses, representing a promising candidate to manage obesity and obesity-induced secondary sequels. However, further preclinical and clinical studies would be highly valuable in further evaluating beneficial effects of resveratrol as an anti-obesity agent.

References

[1] Wing RR, Mathews KA, Kuller LH, Meilahn EN, Plantinga P. Waist to hip ratio in middle-aged women. Associations with behavioral and psychological factors and with changes in cardiovascular risk factors. Arterioscler Thromb 1991;11:1250–7.

[2] Wellman NS, Friedberg B. Causes and consequences of adult obesity: health, social and economic impacts in the United States. Asia Pac J Clin Nutr 2002;11(Suppl. 8):S705–9.

[3] Ogden CL, Troiano RP, Briefel RR, Kuczmarski RJ, Flegal KM, Jhonson CL. Prevalence of overweight among school children in the United States, 1971 through 1994. Pediatrics 1997;99:E1.

[4] Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999–2000. JAMA 2002;288:1728–32.

[5] Kono Y, Yoshinaga M, Oku S, Nomura Y, Nakamura M, Aihoshi S. Effects of obesity on echocardiographic parameters in children. Int J Cardiol 1994;1:7–13.

[6] Law CM, Shiell AW, Newsome CA, Syddall HE, Shinebourne EM, Fayers PM, et al. Fetal, infant and childhood growth and adult blood pressure: a longitudinal study from birth to 22 years of age. Circulation 2002;105:1088–92.

[7] Lapeyre-Mestre M, Sulem P, Chastan E, Niezborala M, Briant D, Jansou P, et al. Consumption of antihypertenstive agents in obese patients: a cross-sectional study in a sample of 3291 wage-earners in Toulous region. Arch Mal Coeur Vaiss 2000;93:925–9.

[8] Kuch B, Muscholl M, Luchner A, Döring A, Riegger GA, Schunkert H, et al. Gender specific differences in left ventricular adaptation to obesity and hypertenstion. J Hum Hypertens 1998;10:685–91.

[9] Singh RB, Rastogi V, Rastogi SS, Niaz MA, Beegom R. Effects of diet and moderate exercise on central obesity and associated disturbances, myocardial infarction and mortality in patients with and without coronary artery disease. J Am Coll Nutr 1996;15:592–601.

[10] Jen CJ, Chan HP, Chen HI. Chronic exercise improves endothelial calcium signalling and vasodilatation in hypercholesterolemic rabbit femoral artery. Arterioscler Thromb Vasc Biol 2002;22:1219–24.

[11] Gutin B, Barbeau P, Owens S, Lemmon CR, Bauman M, Allison J, et al. Effects of exercise intensity on cardiovascular fitness, total body composition, and visceral adiposity of obese adolescents. Am J Clin Nutr 2002;75:818–26.

[12] Benotti PM, Bistrain B, Benotti JR, Blackburn G, Forse RA. Heart disease and hypertension in severe obesity: the benefits of weight reduction. Am J Clin Nutr 1992;55, 586S-S590.

[13] Duflou J, Virmani R, Robin I, Burke A, Farb A, Smialek J. Sudden death as a result of heart disease in morbid obesity. Am J Heart 1995;130:306–13.

[14] French SA, Folsom AR, Jeffery RW, Zheng W, Mink PJ, Baxter JE. Weight variability and incident disease in older women: the Iowa Women's Health Study. Int J Obes Relat Metab Disord 1997;21:217–23.

[15] Rosengren A, Wedel H, Wilhelmsen L. Body weight and weight gain during adult life in men in relation to coronary heart disease and mortality. A prospective population study. Eur Heart J 1999;20:269–77.

[16] Corona-Muniz I, Camacho Hernandez R, Escobeda de la P. Obesity, central body fat distribution and ischemic cardiopathy in the Mexican population. Arch Inst Cardiol Mex 1996;66:143–50.

[17] Ross SJ, Poehlman ET, Johnson RK, Ades PA. Body fat distribution predicts cardiac risk factors in older female coronary patients. J Cardiopulm Rehabil 1997;17:419–27.

[18] Lakka HM, Lakka TA, Tuomilehto J, Salonen JT. Abdominal obesity is associated with increased risk of acute coronary events in men. Eur Heart J 2002;23:706–13.

[19] Scaglione R, Parrinello G, Corrao S, Ganguzza A, Di Chiara T, Arnone S, et al. Prevalence of obesity and ischaemic heart disease in hypertensive subjects. Eur Rev Med Pharmacol Sci 1997;1:69–75.

[20] Aubin MC, Lajoie C, Clément R, Gosselin H, Calderone A, Perrault LP. Female rats fed a high-fat diet were associated with vascular dysfunction and cardiac fibrosis in the absence of overt obesity and hyperlipidemia: therapeutic potential of resveratrol. J Pharmacol Exp Ther 2008;325:961–8.

[21] Mombouli J-V, Vanhoutte PM. Endothelial dysfunction: from physiology to therapy. J Mol Cell Cardiol 1999;31:61—74.

[22] Cooke JP, Dzau VJ. Nitric oxide synthase: role in the genesis of vascular disease. Annu Rev Med 1997;48:489—509.

[23] Shimokawa H. Primary endothelial dysfunction: atherosclerosis. J Mol Cell Cardiol 1999;31:23—37.

[24] Creager MA, Cooke JP, Mendelsohn ME, Gallagher SJ, Coleman SM, Loscalzo J, et al. Impaired vasodilation of forearm resistance vessels in hypercholesterolemic humans. J Clin Invest 1990;86:228—34.

[25] Steinberg HO, Chacker H, Leaming R, Johnson A, Brechtel G, Baron AD. Obesity/insulin resistance is associated with endothelial dysfunction: implications for the syndrome of insulin resistance. J Clin Invest 1996;97:2601—10.

[26] Boulanger CM. Secondary endothelial dysfunction: hypertension and heart failure. J Mol Cell Cardiol 1999;31:39—49.

[27] Perticone F, Cervolo R, Mafald C, Ventura G, Iacopino S, Sinopoli F, et al. Obesity and body fat distribution induce endothelial dysfunction by oxidative stress. Diabetes 2001;50:159—65.

[28] Pinkney JH, Stehouwer CDA, Coppack SW, Yudkin JS. Endothelial dysfunction: cause of the insulin resistance syndrome. Diabetes 1997;46:S9—13.

[29] Lewis TV, Dart AM, Chin-Dusting JP. Endothelium-dependent relaxation by acetylcholine is impaired in hypertriglyceridemic humans with normal levels of plasma LDL cholesterol. J Am Coll Cardiol 1999;33:805—12.

[30] McVeigh GE, Brennan GM, Johnston GD, McDermott BJ, McGarth LT, Henry WR, et al. Impaired endothelium-dependent and independent vasodilation in patients with type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1992;35:771—6.

[31] Arcaro G, Zamboni M, Rossi L, Turcato E, Covi G, Armellini F, et al. Body fat distribution predicts the degree of endothelial dysfunction in uncomplicated obesity. Int J Obese 1999;23:936—42.

[32] Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000;101:1899—906.

[33] Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR, Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation 2000;101:948—54.

[34] Traupe T, D'Uscio LV, Muenter K, Morawietz H, Vetter W, Barton M. Effects of obesity on endothelium-dependent reactivity during acute nitric oxide synthase inhibition: modulatory role of endothelin. Clin Sci 2002;103, 13S-S15.

[35] Tousoulis D, Davies G, Tentolouris C, Crake T, Toutouzas P. Coronary stenosis dilatation induced by L-arginine. Lancet 1997;349:1812—3.

[36] Creager MA, Gallagher SJ, Girerd XJ, Coleman SM, Dzau VJ, Cooke JP. L-arginine improves endothelium-dependent vasodilation in hypercholesterolemic humans. J Clin Invest 1992;90:1248—53.

[37] Panza JA, Casino PR, Badar DM, Quuyumi AA. Effects of increased availability of endothelium-derived nitric oxide precursor on endothelium-dependent vascular relaxation in normal subjects and in patients with essential hypertension. Circulation 1993;87:1475—81.

[38] Boger RH, Bode-Boger SM, Thiele W, Creutzig A, Alexander K, Forlich JR. Restoring vascular nitric oxide formation by L-arginine improves the symptoms of intermittent claudication in patients with peripheral arterial occlusive disease. J AM Coll Cardiol 1998;32:1336—44.

[39] Uenobe F, Nakamura S, Miyazawa M. Antimutagenic effects of resveratrol against Trp-P-1. Mutat Res 1997;373:197—200.

[40] Orsini F, Pelizzoni F, Verotta L, Aburjai T. Isolation, synthesis, and antiplatelet aggregation activity of resveratrol 3-O-b-D-glucopyranoside and related compounds. J Nat Prod 1997;60:1082—7.

[41] Sato M, Suzuki Y, Okuda T, Yokotsuka K. Content of resveratrol, piceid and their isomers in commercially available wines made from grapes cultivated in Japan. Biosci Biotechnol Biochem 1997;61:1800—5.

[42] Wang D, Xu Y, Liu W. Tissue distribution and excretion of resveratrol in rat after oral administration of *Polygonum cuspidatum* extract (PCE). Phytomedicine 2008;15:859—66.

[43] Maier-Salamon A, Hagenauer B, Reznicek G, Szekeres T, Thalhammer T, Jäger W. Metabolism and disposition of resveratrol in the isolated perfused rat liver: role of Mrp2 in the biliary excretion of glucuronides. J Pharm Sci 2008;97:1615—28.

[44] Boocock DJ, Faust GE, Patel KR, Schinas AM, Brown VA, Ducharme MP, et al. Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent. Cancer Epidemiol Biomarkers Prev 2007;16:1246—52.

[45] Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, et al. Resveratrol improves health and survival of mice on a high-calorie diet. Nature 2006;444:337—42.

[46] Lekli I, Szabo G, Juhasz B, Das S, Das M, Varga E, et al. Protective mechanisms of resveratrol against ischemia-reperfusion-induced damage in hearts obtained from Zucker obese rats: the role of GLUT-4 and endothelin. Am J Physiol Heart Circ Physiol 2008;294:H859—66.

[47] Rayalam S, Yang JY, Ambati S, Della-Fera MA, Baile CA. Resveratrol induces apoptosis and inhibits adipogenesis in 3T3-L1 adipocytes. Phytother Res. 2008 August 7 [Epub ahead of print].

[48] Rayalam S, Della-Fera MA, Yang JY, Park HJ, Ambati S, Baile CA. Resveratrol potentiates genistein's antiadipogenic and proapoptotic effects in 3T3-L1 adipocytes. J Nutr 2007;137:2668—73.

[49] Dasgupta B, Milbrandt J. Resveratrol stimulates AMP kinase activity in neurons. Proc Natl Acad Sci USA 2007;104:7217—22.

[50] Shang J, Chen LL, Xiao FX, Sun H, Ding HC, Xiao H. Resveratrol improves non-alcoholic fatty liver disease by activating AMP-activated protein kinase. Acta Pharmacol Sinica 2008;29:698—706.

[51] Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell 2006;127:1109—22.

[52] Bujanda L, Hijona E, Larzabal M, Beraza M, Aldazabal P, García-Urkia N, et al. Resveratrol inhibits nonalcoholic fatty liver disease in rats. BMC Gastroenterol Sep 9 2008;8:40.

[53] Zhu J, Yong W, Wu X, Yu Y, Lv J, Liu C, et al. Anti-inflammatory effect of resveratrol on TNF-alpha-induced MCP-1 expression in adipocytes. Biochem Biophys Res Commun 2008;369:471—7.

[54] Ahn J, Lee H, Kim S, Ha T. Resveratrol inhibits TNF-alpha-induced changes of adipokines in 3T3-L1 adipocytes. Biochem Biophys Res Commun 2007;364:972—7.

[55] de Jesus Soares T, Volpini RA, Francescato HD, Costa RS, da Silva CG, Coimbra TM. Effects of resveratrol on glycerol-induced renal injury. Life Sci 2007;81:647—56.

[56] Sharma S, Anjaneyulu M, Kulkarni SK, Chopra K. Resveratrol, a polyphenolic phytoalexin, attenuates diabetic nephropathy in rats. Pharmacology 2006;76:69—75.

[57] Morales AI, Buitrago JM, Santiago JM, Fernández-Tagarro M, López-Novoa JM, Pérez-Barriocanal F. Protective effect of trans-resveratrol on gentamicin-induced nephrotoxicity. Antioxid Redox Signal 2002;4:893—8.

[58] Roberts CK, Barnard RJ, Sindhu RK, Jurczak M, Ehdaie A, Vaziri ND. A high-fat, refined-carbohydrate diet induces endothelial dysfunction and oxidant/antioxidant imbalance and depresses NOS protein expression. J Appl Physiol 2005;98:203—10.

[59] Roberts CK, Vaziri ND, Wang XQ, Barnard RJ. Enhanced NO inactivation and hypertension induced by a high-fat, refined-carbohydrate diet. Hypertension 2000;36:423—9.

[60] Naderali EK, Doyle PJ, Williams G. Resveratrol induces vasorelaxation of mesenteric and uterine arteries from female guinea-pigs. Clin Sci 2000;98:537—43.

[61] Naderali EK, Smith SL, Doyle PJ, Williams G. The mechanism of resveratrol-induced vasorelaxation differs in the mesenteric resistance arteries of lean and obese rats. Clin Sci 2001;100:55—60.

[62] Klinge CM, Blankenship KA, Risinger KE, Bhatnagar S, Noisin EL, Sumanasekera WK, et al. Resveratrol and estradiol rapidly activate MAPK signaling through estrogen receptors alpha and beta in endothelial cell. J Biol Chem 2005;280:7460—8.

[63] Silan C. The effects of chronic resveratrol treatment on vascular responsiveness of streptozotocin-induced diabetic rats. Biol Pharm Bull 2008;31:897—902.

[64] Chander V, Chopra K. Possible role of nitric oxide in the protective effect of resveratrol in 5/6th nephrectomized rats. J Surg Res 2006;133:129—35.

[65] Penumathsa SV, Koneru S, Samuel SM, Maulik G, Bagchi D, Yet SF, et al. Strategic targets to induce neovascularization by resveratrol in hypercholesterolemic rat myocardium: role of caveolin-1, endothelial nitric oxide synthase, hemeoxygenase-1, and vascular endothelial growth factor. Free Radic Biol Med 2008;45:1027—34.

[66] Thirunavukkarasu M, Penumathsa SV, Koneru S, Juhasz B, Zhan L, Otani H, et al. Resveratrol alleviates cardiac dysfunction in streptozotocin-induced diabetes: role of nitric oxide, thioredoxin, and heme oxygenase. Free Radic Biol Med 2007;43:720—9.

[67] Thirunavukkarasu M, Koneru S, Juhasz B, Zhan L, Pant R, Menon VP, et al. Statin and resveratrol in combination induces cardioprotection against myocardial infarction in hypercholesterolemic rat. J Mol Cell Cardiol 2007;42:508—16.

[68] Lefèvre J, Michaud SE, Haddad P, Dussault S, Ménard C, Groleau J, et al. Moderate consumption of red wine (cabernet sauvignon) improves ischemia-induced neovascularization in ApoE-deficient mice: effect on endothelial progenitor cells and nitric oxide. FASEB J 2007;21:3845—52.

[69] Das S, Alagappan VK, Bagchi D, Sharma HS, Maulik N, Das DK. Coordinated induction of iNOS-VEGF-KDR-eNOS after resveratrol consumption: a potential mechanism for resveratrol preconditioning of the heart. Vascul Pharmacol 2005;42:281—9.