REVIEW

Obesity and cardiovascular dysfunction: A role for resveratrol?

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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.

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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 heart 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 monogluconide 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 5g) on healthy volunteers reported recovery of resveratrol and six metabolites from plasma and urine samples. Peak plasma levels of resveratrol at the highest dose (5g) occurred at 1.5h 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 4h 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 nephotoxic 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 rats 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]. Hypercholesterolaemia 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 hypercholesterolaemia 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-resveratrol 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


Obesity and cardiovascular dysfunction


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