Published in final edited form as:

Rev Endocr Metab Disord. 2013 March ; 14(1): 87–99. doi:10.1007/s11154-013-9237-9.

The Vascular Endothelium in Diabetes – A Therapeutic Target?

Kieren Mather, MD FRCPC

Indiana University School of Medicine

Abstract

Insulin resistance affects the vascular endothelium, and contributes to systemic insulin resistance by directly impairing the actions of insulin to redistribute blood flow as part of its normal actions driving muscle glucose uptake. Impaired vascular function is a component of the insulin resistance syndrome, and is a feature of type 2 diabetes. On this basis, the vascular endothelium has emerged as a therapeutic target where the intent is to improve systemic metabolic state by improving vascular function. We review the available literature presenting studies in humans, evaluating the effects of metabolically targeted and vascular targeted therapies on insulin action and systemic metabolism. Therapies that improve systemic insulin resistance exert strong concurrent effects to improve vascular function and vascular insulin action. RAS-acting agents and statins have widely recognized beneficial effects on vascular function but have not uniformly produced the hoped-for metabolic benefits. These observations support the notion that systemic metabolic benefits can arise from therapies targeted at the endothelium, but improving vascular insulin action does not result from all treatments that improve endothelium-dependent vasodilation. A better understanding of the mechanisms of insulin's actions in the vascular wall will advance our understanding of the specificity of these responses, and allow us to better target the vasculature for metabolic benefits.

Introduction

The vascular endothelium serves as the interface between the blood and the enclosing vascular structures. This unicellular layer serves a number of crucial roles in physiology and pathophysiology, including regulating vascular tone and promoting a local anti-inflammatory and anti-fibrotic milieu. The endothelium also contributes to the regulation of systemic metabolism by virtue of actions of fuel substrates, insulin, and other regulatory factors directly at the level of the vascular endothelium. In the present review we will summarize the effects of insulin resistance and diabetes mellitus on the endothelium, and mechanisms integrating vascular function and metabolism. This will provide context and rationale for a review of efforts targeting the endothelium for metabolic benefits in obesity, insulin resistance, and type 2 diabetes.

Role of the vasculature in normal metabolic physiology

The vasoregulatory function of the vascular endothelium is now recognized to contribute importantly to the net, integrated action of insulin in skeletal muscle [1-4,5]. Similar to the effect of acetylcholine to induce a receptor-mediated activation of production of nitric oxide by the endothelium, insulin acts through traditional insulin receptors on the vascular endothelium to stimulate production of nitric oxide and induce vasodilation [6-9]. The endothelial insulin response is parallel to that in traditional insulin-responsive tissues, acting

through a PI3 kinase pathway to activate the serine protease Akt/Protein Kinase B, which in turn activates endothelial nitric oxide synthase (eNOS, also known as NOS3).

This set of functions mediates insulin-mediated vasodilation in skeletal muscle and contribute to normal metabolic regulation of fuel disposal [2,5,10,11]. Skeletal muscle is not fully perfused at rest, with an incompletely understood mechanism regulating tissue perfusion and providing temporary and shifting perfusion to subsegments of the whole muscle. This reserve capacity for perfusion to the muscle allows the marked increase in perfusion that is required to support increased metabolic activity when the muscle is activated. This same system, via endothelial insulin receptor activation, supports increased perfusion of skeletal muscle in the postprandial state as part of the process of insulin-stimulated postprandial glucose storage into muscle [12-14]. The experiments that first demonstrated this effect in humans used limb-balance studies, evaluating insulin-mediated vasodilation at rest under insulin stimulation with and without the competitive NOS antagonist L-N monomethylarginine (L-NMMA) [15,16]. L-NMMA blocked insulin-stimulated increases in limb blood flow and reduced insulin-stimulated limb glucose disposal. These and subsequent studies suggest that insulin's vascular actions contribute ~10-40% of the net action of insulin to stimulate glucose uptake in skeletal muscle under resting conditions [15-17]. Subsequent experiments using other methods, in particular studies using microbubble ultrasound to more specifically quantify microvascular perfusion, have confirmed the effect and localized the vascular action of insulin to microvessels [12-14,4,18].

Insulin was only the first metabolically important hormone to be shown to induce endothelium-dependent vasodilation. Others with more recently established actions in animal models and in humans include leptin [19,20], adiponectin [21,22], and glucagon-like peptide-1 (GLP-1) [23-25]. Similar to insulin, the concentrations and dynamics of these factors are significantly altered under conditions of obesity and type 2 diabetes. The importance of these more recently studied factors to routine vascular health, and their contributions to the normal physiologic functions of metabolically active tissues, remains to be demonstrated.

Vascular dysfunction in insulin resistance/diabetes

Diabetes mellitus and insulin resistance without overt diabetes are associated with endothelial dysfunction [5,11]. Studies exploring potential mechanisms for these effects have tested individual diabetes-associated factors as potential contributors to vascular dysfunction. In general these studies test whether the factor in question can induce vascular dysfunction in the non-diabetic state, then by subtraction or reduction of the factor in question whether that factor is an important contributor to dysfunction in diabetes. These studies have provided targets for interventions aimed at improving vascular function in insulin resistance and diabetes.

Therapies that target the endothelium

The endothelium has emerged as a therapeutic target in diabetes. This can be conceived as targeting improvements in diabetes-associated vascular risk, or targeting metabolic improvements by augmenting vascular insulin action through generic improvements in endothelial function or more directly improving vascular insulin action. Although these are conceptually distinct targets, clearly a therapy that improves endothelial function has the potential to simultaneously benefit both vascular and metabolic disease. For the purposes of the current review, we will focus on the assessment of metabolic effects of vascular therapies. The principal underlying hypothesis for these therapies is that, given the dependence of tissue insulin sensitivity on insulin action in the endothelium, whole-body

insulin sensitivity and specifically vascular insulin sensitivity can be improved by therapies that reduce obesity/diabetes-associated metabolic abnormalities, improve tissue insulin sensitivity, or directly improve endothelial function.

The conceptual approaches can be divided into those targeting metabolic abnormalities, and those targeting the vasculature directly.

Metabolic Therapies: Glucose lowering

In cross-sectional studies, hyperglycemia is clearly associated with impaired vascular function and specifically with impaired endothelium-dependent vasodilation [26,27]. A direct detrimental role of hyperglycemia on the vasculature has been demonstrated most clearly by findings of acute impairment with experimentally induced hyperglycemia [28,29]. Demonstrating improvement in vascular function with reductions in glucose is more difficult, because of confounding effects of most glucose-lowering therapies independent of benefits via glucose lowering. For example, glucose reductions with insulin therapy have been shown to improve endothelial function, but these benefits cannot be cleanly attributed to the glucose lowering effect alone [30,31]. Even therapies that modulate glucose concentrations independent of direct effects on beta cell function or insulin sensitivity in peripheral tissues can produce secondary improvements in these parameters, as will be discussed below. With these limitations in mind, we can evaluate the effects of direct glucose-lowering therapies on vascular function.

The alpha-glucosidase inhibitors delay digestion and absorption of ingested carbohydrates. These therapies produce reductions in glucose excursions without direct effects on beta cell function or insulin sensitivity. Also these agents are not systemically absorbed and therefore confounding by direct effects on the vasculature is minimal. In clinical studies acarbose failed to improve agonist-induced endothelium-dependent vasodilation in subjects with type 2 DM [32], and miglitol has been shown to improve reactive hyperemia-vasodilation where voglibose did not [33]. Miglitol also showed immediate improvement in the prandial effect to augment vasodilation [34], through mechanisms that may involve acute effects on glucose excursion or secondary effects on meal-related hormones. Effects of agents in this class to improve whole-body insulin sensitivity have been reported [35,36,33], but no studies have used these agents to evaluate effects of glucose lowering on vascular insulin sensitivity.

Another class that may be informative regarding direct effects of glucose lowering on vascular function is the glucosuric SGLT-2 inhibitors. These agents are systemically absorbed following ingestion, and act at the kidney to lower the threshold for urinary loss of glucose [37]. This class of agents is early in development, and neither preclinical studies nor clinical studies addressing effects on vascular function have been published to date.

With this limited dataset, we can conclude that there is modest but not convincing data that therapies directed at glucose lowering without concurrent effects in other metabolic parameters may improve endothelial function.

Metabolic Therapies: Insulin sensitizers

Experimental evidence has shown that insulin resistance at the level of the endothelium contributes to vascular dysfunction. In whole-animal or human experiments with insulin sensitizing therapies there are effects on systemic metabolism beyond the direct effects on insulin action, and net benefits at the level of the endothelium may reflect all of these concurrent effects. Nevertheless studies have been undertaken using insulin sensitizing therapies to target improvements in vascular function.

Metformin, a biguanide, acts predominantly at the liver to improve hepatic insulin sensitivity, and through resulting improvements in systemic metabolism as well as direct extrahepatic actions has concurrent effects on insulin sensitivity in other tissues [38,39]. In clinical studies metformin has shown beneficial effects on endothelial function in insulin resistant subjects with Type 2 diabetes, and in other groups with insulin resistance [40-43]. In some studies, metformin did not produce a significant benefit when compared against concurrently studied thiazolidinediones [44,45], and it is not always the case that the improvement in vascular function is proportional to improved measures of insulin resistance. Nevertheless, the principal effect of metformin is on insulin resistance, and metformin therapy appears to improve vascular function.

The thiazolidinedione (TZD) class of antidiabetic agents has proven problematic in clinical applications, and at present the use of these agents is waning. Nevertheless these agents are extremely informative regarding questions of the interrelationships of insulin resistance, fatty acid disposition, and vascular health. Through effects on cellular fatty acid handling, principally in adipose tissue, TZDs improve peripheral and hepatic insulin sensitivity [46]. These agents produce concurrent improvements in insulin sensitivity and vascular function in Type 2 diabetes and related states of insulin resistance [47-49,44,50-53,45]. The exact mechanism of these beneficial effects is debated, with many studies invoking mechanisms of benefit beyond improvements in insulin resistance [47,50,52,54-59,53]. Pioglitazone improved insulin-mediated vasodilation in one study where this was directly assessed. Overall, these agents induce concurrent and associated improvements in insulin resistance and vascular function. Together with the parallel results from studies using metformin, these studies support the targeting of insulin resistance as an approach to treating the endothelium in Type 2 diabetes.

Metabolic Therapies: Fatty acid lowering

Elevated fatty acids are a component of the insulin resistance phenotype, and likely contribute directly to tissue insulin resistance and to endothelial dysfunction. In cross-sectional studies there is an association between elevated fatty acid concentrations and vascular dysfunction [60,61]. Experimental studies have demonstrated impairments in vascular function measurements in healthy control subjects with experimentally induced elevation in fatty acid concentrations [62,61,63]. Therapies that target fatty acid lowering may therefore be of benefit for vascular function. TZDs, discussed above, induce improvements in insulin resistance by manipulating cellular handling of fatty acids and may exert the beneficial effects described above via these changes. Studies separating effects on insulin sensitivity from effects on fatty acids in the beneficial effects of TZDs on the vasculature have not been performed. Similarly, insulin treatment suppresses fatty acid concentrations and this effect may contribute to the net beneficial effects of insulin treatment on the vascular endothelium. Studies separating these effects from glucose lowering and direct effects of insulin on the vascular wall have not been performed.

Other therapeutic approaches provide more focused fatty acid lowering. Acipimox, an inhibitor of lipolysis [64], has been studied in the context of experimental elevations in non-esterified fatty acids and found to concurrently reverse fatty acid-induced insulin resistance and microvascular dysfunction[63]. In one study, gemfibrozil (a PPAR α agonist with predominantly triglyceride-lowering action) concurrently improved vascular function and insulin sensitivity [65]. Niacin, which is used clinically for its widespread effects to lower lipid species, acts through receptor-dependent and receptor-independent mechanisms as a fatty acid lowering agent [66,67]. In non-diabetic populations, niacin therapy produces improvements in endothelium-dependent vasodilation [68,69]. However, despite fatty acid lowering effects niacin treatment improvements in insulin resistance have not been

universally observed [70-72]. And no published data evaluate concurrent effects of niacin on insulin resistance and vascular function, or on insulin-mediated vasodilation.

Fish oil, with omega-3 fatty acids as the main identified therapeutic constituents, present another widely used agent with lipid lowering effects including reductions in non-esterified fatty acids [73]. In the context of these complex lipid alterations, fish oil supplementation does not significantly improve insulin resistance [74,75] but has beneficial vascular effects in populations with diabetes or obesity-related metabolic dysfunction [76-78]. Effects on vascular insulin responses have not been evaluated to date.

In summary, the data most strongly linking improvements in vascular function with reductions in non-esterified fatty acids comes from studies with TZDs, but those data are confounded by concurrent effects on whole-body insulin sensitivity. Therapies with fatty acid-lowering effects but without confounding effects on insulin sensitivity have not been systematically evaluated for effects on vascular function, but the available data provides modest support for targeting fatty acid reductions as a component of therapies aimed at the vascular endothelium in diabetes.

Metabolic Therapies: Anti-inflammatories

The activation of the innate immune system in insulin resistance is another viable therapeutic target. Insulin resistant states, and hyperglycemic states in the absence of insulin resistance, are now well recognized to be associated with low-level activation of systemic inflammatory responses [79,80]. This effect is manifest as elevations in C-reactive protein, and as increased activity of the tumor necrosis factor (TNF) system in multiple tissues [80-82]. The seminal observation in animal studies that overexpression of TNF α induced an insulin resistant state associated with vascular dysfunction [83,84] prompted studies in humans that confirmed the importance of inflammation in the human condition [85,86]. Experimental elevation of fatty acids induces a systemic inflammatory condition, and this appears to be mediated by induction of TNF α -mediated cellular inflammatory responses [87,88]. Inflammatory effects of hyperglycemia have also been observed although less convincingly focused on TNF α responses [89,90].

Anti-inflammatory approaches that have been evaluated include small-molecule agents that interfere with intracellular signaling, and monoclonal antibodies that interfere with targeted extracellular components of the innate immune system. Studies evaluating effects of these therapies on insulin resistance and studies evaluating effects on vascular function have been performed, but very few studies have evaluated concurrent effects on both axes.

Monoclonal antibodies against the TNF α system are now widely applied in clinical rheumatology. Beneficial effects to reduce insulin resistance have been reported in populations with systemic inflammatory disease and in traditionally insulin resistant and type 2 diabetic populations [91-96], although others report no such benefit [97,98,93,99]. Similarly, in populations with systemic inflammatory disease such therapies can improve vascular function [100-104]. In the few studies that have evaluated effects on vascular function in populations with insulin resistance or type 2 diabetes, improvement in vascular function has been difficult to demonstrate [91,105].

Recently, salsalate has been found to impair TNF α -mediated inflammation in addition to the originally recognized anti-inflammatory effects mediated by inhibition of cyclooxygenase [106]. Subsequent studies have clearly demonstrated beneficial effects on glycemia with salsalate, although surprisingly these cannot be clearly attributed to improvements in insulin resistance [107-109]. Early studies in non-diabetic populations have found that salsalate can improve vascular function [110,111], but studies in traditionally

insulin resistant or type 2 diabetic subjects have not been published and no data are currently available to connect changes in insulin sensitivity with changes in vascular function.

Overall these data produce a perhaps surprising observation that therapeutically targeting the activated intrinsic inflammatory response in insulin resistance/Type 2 DM is beneficial for insulin resistance but not necessarily beneficial for vascular function. Further data with TNF α antagonists, and data with salsalate may clarify this circumstance. As with other potential therapeutic targets, studies concurrently assessing effects on both axes will be most informative.

Metabolic Therapies: Advanced Glycosylation Endproducts

The chemical reaction whereby proteins are glycosylated is spontaneous, indiscriminate and proportional to glucose concentrations. This produces a variety of circulating glycosylated proteins and their breakdown products, which are sensed at cell membranes through the receptors for advanced glycosylation products (R-AGEs) [112]. These receptors mediate cellular injury in endothelial cells, producing impaired NO production and affecting transcription of eNOS [113,114]. Glucose reducing therapies reduce AGE generation, and as reviewed above these effects can produce improvements in vascular function. Unexpectedly, angiotensin converting enzyme inhibitors and angiotensin receptor blockers, which provide vascular benefits and are commonly used in diabetes, can also improve AGE concentrations independent of glucose lowering [115,116]. Although blocking the receptors for AGE is conceptually obvious as a therapeutic approach, no data have been published on this topic. A number of agents are under development as direct AGE breakers, and show promising effects in animal models of diabetes [117,118]. Human studies using direct AGE breakers in non-diabetic populations have indicated some success blocking effects of AGEs on the vasculature [119,120]. Data evaluating these direct blockers in diabetic populations have not been published. One study in diabetic subjects has been published demonstrating a beneficial effect of benfotiamine (which can prevent AGE formation in vitro) to prevent acute impairment of endothelial function by ingested AGEs [121]. This is useful as a test of the concept, but it is not clear whether the reported benefit was via reduced production of endogenous AGEs or through effects on the concentrations of the ingested AGEs.

Vascular Therapies—The dependence of insulin on the endothelium for a portion of its tissue actions, and concordance of tissue insulin resistance with vascular insulin resistance in the setting of endothelial dysfunction, prompts the hypothesis that treatments primarily targeting vascular function might improve insulin sensitivity simply by allowing improved vascular insulin response. These questions have been asked with the major clinically available therapies targeting the vasculature directly.

Vascular Therapies: Renin-Angiotensin System Antagonists

Hypertension is a common feature of obesity/insulin resistance, and is itself associated with impairments in endothelial function even in the absence of obesity. Notably, insulin resistance is prevalent even among non-obese subjects with hypertension, suggesting that impaired endothelial function is a key link between vascular and metabolic dysfunction [122,123]. In multiple studies, treatment with antihypertensive agents in general and specifically those targeted at components of the renin-angiotensin system has been shown to improve endothelium-dependent vasodilation in hypertension (reviewed in [124]).

As a general statement, treatment of insulin resistant subjects with ACEI or ARB improves endothelial function but produces mixed effects on whole-body insulin sensitivity. A reasonable number of studies have been performed in humans exploring whether treatment with these classes of agents can improve whole-body insulin sensitivity, unfortunately

producing a mixed literature [125-129]. Fewer studies have directly evaluated concurrent effects on tissue and vascular insulin sensitivity [130,129], but this subset again produced conflicting evidence for RAS-targeted treatment to improve insulin-mediated vasodilation in humans.

These conflicting results do not appear to be attributable to agent-specific effects, or to differences by class of treatment. Even the studies that have involved randomized treatment assignments and double-blind crossover designs have produced contradictory results. No meta-analysis of these studies has been produced to date. The fact of intermittently demonstrating positive findings could indicate that treatment with a RAS-acting agent is in fact capable of improving whole-body insulin resistance, but the true effect size is moderately smaller than the demonstrable effect size in studies to date. Alternatively, it could be that there is no effect of RAS-acting agents on insulin sensitivity, and the individual studies reporting positive findings represent false positives. This possibility seems unlikely in part because positive findings have been demonstrated by multiple investigators, in well-designed studies with adequate control conditions. A third possibility is that the actions of RAS-acting agents on whole-body insulin responses is more complicated than currently appreciated, producing an effect that is incompletely measured in studies to date. Clearly further work is needed to better understand the physiology underlying these effects, and better understand the role of RAS-acting agents in the clinical approach to vascular and metabolic disease in diabetes and obesity. Currently available data allows us to confidently claim beneficial effects on vascular function and cardiovascular risk with RAS-acting agents, but the claim of improvement also in insulin sensitivity cannot be confidently made.

Vascular Therapies: Statins

The HMGCoA-reductase inhibitors, collectively called the statins, are remarkably effective cholesterol-lowering agents, and confer cardiovascular benefit in populations with CVD risk including those with obesity/insulin resistance and diabetes [131]. These agents have readily demonstrated beneficial effects on multiple aspects of vascular biology, including improvements in endothelial function and reductions in systemic inflammation [132-134].

On this basis it is natural to hypothesize that statin treatment would be associated with an improvement in insulin sensitivity, or at least an improvement in vascular insulin sensitivity. However, studies to date evaluating this question have shown no benefit on insulin resistance despite demonstrable improvements in endothelium-dependent vasodilation [134-136]. No direct studies of effects of statins on insulin-mediated vasodilation have been published.

Recent observations of an effect of statins to increase the incidence of diabetes in large-scale clinical trials of cholesterol-lowering for CVD benefits [137-140] are consistent with these observations. The assumption that therapies that improve vascular function should improve tissue metabolism is clearly not valid with statins, for unknown reasons. It could be the case that therapeutic improvement in vascular function is not sufficient to improve insulin resistance-mediated tissue vascular dysfunction. Another (non-exclusive) alternative is that there are concurrent effects of statins that aggravate metabolic status, or otherwise act in an adverse manner despite otherwise beneficial effects induced by improvements in vascular function. Combining these observations with those from the RAS-acting agents provides some support for the first of these interpretations. With each of these classes, there is a clearly demonstrable improvement in endothelial function, with associated reductions in cardiovascular disease risk. But despite this improvement, benefits on tissue insulin sensitivity do not follow. This suggests that improving endothelium-dependent vasodilation *per se* is not sufficient to improve vascular insulin action and the component of tissue insulin sensitivity that is dependent on vascular function.

Vascular Therapies: Targeting NO/ET-1 Balance

Vascular tone is closely regulated, and as in most biological systems this requires the actions of opposing factors. In the vasculature of skeletal muscle NO is the dominant dilator. eNOS produces NO tonically as part of a regulated balance of dilators and constrictors controlling vascular tone, and production can be acutely stimulated by agonists including insulin [16]. As noted, insulin's vasodilator action is mediated by NO, and impaired vascular insulin response is manifest as a lack of effect of insulin to produce NO, producing the resulting impairment in insulin-induced vasodilation. In the vasculature endothelin-1 (ET-1) is the dominant vasoconstrictor opposing the dilator effects of NO [141,142]. This constrictor is also tonically produced, but in contrast to NO the production or action of ET-1 does not change significantly in response to acute stimuli. Regulators of the tonic production of ET-1 include fatty acids, glucose, and insulin but in vivo experimentation suggests that nitric oxide itself regulates ET-1 production at least as potently as these metabolic factors [143-145,85]. Obesity/insulin resistance and diabetes are associated with increased ET-1 tone, and ET-1 is an important contributor to abnormalities in vascular tone, to impaired endothelium-dependent responses, and also to impairment in the vascular components of insulin action.

A number of NO-delivery therapies are under development [146-148] but to date these have not been tested in clinical studies addressing metabolic benefits. Other approaches to enhancing bioavailability of nitric oxide have been pursued. These include using arginase inhibitors to augment availability of the NOS substrate L-arginine [149,150], or using enzyme inhibitors preserving the availability of the NOS cofactor tetrahydrobiopterin, or direct supplementation with tetrahydrobiopterin [151,152]. One study with tetrahydrobiopterin found beneficial effects on insulin resistance, although in that study there was no concurrent improvement in vascular function [153]. Asymmetric dimethylarginine (ADMA) is a regulated, endogenous inhibitor of NOS, and its levels are associated with vascular dysfunction [154-156]. No therapies have been developed as yet to manipulate ADMA concentrations (with the possible exception of ECGC from green tea, discussed below), but reductions in ADMA have been observed concurrent with improved endothelial function from statins, RAS antagonists, and other vascular therapies [157-160].

Working further downstream, the phosphodiesterase (PDE)-5 inhibitors have proven clinically useful as direct vascular-acting NO preserving therapies including in subjects with diabetes. In preclinical studies and a small number of clinical studies there appears to be the predicted benefit on endothelium-dependent vasodilation [161,162]. One preclinical study suggests that PDE5 inhibition may provide an insulin sensitizing effect [163] but this idea has not been tested in humans to date. Given the ready clinical availability, acceptability, and low toxicity of these agents this approach warrants further exploration.

In physiologic studies ET-1 antagonism improves vasodilation in obesity or diabetes [164-166], and antagonizing ET-1 action in the vasculature can improve insulin resistance including vascular insulin resistance [167,165,168,169]. Due in part to toxicity concerns, ET-1 antagonists have been approved only for restricted clinical uses (bosentan for primary pulmonary hypertension, and atrasentan for prostate cancer metastasis prevention). Whether agents of this class are of benefit for vascular metabolic actions in clinical obesity or diabetes is unknown, although the available data suggest a clear opportunity for benefit for both vascular outcomes and metabolic balance.

Alternative Medicines

Studies of nontraditional medicines including plant-derived therapies have provided surprising insights into insulin signaling in endothelial cells, and provided some evidence for

concurrent benefits on tissue insulin action and whole-body insulin sensitivity. Green tea-derived catechins, in particular epigallocatechin gallate (EGCG), exert beneficial effects on endothelial function in cultured cells and in animal models, via mechanisms shared with the insulin response system [170-172]. Acute physiologic effects of EGCG to improve endothelium-dependent vasodilator function have been evaluated in humans with or without CVD risk factors [173,174], but studies in obesity and diabetes are lacking. In animals, concurrent effects on insulin resistance and vascular function have been reported [172]. To date one study has been published evaluating these parameters in humans, and found significant effect of green tea extract on post-meal blood pressure and insulin response, with interesting differences by catechol-O-methyl transferase (COMT) genotype [175]. The fact of shared mechanisms with insulin signaling in endothelium and promising pre-clinical data in animals suggests that green tea-based therapies may be of particular benefit in insulin resistance-associated vascular dysfunction, but this has not yet been rigorously assessed.

The weak androgen dihydroepiandrosterone (DHEA) also exerts effects on endothelial cells, again using mechanisms parallel to insulin signaling pathways [176]. In human studies DHEA supplementation in individuals who are not deficient produces improved endothelium-dependent vasodilation [177,178], and has also been shown to concurrently improve insulin resistance [177]. This is at odds with the observation that DHEA concentrations are spontaneously elevated in individuals with the polycystic ovarian syndrome (PCOS), which is associated with insulin resistance and vascular dysfunction [179], but leaves open the possibility that this agent could produce beneficial effects when used as a supplement in non-PCOS populations.

Resveratrol is a plant-derived stilbene polyphenol found in red wine, with potent endothelium-independent vasodilating effects [180]. Among multiple claimed beneficial health effects are increased transcription and action of nitric oxide synthase [181] and reduced ET-1 production or action [182,183]. Clinical studies have shown beneficial effects on vascular function [184,185] but where systemic metabolism has been evaluated, no effects on whole-body metabolism were observed [184].

Emerging targets

Many of the above factors have been under investigation for decades, while others have been more recently discovered. Further, the pace of progress continues to accelerate and many novel discoveries have potential impact on vascular and metabolic status in diabetes. Advances in this field can be expected from emerging work including micro RNA species [186,187], modulation of endoplasmic reticulum stress [188,189], control of autophagy [190,191], and new approaches to management of hormonal control of systemic metabolism such as GLP-1-receptor targeted adducts [192], or mixed hormonal therapies [193,194]. Bringing these discoveries into the current body of knowledge regarding integrated effects of the vascular endothelium on vascular and metabolic disease may provide needed advances in our approach to targeting the endothelium in obesity/insulin resistance and type 2 diabetes.

Summary and Future Directions

Insulin resistance affects the vascular endothelium, and contributes to systemic insulin resistance by directly impairing the actions of insulin to redistribute blood flow as part of its normal actions driving muscle glucose uptake. Impaired vascular function is a component of the insulin resistance syndrome, and is a feature of type 2 diabetes. On this basis, the vascular endothelium has emerged as a therapeutic target where the intent is to improve systemic metabolic state by improving vascular function.

Many pathophysiologic features of obesity, insulin resistance, and type 2 diabetes exert direct impairment in vascular function and contribute to the adverse vascular phenotype. Individually targeting key pathophysiologic features is generally successful in terms of improving vascular function, but only approaches that address insulin sensitivity or fat distribution have provided consistent data showing concurrent improvements in systemic metabolic status. Mechanistically it appears that therapies directly targeting improved NO bioavailability or direct ET-1 antagonism may produce concurrent vascular and metabolic benefits, but it is not sufficient to improve the NO/ET-1 balance by therapies acting solely on the endothelium. In particular, RAS-acting agents and statins have widely recognized beneficial effects on vascular function but have not produced the hoped-for metabolic benefits. These observations support the notion that systemic metabolic benefits can arise from therapies targeted at the endothelium, but improving vascular insulin action does not result from all treatments that improve endothelium-dependent vasodilation. A better understanding of the mechanisms of insulin's actions in the vascular wall will advance our understanding of the specificity of these responses, and allow us to better target the vasculature for metabolic benefits.

REFERENCES

1. Baron AD, Clark MG. Role of blood flow in the regulation of muscle glucose uptake. Annual review of nutrition. 1997; 17:487–499.
2. Baron AD, Tarshoby M, Hook G, Lazaridis EN, Cronin J, Johnson A, et al. Interaction between insulin sensitivity and muscle perfusion on glucose uptake in human skeletal muscle: evidence for capillary recruitment. Diabetes. 2000; 49(5):768–774. [PubMed: 10905485]
3. Tack CJ, Ong MK, Lutterman JA, Smits P. Insulin-induced vasodilatation and endothelial function in obesity/insulin resistance. Effects of troglitazone. Diabetologia. 1998; 41(5):569–576. [PubMed: 9628275]
4. Barrett EJ, Eggleston EM, Inyard AC, Wang H, Li G, Chai W, et al. The vascular actions of insulin control its delivery to muscle and regulate the rate-limiting step in skeletal muscle insulin action. Diabetologia. 2009; 52(5):752–764. [PubMed: 19283361]
5. Cleland SJ, Petrie JR, Ueda S, Elliott HL, Connell JM. Insulin as a vascular hormone: implications for the pathophysiology of cardiovascular disease. Clinical and experimental pharmacology & physiology. 1998; 25(3-4):175–184. [PubMed: 9590566]
6. Hsueh WA, Law RE. Insulin signaling in the arterial wall. The American journal of cardiology. 1999; 84(1A):21J–24J.
7. Montagnani M, Ravichandran LV, Chen H, Esposito DL, Quon MJ. Insulin receptor substrate-1 and phosphoinositide-dependent kinase-1 are required for insulin-stimulated production of nitric oxide in endothelial cells. Molecular endocrinology. 2002; 16(8):1931–1942. [PubMed: 12145346]
8. Vincent MA, Montagnani M, Quon MJ. Molecular and physiologic actions of insulin related to production of nitric oxide in vascular endothelium. Current diabetes reports. 2003; 3(4):279–288. [PubMed: 12866989]
9. Zeng G, Nystrom FH, Ravichandran LV, Cong LN, Kirby M, Mostowski H, et al. Roles for insulin receptor, PI3-kinase, and Akt in insulin-signaling pathways related to production of nitric oxide in human vascular endothelial cells. Circulation. 2000; 101(13):1539–1545. [PubMed: 10747347]
10. Mather K, Anderson TJ, Verma S. Insulin action in the vasculature: physiology and pathophysiology. Journal of vascular research. 2001; 38(5):415–422. [PubMed: 11561143]
11. Muniyappa R, Montagnani M, Koh KK, Quon MJ. Cardiovascular actions of insulin. Endocrine reviews. 2007; 28(5):463–491. [PubMed: 17525361]
12. Rattigan S, Barrett EJ, Clark MG. Insulin-mediated capillary recruitment in skeletal muscle: is this a mediator of insulin action on glucose metabolism? Current diabetes reports. 2003; 3(3):195–200. [PubMed: 12762965]
13. Clerk LH, Vincent MA, Lindner JR, Clark MG, Rattigan S, Barrett EJ. The vasodilatory actions of insulin on resistance and terminal arterioles and their impact on muscle glucose uptake. Diabetes/ metabolism research and reviews. 2004; 20(1):3–12. [PubMed: 14737741]

14. Vincent MA, Clerk LH, Rattigan S, Clark MG, Barrett EJ. Active role for the vasculature in the delivery of insulin to skeletal muscle. *Clinical and experimental pharmacology & physiology*. 2005; 32(4):302–307. [PubMed: 15810996]
15. Scherrer U, Randin D, Vollenweider P, Vollenweider L, Nicod P. Nitric oxide release accounts for insulin's vascular effects in humans. *The Journal of clinical investigation*. 1994; 94(6):2511–2515. [PubMed: 7989610]
16. Steinberg HO, Brechtel G, Johnson A, Fineberg N, Baron AD. Insulin-mediated skeletal muscle vasodilation is nitric oxide dependent. A novel action of insulin to increase nitric oxide release. *The Journal of clinical investigation*. 1994; 94(3):1172–1179. [PubMed: 8083357]
17. Cleland SJ, Petrie JR, Small M, Elliott HL, Connell JM. Insulin action is associated with endothelial function in hypertension and type 2 diabetes. *Hypertension*. 2000; 35(1 Pt 2):507–511. [PubMed: 10642350]
18. Barrett EJ, Wang H, Upchurch CT, Liu Z. Insulin regulates its own delivery to skeletal muscle by feed-forward actions on the vasculature. *American journal of physiology. Endocrinology and metabolism*. 2011; 301(2):E252–263. [PubMed: 21610226]
19. Kimura K, Tsuda K, Baba A, Kawabe T, Boh-oka S, Ibata M, et al. Involvement of nitric oxide in endothelium-dependent arterial relaxation by leptin. *Biochemical and biophysical research communications*. 2000; 273(2):745–749. [PubMed: 10873674]
20. Benkhoff S, Loot AE, Pierson I, Sturza A, Kohlstedt K, Fleming I, et al. Leptin potentiates endothelium-dependent relaxation by inducing endothelial expression of neuronal NO synthase. *Arteriosclerosis, thrombosis, and vascular biology*. 2012; 32(7):1605–1612.
21. Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. *The Journal of biological chemistry*. 2003; 278(45):45021–45026. [PubMed: 12944390]
22. Ouchi N, Ohishi M, Kihara S, Funahashi T, Nakamura T, Nagaretani H, et al. Association of hypoadiponectinemia with impaired vasoreactivity. *Hypertension*. 2003; 42(3):231–234. [PubMed: 12860835]
23. Nystrom T, Gutniak MK, Zhang Q, Zhang F, Holst JJ, Ahren B, et al. Effects of glucagon-like peptide-1 on endothelial function in type 2 diabetes patients with stable coronary artery disease. *American journal of physiology. Endocrinology and metabolism*. 2004; 287(6):E1209–E1215. [PubMed: 15353407]
24. Basu A, Charkoudian N, Schrage W, Rizza RA, Basu R, Joyner MJ. Beneficial effects of GLP-1 on endothelial function in humans: dampening by glyburide but not by glimepiride. *American journal of physiology. Endocrinology and metabolism*. 2007; 293(5):E1289–E1295. [PubMed: 17711996]
25. Ceriello A, Esposito K, Testa R, Bonfigli AR, Marra M, Giugliano D. The possible protective role of glucagon-like peptide 1 on endothelium during the meal and evidence for an “endothelial resistance” to glucagon-like peptide 1 in diabetes. *Diabetes care*. 2011; 34(3):697–702. [PubMed: 21273492]
26. Esper RJ, Vilarino JO, Machado RA, Paragano A. Endothelial dysfunction in normal and abnormal glucose metabolism. *Advances in cardiology*. 2008; 45:17–43. [PubMed: 18230954]
27. Han KA, Patel Y, Lteif AA, Chisholm R, Mather KJ. Contributions of dysglycaemia, obesity, and insulin resistance to impaired endothelium-dependent vasodilation in humans. *Diabetes/ metabolism research and reviews*. 2011; 27(4):354–361. [PubMed: 21309061]
28. Williams SB, Goldfine AB, Timimi FK, Ting HH, Roddy MA, Simonson DC, et al. Acute hyperglycemia attenuates endothelium-dependent vasodilation in humans in vivo. *Circulation*. 1998; 97(17):1695–1701. [PubMed: 9591763]
29. Kawano H, Motoyama T, Hirashima O, Hirai N, Miyao Y, Sakamoto T, et al. Hyperglycemia rapidly suppresses flow-mediated endothelium-dependent vasodilation of brachial artery. *Journal of the American College of Cardiology*. 1999; 34(1):146–154. [PubMed: 10400004]
30. Vehkavaara S, Makimattila S, Schlenzka A, Vakkilainen J, Westerbacka J, Yki-Jarvinen H. Insulin therapy improves endothelial function in type 2 diabetes. *Arteriosclerosis, thrombosis, and vascular biology*. 2000; 20(2):545–550.

31. Joya-Galeana J, Fernandez M, Cervera A, Reyna S, Ghosh S, Triplitt C, et al. Effects of insulin and oral anti-diabetic agents on glucose metabolism, vascular dysfunction and skeletal muscle inflammation in type 2 diabetic subjects. *Diabetes/metabolism research and reviews*. 2011; 27(4): 373–382. [PubMed: 21309063]
32. Pistrosch F, Schaper F, Passauer J, Koehler C, Bornstein SR, Hanefeld M. Effects of the alpha glucosidase inhibitor acarbose on endothelial function after a mixed meal in newly diagnosed type 2 diabetes. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme*. 2009; 41(2):104–108. [PubMed: 19061152]
33. Emoto T, Sawada T, Hashimoto M, Kageyama H, Terashita D, Mizoguchi T, et al. Effect of 3-month repeated administration of miglitol on vascular endothelial function in patients with diabetes mellitus and coronary artery disease. *The American journal of cardiology*. 2012; 109(1): 42–46. [PubMed: 21944671]
34. Hiki M, Shimada K, Kiyanagi T, Fukao K, Hirose K, Ohsaka H, et al. Single administration of alpha-glucosidase inhibitors on endothelial function and incretin secretion in diabetic patients with coronary artery disease - Juntendo University trial: effects of miglitol on endothelial vascular reactivity in type 2 diabetic patients with coronary heart disease (J-MACH). *Circulation journal : official journal of the Japanese Circulation Society*. 2010; 74(7):1471–1478. [PubMed: 20519875]
35. Chiaasson JL. The effect of acarbose on insulin sensitivity in subjects with impaired glucose tolerance. *Diabetic medicine : a journal of the British Diabetic Association*. 1996; 13(3 Suppl 2):S23–24. [PubMed: 8689858]
36. Matsumoto K, Yano M, Miyake S, Ueki Y, Yamaguchi Y, Akazawa S, et al. Effects of voglibose on glycemic excursions, insulin secretion, and insulin sensitivity in non-insulin-treated NIDDM patients. *Diabetes care*. 1998; 21(2):256–260. [PubMed: 9539992]
37. Bhartia M, Tahrani AA, Barnett AH. SGLT-2 inhibitors in development for type 2 diabetes treatment. *The review of diabetic studies : RDS*. 2011; 8(3):348–354. [PubMed: 22262072]
38. Giannarelli R, Aragona M, Coppelli A, Del Prato S. Reducing insulin resistance with metformin: the evidence today. *Diabetes & metabolism*. 2003; 29(4 Pt 2):6S28–35. [PubMed: 14502098]
39. Radziuk J, Bailey CJ, Wiernsperger NF, Yudkin JS. Metformin and its liver targets in the treatment of type 2 diabetes. *Current drug targets. Immune, endocrine and metabolic disorders*. 2003; 3(2): 151–169.
40. Mather KJ, Verma S, Anderson TJ. Improved endothelial function with metformin in type 2 diabetes mellitus. *Journal of the American College of Cardiology*. 2001; 37(5):1344–1350. [PubMed: 11300445]
41. Diamanti-Kandarakis E, Alexandraki K, Protogerou A, Piperi C, Papamichael C, Aessopos A, et al. Metformin administration improves endothelial function in women with polycystic ovary syndrome. *European journal of endocrinology / European Federation of Endocrine Societies*. 2005; 152(5):749–756. [PubMed: 15879361]
42. Vitale C, Mercuro G, Cornoldi A, Fini M, Volterrani M, Rosano GM. Metformin improves endothelial function in patients with metabolic syndrome. *Journal of internal medicine*. 2005; 258(3):250–256. [PubMed: 16115299]
43. de Aguiar LG, Bahia LR, Villela N, Laflor C, Sicuro F, Wiernsperger N, et al. Metformin improves endothelial vascular reactivity in first-degree relatives of type 2 diabetic patients with metabolic syndrome and normal glucose tolerance. *Diabetes care*. 2006; 29(5):1083–1089. [PubMed: 16644641]
44. Natali A, Baldeweg S, Toschi E, Capaldo B, Barbaro D, Gastaldelli A, et al. Vascular effects of improving metabolic control with metformin or rosiglitazone in type 2 diabetes. *Diabetes care*. 2004; 27(6):1349–1357. [PubMed: 15161787]
45. Naka KK, Papathanassiou K, Bechlioulis A, Pappas K, Kazakos N, Kanioglou C, et al. Effects of pioglitazone and metformin on vascular endothelial function in patients with type 2 diabetes treated with sulfonylureas. *Diabetes & vascular disease research : official journal of the International Society of Diabetes and Vascular Disease*. 2012; 9(1):52–58.
46. Martens FM, Visseren FL, Lemay J, de Koning EJ, Rabelink TJ. Metabolic and additional vascular effects of thiazolidinediones. *Drugs*. 2002; 62(10):1463–1480. [PubMed: 12093315]

47. Pistrosch F, Passauer J, Fischer S, Fuecker K, Hanefeld M, Gross P. In type 2 diabetes, rosiglitazone therapy for insulin resistance ameliorates endothelial dysfunction independent of glucose control. *Diabetes care*. 2004; 27(2):484–490. [PubMed: 14747233]
48. Watanabe Y, Sunayama S, Shimada K, Sawano M, Hoshi S, Iwama Y, et al. Troglitazone improves endothelial dysfunction in patients with insulin resistance. *Journal of atherosclerosis and thrombosis*. 2000; 7(3):159–163. [PubMed: 11480457]
49. Caballero AE, Saouaf R, Lim SC, Hamdy O, Abou-Elenin K, O'Connor C, et al. The effects of troglitazone, an insulin-sensitizing agent, on the endothelial function in early and late type 2 diabetes: a placebo-controlled randomized clinical trial. *Metabolism: clinical and experimental*. 2003; 52(2):173–180. [PubMed: 12601628]
50. Wang TD, Chen WJ, Lin JW, Chen MF, Lee YT. Effects of rosiglitazone on endothelial function, C-reactive protein, and components of the metabolic syndrome in nondiabetic patients with the metabolic syndrome. *The American journal of cardiology*. 2004; 93(3):362–365. [PubMed: 14759393]
51. Forst T, Lubben G, Hohberg C, Kann P, Sachara C, Gottschall V, et al. Influence of glucose control and improvement of insulin resistance on microvascular blood flow and endothelial function in patients with diabetes mellitus type 2. *Microcirculation*. 2005; 12(7):543–550. [PubMed: 16207627]
52. Martens FM, Visseren FL, de Koning EJ, Rabelink TJ. Short-term pioglitazone treatment improves vascular function irrespective of metabolic changes in patients with type 2 diabetes. *Journal of cardiovascular pharmacology*. 2005; 46(6):773–778. [PubMed: 16306801]
53. Tsuchiya K, Akaza I, Yoshimoto T, Hirata Y. Pioglitazone improves endothelial function with increased adiponectin and high-density lipoprotein cholesterol levels in type 2 diabetes. *Endocrine journal*. 2009; 56(5):691–698. [PubMed: 19506330]
54. Esposito K, Ciotola M, Carleo D, Schisano B, Saccomanno F, Sasso FC, et al. Effect of rosiglitazone on endothelial function and inflammatory markers in patients with the metabolic syndrome. *Diabetes care*. 2006; 29(5):1071–1076. [PubMed: 16644639]
55. Goya K, Sumitani S, Otsuki M, Xu X, Yamamoto H, Kurebayashi S, et al. The thiazolidinedione drug troglitazone up-regulates nitric oxide synthase expression in vascular endothelial cells. *Journal of diabetes and its complications*. 2006; 20(5):336–342. [PubMed: 16949522]
56. Wang CH, Ting MK, Verma S, Kuo LT, Yang NI, Hsieh IC, et al. Pioglitazone increases the numbers and improves the functional capacity of endothelial progenitor cells in patients with diabetes mellitus. *American heart journal*. 2006; 152(6):1051, e1051–1058.
57. Kelly AS, Thelen AM, Kaiser DR, Gonzalez-Campoy JM, Bank AJ. Rosiglitazone improves endothelial function and inflammation but not asymmetric dimethylarginine or oxidative stress in patients with type 2 diabetes mellitus. *Vascular medicine*. 2007; 12(4):311–318. [PubMed: 18048467]
58. Rudofsky G, Jr. Reismann P, Grafe IA, Konrade I, Djuric Z, Tafel J, et al. Improved vascular function upon pioglitazone treatment in type 2 diabetes is not associated with changes in mononuclear NF-kappaB binding activity. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme*. 2007; 39(9):665–671. [PubMed: 17846974]
59. Patel SR, Mailloux LM, Coppola JT, Mindrescu C, Staniloae CS. Pioglitazone increases adiponectin levels in nondiabetic patients with coronary artery disease. *Coronary artery disease*. 2008; 19(5):349–353. [PubMed: 18580598]
60. Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, Baron AD. Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. *The Journal of clinical investigation*. 1996; 97(11):2601–2610. [PubMed: 8647954]
61. de Kreutzenberg SV, Crepaldi C, Marchetto S, Calo L, Tiengo A, Del Prato S, et al. Plasma free fatty acids and endothelium-dependent vasodilation: effect of chain-length and cyclooxygenase inhibition. *The Journal of clinical endocrinology and metabolism*. 2000; 85(2):793–798. [PubMed: 10690892]
62. Steinberg HO, Tarshoby M, Monestel R, Hook G, Cronin J, Johnson A, et al. Elevated circulating free fatty acid levels impair endothelium-dependent vasodilation. *The Journal of clinical investigation*. 1997; 100(5):1230–1239. [PubMed: 9276741]

63. de Jongh RT, Serne EH, Ijzerman RG, de Vries G, Stehouwer CD. Free fatty acid levels modulate microvascular function: relevance for obesity-associated insulin resistance, hypertension, and microangiopathy. *Diabetes*. 2004; 53(11):2873–2882. [PubMed: 15504968]
64. Lovisolo PP, Briatico-Vangosa G, Orsini G, Ronchi R, Angelucci R, Valzelli G. Pharmacological profile of a new anti-lipolytic agent: 5-methylpyrazine-2-carboxylic acid 4-oxide (acipimox) (1) I - Mechanism of action. *Pharmacological research communications*. 1981; 13(2):151–161. [PubMed: 6261266]
65. Avogaro A, Miola M, Favaro A, Gottardo L, Pacini G, Manzato E, et al. Gemfibrozil improves insulin sensitivity and flow-mediated vasodilatation in type 2 diabetic patients. *European journal of clinical investigation*. 2001; 31(7):603–609. [PubMed: 11454015]
66. Kamanna VS, Kashyap ML. Mechanism of action of niacin. *The American journal of cardiology*. 2008; 101(8A):20B–26B. [PubMed: 18157959]
67. Lukasova M, Hanson J, Tunaru S, Offermanns S. Nicotinic acid (niacin): new lipid-independent mechanisms of action and therapeutic potentials. *Trends in pharmacological sciences*. 2011; 32(12):700–707. [PubMed: 21944259]
68. Andrews TC, Whitney EJ, Green G, Kalenian R, Personius BE. Effect of gemfibrozil +/- niacin +/- cholestyramine on endothelial function in patients with serum low-density lipoprotein cholesterol levels <160 mg/dl and high-density lipoprotein cholesterol levels <40 mg/dl. *The American journal of cardiology*. 1997; 80(7):831–835. [PubMed: 9381993]
69. Warnholtz A, Wild P, Ostad MA, Elsnér V, Stieber F, Schinzel R, et al. Effects of oral niacin on endothelial dysfunction in patients with coronary artery disease: results of the randomized, double-blind, placebo-controlled INEF study. *Atherosclerosis*. 2009; 204(1):216–221. [PubMed: 18822413]
70. Johnston P, Hollenbeck C, Sheu W, Chen YD, Reaven GM. Acute changes in plasma non-esterified fatty acid concentration do not change hepatic glucose production in people with type 2 diabetes. *Diabetic medicine : a journal of the British Diabetic Association*. 1990; 7(10):871–875. [PubMed: 2149683]
71. Alvarsson M, Grill V. Impact of nicotinic acid treatment on insulin secretion and insulin sensitivity in low and high insulin responders. *Scandinavian journal of clinical and laboratory investigation*. 1996; 56(6):563–570. [PubMed: 8903118]
72. Kelly JJ, Lawson JA, Campbell LV, Storlien LH, Jenkins AB, Whitworth JA, et al. Effects of nicotinic acid on insulin sensitivity and blood pressure in healthy subjects. *Journal of human hypertension*. 2000; 14(9):567–572. [PubMed: 10980588]
73. Shearer GC, Savinova OV, Harris WS. Fish oil -- how does it reduce plasma triglycerides? *Biochimica et biophysica acta*. 2012; 1821(5):843–851. [PubMed: 22041134]
74. Rivellese AA, Maffettone A, Iovine C, Di Marino L, Annuzzi G, Mancini M, et al. Long-term effects of fish oil on insulin resistance and plasma lipoproteins in NIDDM patients with hypertriglyceridemia. *Diabetes care*. 1996; 19(11):1207–1213. [PubMed: 8908381]
75. Muurling M, Mensink RP, Pijl H, Romijn JA, Havekes LM, Voshol PJ. A fish oil diet does not reverse insulin resistance despite decreased adipose tissue TNF-alpha protein concentration in ApoE-3*Leiden mice. *The Journal of nutrition*. 2003; 133(11):3350–3355. [PubMed: 14608043]
76. McVeigh GE, Brennan GM, Johnston GD, McDermott BJ, McGrath LT, Henry WR, et al. Dietary fish oil augments nitric oxide production or release in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia*. 1993; 36(1):33–38. [PubMed: 8436250]
77. Mori TA, Watts GF, Burke V, Hilme E, Puddey IB, Beilin LJ. Differential effects of eicosapentaenoic acid and docosahexaenoic acid on vascular reactivity of the forearm microcirculation in hyperlipidemic, overweight men. *Circulation*. 2000; 102(11):1264–1269. [PubMed: 10982541]
78. Rizza S, Tesauro M, Cardillo C, Galli A, Iantorno M, Gigli F, et al. Fish oil supplementation improves endothelial function in normoglycemic offspring of patients with type 2 diabetes. *Atherosclerosis*. 2009; 206(2):569–574. [PubMed: 19394939]
79. Eckel RH, Wassef M, Chait A, Sobel B, Barrett E, King G, et al. Prevention Conference VI: Diabetes and Cardiovascular Disease: Writing Group II: pathogenesis of atherosclerosis in diabetes. *Circulation*. 2002; 105(18):e138–143. [PubMed: 11994264]

80. Natali A, Toschi E, Baldeweg S, Ciociaro D, Favilla S, Sacca L, et al. Clustering of insulin resistance with vascular dysfunction and low-grade inflammation in type 2 diabetes. *Diabetes*. 2006; 55(4):1133–1140. [PubMed: 16567539]
81. Nystrom T, Nygren A, Sjöholm A. Increased levels of tumour necrosis factor- α (TNF- α) in patients with Type II diabetes mellitus after myocardial infarction are related to endothelial dysfunction. *Clinical science*. 2006; 110(6):673–681. [PubMed: 16466346]
82. Gokulakrishnan K, Deepa R, Mohan V. Association of high sensitivity C-reactive protein (hsCRP) and tumour necrosis factor- α (TNF- α) with carotid intimal medial thickness in subjects with different grades of glucose intolerance—the Chennai Urban Rural Epidemiology Study (CURES-31). *Clinical biochemistry*. 2008; 41(7-8):480–485. [PubMed: 18328265]
83. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor- α : direct role in obesity-linked insulin resistance. *Science*. 1993; 259(5091):87–91. [PubMed: 7678183]
84. Hotamisligil GS, Spiegelman BM. Tumor necrosis factor α : a key component of the obesity-diabetes link. *Diabetes*. 1994; 43(11):1271–1278. [PubMed: 7926300]
85. Patel JN, Jager A, Schalkwijk C, Corder R, Douthwaite JA, Yudkin JS, et al. Effects of tumour necrosis factor- α in the human forearm: blood flow and endothelin-1 release. *Clinical science*. 2002; 103(4):409–415. [PubMed: 12241541]
86. Rask-Madsen C, Dominguez H, Ihlemann N, Hermann T, Kober L, Torp-Pedersen C. Tumor necrosis factor- α inhibits insulin's stimulating effect on glucose uptake and endothelium-dependent vasodilation in humans. *Circulation*. 2003; 108(15):1815–1821. [PubMed: 14530204]
87. Kim F, Tysseling KA, Rice J, Pham M, Haji L, Gallis BM, et al. Free fatty acid impairment of nitric oxide production in endothelial cells is mediated by IKK β . *Arteriosclerosis, thrombosis, and vascular biology*. 2005; 25(5):989–994.
88. Harvey KA, Walker CL, Pavlina TM, Xu Z, Zaloga GP, Siddiqui RA. Long-chain saturated fatty acids induce pro-inflammatory responses and impact endothelial cell growth. *Clinical nutrition*. 2010; 29(4):492–500. [PubMed: 19926177]
89. Nitenberg A, Cosson E, Pham I. Postprandial endothelial dysfunction: role of glucose, lipids and insulin. *Diabetes & metabolism*. 2006; 32:2S28–33. Spec No2. [PubMed: 17375404]
90. Lalla E, Lamster IB, Stern DM, Schmidt AM. Receptor for advanced glycation end products, inflammation, and accelerated periodontal disease in diabetes: mechanisms and insights into therapeutic modalities. *Annals of periodontology / the American Academy of Periodontology*. 2001; 6(1):113–118. [PubMed: 11887453]
91. Dominguez H, Storgaard H, Rask-Madsen C, Steffen Hermann T, Ihlemann N, Baunbjerg Nielsen D, et al. Metabolic and vascular effects of tumor necrosis factor- α blockade with etanercept in obese patients with type 2 diabetes. *Journal of vascular research*. 2005; 42(6):517–525. [PubMed: 16155368]
92. Gonzalez-Gay MA, De Matias JM, Gonzalez-Juanatey C, Garcia-Porrua C, Sanchez-Andrade A, Martin J, et al. Anti-tumor necrosis factor- α blockade improves insulin resistance in patients with rheumatoid arthritis. *Clinical and experimental rheumatology*. 2006; 24(1):83–86. [PubMed: 16539824]
93. Koutroubakis IE, Oustamanolakis P, Malliaraki N, Karmiris K, Chalkiadakis I, Ganotakis E, et al. Effects of tumor necrosis factor α inhibition with infliximab on lipid levels and insulin resistance in patients with inflammatory bowel disease. *European journal of gastroenterology & hepatology*. 2009; 21(3):283–288. [PubMed: 19279474]
94. Marra M, Campanati A, Testa R, Sirolla C, Bonfigli AR, Franceschi C, et al. Effect of etanercept on insulin sensitivity in nine patients with psoriasis. *International journal of immunopathology and pharmacology*. 2007; 20(4):731–736. [PubMed: 18179745]
95. Stanley TL, Zanni MV, Johnsen S, Rasheed S, Makimura H, Lee H, et al. TNF- α antagonism with etanercept decreases glucose and increases the proportion of high molecular weight adiponectin in obese subjects with features of the metabolic syndrome. *The Journal of clinical endocrinology and metabolism*. 2011; 96(1):E146–150. [PubMed: 21047923]
96. Yazdani-Biuki B, Stelzl H, Brezinschek HP, Hermann J, Mueller T, Krippel P, et al. Improvement of insulin sensitivity in insulin resistant subjects during prolonged treatment with the anti-TNF-

- alpha antibody infliximab. *European journal of clinical investigation*. 2004; 34(9):641–642. [PubMed: 15379764]
97. Di Rocco P, Manco M, Rosa G, Greco AV, Mingrone G. Lowered tumor necrosis factor receptors, but not increased insulin sensitivity, with infliximab. *Obesity research*. 2004; 12(4):734–739. [PubMed: 15090644]
 98. Ferraz-Amaro I, Arce-Franco M, Muniz J, Lopez-Fernandez J, Hernandez-Hernandez V, Franco A, et al. Systemic blockade of TNF-alpha does not improve insulin resistance in humans. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme*. 2011; 43(11):801–808. [PubMed: 22009376]
 99. Martinez-Abundis E, Reynoso-von Drateln C, Hernandez-Salazar E, Gonzalez-Ortiz M. Effect of etanercept on insulin secretion and insulin sensitivity in a randomized trial with psoriatic patients at risk for developing type 2 diabetes mellitus. *Archives of dermatological research*. 2007; 299(9): 461–465. [PubMed: 17726611]
 100. Hurlimann D, Forster A, Noll G, Enseleit F, Chenevard R, Distler O, et al. Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. *Circulation*. 2002; 106(17):2184–2187. [PubMed: 12390945]
 101. Gonzalez-Juanatey C, Testa A, Garcia-Castelo A, Garcia-Porrúa C, Llorca J, Gonzalez-Gay MA. Active but transient improvement of endothelial function in rheumatoid arthritis patients undergoing long-term treatment with anti-tumor necrosis factor alpha antibody. *Arthritis and rheumatism*. 2004; 51(3):447–450. [PubMed: 15188332]
 102. Cardillo C, Schinzari F, Mores N, Mettimano M, Melina D, Zoli A, et al. Intravascular tumor necrosis factor alpha blockade reverses endothelial dysfunction in rheumatoid arthritis. *Clinical pharmacology and therapeutics*. 2006; 80(3):275–281. [PubMed: 16952494]
 103. Bosello S, Santoliquido A, Zoli A, Di Campli C, Flore R, Tondi P, et al. TNF-alpha blockade induces a reversible but transient effect on endothelial dysfunction in patients with long-standing severe rheumatoid arthritis. *Clinical rheumatology*. 2008; 27(7):833–839. [PubMed: 18075712]
 104. Schinzari F, Armuzzi A, De Pascalis B, Mores N, Tesaro M, Melina D, et al. Tumor necrosis factor-alpha antagonism improves endothelial dysfunction in patients with Crohn's disease. *Clinical pharmacology and therapeutics*. 2008; 83(1):70–76. [PubMed: 17507924]
 105. Wascher TC, Lindeman JH, Sourij H, Kooistra T, Pacini G, Roden M. Chronic TNF-alpha neutralization does not improve insulin resistance or endothelial function in “healthy” men with metabolic syndrome. *Molecular medicine*. 2011; 17(3-4):189–193. [PubMed: 21103669]
 106. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *The Journal of clinical investigation*. 2006; 116(7):1793–1801. [PubMed: 16823477]
 107. Fleischman A, Shoelson SE, Bernier R, Goldfine AB. Salsalate improves glycemia and inflammatory parameters in obese young adults. *Diabetes care*. 2008; 31(2):289–294. [PubMed: 17959861]
 108. Goldfine AB, Silver R, Aldhahi W, Cai D, Tatro E, Lee J, et al. Use of salsalate to target inflammation in the treatment of insulin resistance and type 2 diabetes. *Clinical and translational science*. 2008; 1(1):36–43. [PubMed: 19337387]
 109. Goldfine AB, Fonseca V, Jablonski KA, Pyle L, Staten MA, Shoelson SE. The effects of salsalate on glycemic control in patients with type 2 diabetes: a randomized trial. *Annals of internal medicine*. 2010; 152(6):346–357. [PubMed: 20231565]
 110. Gupta SK, Johnson RM, Saha C, Mather KJ, Greenwald ML, Waltz JS, et al. Improvement in HIV-related endothelial dysfunction using the anti-inflammatory agent salsalate: a pilot study. *AIDS*. 2008; 22(5):653–655. [PubMed: 18317009]
 111. Pierce GL, Lesniewski LA, Lawson BR, Beske SD, Seals DR. Nuclear factor- κ B activation contributes to vascular endothelial dysfunction via oxidative stress in overweight/obese middle-aged and older humans. *Circulation*. 2009; 119(9):1284–1292. [PubMed: 19237660]
 112. Schmidt AM, Yan SD, Yan SF, Stern DM. The biology of the receptor for advanced glycation end products and its ligands. *Biochimica et biophysica acta*. 2000; 1498(2-3):99–111. [PubMed: 11108954]

113. Rashid G, Benchetrit S, Fishman D, Bernheim J. Effect of advanced glycation end-products on gene expression and synthesis of TNF-alpha and endothelial nitric oxide synthase by endothelial cells. *Kidney international*. 2004; 66(3):1099–1106. [PubMed: 15327404]
114. Soro-Paavonen A, Zhang WZ, Venardos K, Coughlan MT, Harris E, Tong DC, et al. Advanced glycation end-products induce vascular dysfunction via resistance to nitric oxide and suppression of endothelial nitric oxide synthase. *Journal of hypertension*. 2010; 28(4):780–788. [PubMed: 20186099]
115. van Poppel PC, Netea MG, Smits P, Tack CJ. Vildagliptin improves endothelium-dependent vasodilatation in type 2 diabetes. *Diabetes care*. 2011; 34(9):2072–2077. [PubMed: 21788633]
116. Matsui T, Yamagishi S, Ueda S, Nakamura K, Imaizumi T, Takeuchi M, et al. Telmisartan, an angiotensin II type 1 receptor blocker, inhibits advanced glycation end-product (AGE)-induced monocyte chemoattractant protein-1 expression in mesangial cells through downregulation of receptor for AGEs via peroxisome proliferator-activated receptor-gamma activation. *The Journal of international medical research*. 2007; 35(4):482–489. [PubMed: 17697525]
117. Freidja ML, Tarhouni K, Toutain B, Fassot C, Loufrani L, Henrion D. The AGE-breaker ALT-711 restores high blood flow-dependent remodeling in mesenteric resistance arteries in a rat model of type 2 diabetes. *Diabetes*. 2012; 61(6):1562–1572. [PubMed: 22415880]
118. Kranstuber AL, Del Rio C, Biesiadecki BJ, Hamlin RL, Ottobre J, Gyorke S, et al. Advanced glycation end product cross-link breaker attenuates diabetes-induced cardiac dysfunction by improving sarcoplasmic reticulum calcium handling. *Frontiers in physiology*. 2012; 3:292. [PubMed: 22934044]
119. Hartog JW, Willemsen S, van Veldhuisen DJ, Pasma JL, van Wijk LM, Hummel YM, et al. Effects of alagebrium, an advanced glycation endproduct breaker, on exercise tolerance and cardiac function in patients with chronic heart failure. *European journal of heart failure*. 2011; 13(8):899–908. [PubMed: 21669961]
120. Zieman SJ, Melenovsky V, Clattenburg L, Corretti MC, Capriotti A, Gerstenblith G, et al. Advanced glycation endproduct crosslink breaker (alagebrium) improves endothelial function in patients with isolated systolic hypertension. *Journal of hypertension*. 2007; 25(3):577–583. [PubMed: 17278974]
121. Stirban A, Negrean M, Stratmann B, Gawlowski T, Horstmann T, Gotting C, et al. Benfotiamine prevents macro- and microvascular endothelial dysfunction and oxidative stress following a meal rich in advanced glycation end products in individuals with type 2 diabetes. *Diabetes care*. 2006; 29(9):2064–2071. [PubMed: 16936154]
122. Higashi Y, Oshima T, Sasaki N, Ishioka N, Nakano Y, Ozono R, et al. Relationship between insulin resistance and endothelium-dependent vascular relaxation in patients with essential hypertension. *Hypertension*. 1997; 29(1 Pt 2):280–285. [PubMed: 9039115]
123. Tooke J. The association between insulin resistance and endotheliopathy. *Diabetes, obesity & metabolism*. 1999; 1(Suppl 1):S17–22.
124. Taddei S, Virdis A, Ghiadoni L, Sudano I, Salvetti A. Antihypertensive drugs and reversing of endothelial dysfunction in hypertension. *Current hypertension reports*. 2000; 2(1):64–70. [PubMed: 10981130]
125. Tezcan H, Yavuz D, Toprak A, Akpınar I, Koc M, Deyneli O, et al. Effect of angiotensin-converting enzyme inhibition on endothelial function and insulin sensitivity in hypertensive patients. *Journal of the renin-angiotensin-aldosterone system : JRAAS*. 2003; 4(2):119–123.
126. Yavuz D, Koc M, Toprak A, Akpınar I, Velioglu A, Deyneli O, et al. Effects of ACE inhibition and AT1-receptor antagonism on endothelial function and insulin sensitivity in essential hypertensive patients. *Journal of the renin-angiotensin-aldosterone system : JRAAS*. 2003; 4(3):197–203. [PubMed: 14608527]
127. Tomiyama H, Yambe M, Yamada J, Motobe K, Koji Y, Yoshida M, et al. Discrepancy between improvement of insulin sensitivity and that of arterial endothelial function in patients receiving antihypertensive medication. *Journal of hypertension*. 2007; 25(4):883–889. [PubMed: 17351383]
128. Chou CL, Pang CY, Lee TJ, Fang TC. Direct renin inhibitor prevents and ameliorates insulin resistance, aortic endothelial dysfunction and vascular remodeling in fructose-fed hypertensive rats. *Hypertension research : official journal of the Japanese Society of Hypertension*. 2012

129. Lteif AA, Chisholm RL, Gilbert K, Considine RV, Mather KJ. Effects of losartan on whole body, skeletal muscle and vascular insulin responses in obesity/insulin resistance without hypertension. *Diabetes, obesity & metabolism*. 2012; 14(3):254–261.
130. Hermann TS, Li W, Dominguez H, Ihlemann N, Rask-Madsen C, Major-Pedersen A, et al. Quinapril treatment increases insulin-stimulated endothelial function and adiponectin gene expression in patients with type 2 diabetes. *The Journal of clinical endocrinology and metabolism*. 2006; 91(3):1001–1008. [PubMed: 16352688]
131. Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet*. 2008; 371(9607):117–125. [PubMed: 18191683]
132. Economides PA, Caselli A, Tiani E, Khaodhiar L, Horton ES, Veves A. The effects of atorvastatin on endothelial function in diabetic patients and subjects at risk for type 2 diabetes. *The Journal of clinical endocrinology and metabolism*. 2004; 89(2):740–747. [PubMed: 14764790]
133. Beishuizen ED, Tamsma JT, Jukema JW, van de Ree MA, van der Vijver JC, Meinders AE, et al. The effect of statin therapy on endothelial function in type 2 diabetes without manifest cardiovascular disease. *Diabetes Care*. 2005; 28(7):1668–1674. [PubMed: 15983318]
134. Koh KK, Quon MJ, Han SH, Lee Y, Ahn JY, Kim SJ, et al. Simvastatin improves flow-mediated dilation but reduces adiponectin levels and insulin sensitivity in hypercholesterolemic patients. *Diabetes care*. 2008; 31(4):776–782. [PubMed: 18184901]
135. Kater AL, Batista MC, Ferreira SR. Improved endothelial function with simvastatin but unchanged insulin sensitivity with simvastatin or ezetimibe. *Metabolism: clinical and experimental*. 2010; 59(6):921–926. [PubMed: 20199786]
136. Paradisi G, Bracaglia M, Basile F, Di'Ipolito S, Di Nicuolo F, Ianniello F, et al. Effect of pravastatin on endothelial function and endothelial progenitor cells in healthy postmenopausal women. *Clinical and experimental obstetrics & gynecology*. 2012; 39(2):153–159.
137. Culver AL, Ockene IS, Balasubramanian R, Olendzki BC, Sepavich DM, Wactawski-Wende J, et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. *Archives of internal medicine*. 2012; 172(2):144–152. [PubMed: 22231607]
138. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet*. 2012; 380(9841):565–571. [PubMed: 22883507]
139. Waters DD, Ho JE, Boekholdt SM, Demicco DA, Kastelein JJ, Messig M, et al. Cardiovascular Event Reduction Versus New-Onset Diabetes During Atorvastatin Therapy: Effect of Baseline Risk Factors for Diabetes. *Journal of the American College of Cardiology*. 2012
140. Zaharan NL, Williams D, Bennett K. Statins and Risk of Treated Incident Diabetes in a Primary Care Population. *British journal of clinical pharmacology*. 2012
141. Vanhoutte PM. Endothelium and control of vascular function. State of the Art lecture. *Hypertension*. 1989; 13(6 Pt 2):658–667. [PubMed: 2661425]
142. Luscher TF, Yang Z, Tschudi M, von Segesser L, Stulz P, Boulanger C, et al. Interaction between endothelin-1 and endothelium-derived relaxing factor in human arteries and veins. *Circulation research*. 1990; 66(4):1088–1094. [PubMed: 2180587]
143. Park JY, Takahara N, Gabriele A, Chou E, Naruse K, Suzuma K, et al. Induction of endothelin-1 expression by glucose: an effect of protein kinase C activation. *Diabetes*. 2000; 49(7):1239–1248. [PubMed: 10909984]
144. Piatti PM, Monti LD, Conti M, Baruffaldi L, Galli L, Phan CV, et al. Hypertriglyceridemia and hyperinsulinemia are potent inducers of endothelin-1 release in humans. *Diabetes*. 1996; 45(3):316–321. [PubMed: 8593936]
145. Seljeflot I, Moan A, Aspelin T, Tonnessen T, Kjeldsen SE, Arnesen H. Circulating levels of endothelin-1 during acute hyperinsulinemia in patients with essential hypertension treated with type 1 angiotensin receptor antagonist or placebo. *Metabolism: clinical and experimental*. 1998; 47(3):292–296. [PubMed: 9500565]

146. Guo JP, Siegfried MR, Lefer AM. Endothelial preserving actions of a nitric oxide donor in carotid arterial intimal injury. *Methods and findings in experimental and clinical pharmacology*. 1994; 16(5):347–354. [PubMed: 7934313]
147. Liu GL, Christopher TA, Lopez BL, Gao F, Guo Y, Gao E, et al. SP/W-5186, A cysteine-containing nitric oxide donor, attenuates postischemic myocardial injury. *The Journal of pharmacology and experimental therapeutics*. 1998; 287(2):527–537. [PubMed: 9808677]
148. Rossoni G, Manfredi B, Del Soldato P, Berti F. NCX 4016, a nitric oxide-releasing aspirin, modulates adrenergic vasoconstriction in the perfused rat tail artery. *British journal of pharmacology*. 2002; 137(2):229–236. [PubMed: 12208780]
149. Durante W, Johnson FK, Johnson RA. Arginase: a critical regulator of nitric oxide synthesis and vascular function. *Clinical and experimental pharmacology & physiology*. 2007; 34(9):906–911. [PubMed: 17645639]
150. Shemyakin A, Kovamees O, Rafnsson A, Bohm F, Svenarud P, Settergren M, et al. Arginase Inhibition Improves Endothelial Function in Patients with Coronary Artery Disease and Type 2 Diabetes. *Circulation*. 2012
151. Heitzer T, Krohn K, Albers S, Meinertz T. Tetrahydrobiopterin improves endothelium-dependent vasodilation by increasing nitric oxide activity in patients with Type II diabetes mellitus. *Diabetologia*. 2000; 43(11):1435–1438. [PubMed: 11126415]
152. Meininger CJ, Cai S, Parker JL, Channon KM, Kelly KA, Becker EJ, et al. GTP cyclohydrolase I gene transfer reverses tetrahydrobiopterin deficiency and increases nitric oxide synthesis in endothelial cells and isolated vessels from diabetic rats. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. 2004; 18(15):1900–1902. [PubMed: 15467010]
153. Nystrom T, Nygren A, Sjöholm A. Tetrahydrobiopterin increases insulin sensitivity in patients with type 2 diabetes and coronary heart disease. *American journal of physiology. Endocrinology and metabolism*. 2004; 287(5):E919–925. [PubMed: 15265759]
154. Fard A, Tuck CH, Donis JA, Sciacca R, Di Tullio MR, Wu HD, et al. Acute elevations of plasma asymmetric dimethylarginine and impaired endothelial function in response to a high-fat meal in patients with type 2 diabetes. *Arteriosclerosis, thrombosis, and vascular biology*. 2000; 20(9):2039–2044.
155. Toutouzas K, Riga M, Stefanadi E, Stefanadis C. Asymmetric dimethylarginine (ADMA) and other endogenous nitric oxide synthase (NOS) inhibitors as an important cause of vascular insulin resistance. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et métabolisme*. 2008; 40(9):655–659. [PubMed: 18792879]
156. Sciacqua A, Grillo N, Quero M, Sesti G, Perticone F. Asymmetric dimethylarginine plasma levels and endothelial function in newly diagnosed type 2 diabetic patients. *International journal of molecular sciences*. 2012; 13(11):13804–13815. [PubMed: 23203035]
157. Tang WJ, Hu CP, Chen MF, Deng PY, Li YJ. Epigallocatechin gallate preserves endothelial function by reducing the endogenous nitric oxide synthase inhibitor level. *Canadian journal of physiology and pharmacology*. 2006; 84(2):163–171. [PubMed: 16900942]
158. Yang TL, Chen MF, Xia X, Luo BL, Li YJ. Effect of fenofibrate on the level of asymmetric dimethylarginine in individuals with hypertriglyceridemia. *European journal of clinical pharmacology*. 2006; 62(3):179–184. [PubMed: 16447050]
159. Tomiyama H, Yamada J, Koji Y, Shiina K, Yoshida M, Yamashina A. Effect of telmisartan on forearm postischemic hyperemia and serum asymmetric dimethylarginine levels. *American journal of hypertension*. 2007; 20(12):1305–1311. [PubMed: 18047921]
160. Young JM, Strey CH, George PM, Florkowski CM, Sies CW, Frampton CM, et al. Effect of atorvastatin on plasma levels of asymmetric dimethylarginine in patients with non-ischaemic heart failure. *European journal of heart failure*. 2008; 10(5):463–466. [PubMed: 18430606]
161. Aversa A, Greco E, Bruzziches R, Pili M, Rosano G, Spera G. Relationship between chronic tadalafil administration and improvement of endothelial function in men with erectile dysfunction: a pilot study. *International journal of impotence research*. 2007; 19(2):200–207. [PubMed: 16943794]

162. Aversa A, Vitale C, Volterrani M, Fabbri A, Spera G, Fini M, et al. Chronic administration of Sildenafil improves markers of endothelial function in men with Type 2 diabetes. *Diabetic medicine : a journal of the British Diabetic Association*. 2008; 25(1):37–44. [PubMed: 18199130]
163. Yamashiro K, Milsom AB, Duchene J, Panayiotou C, Urabe T, Hattori N, et al. Alterations in nitric oxide and endothelin-1 bioactivity underlie cerebrovascular dysfunction in ApoE-deficient mice. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2010; 30(8):1494–1503. [PubMed: 20234380]
164. Mather KJ, Mirzamohammadi B, Lteif A, Steinberg HO, Baron AD. Endothelin contributes to basal vascular tone and endothelial dysfunction in human obesity and type 2 diabetes. *Diabetes*. 2002; 51(12):3517–3523. [PubMed: 12453909]
165. Shemyakin A, Bohm F, Wagner H, Efendic S, Bavenholm P, Pernow J. Enhanced endothelium-dependent vasodilatation by dual endothelin receptor blockade in individuals with insulin resistance. *Journal of cardiovascular pharmacology*. 2006; 47(3):385–390. [PubMed: 16633080]
166. Rafnsson A, Bohm F, Settergren M, Gonon A, Brismar K, Pernow J. The endothelin receptor antagonist bosentan improves peripheral endothelial function in patients with type 2 diabetes mellitus and microalbuminuria: a randomised trial. *Diabetologia*. 2012; 55(3):600–607. [PubMed: 22200728]
167. Miller AW, Tulbert C, Puskar M, Busija DW. Enhanced endothelin activity prevents vasodilation to insulin in insulin resistance. *Hypertension*. 2002; 40(1):78–82. [PubMed: 12105142]
168. Ahlborg G, Shemyakin A, Bohm F, Gonon A, Pernow J. Dual endothelin receptor blockade acutely improves insulin sensitivity in obese patients with insulin resistance and coronary artery disease. *Diabetes Care*. 2007; 30(3):591–596. [PubMed: 17327326]
169. Lteif A, Vaishnav P, Baron AD, Mather KJ. Endothelin limits insulin action in obese/insulin-resistant humans. *Diabetes*. 2007; 56(3):728–734. [PubMed: 17327443]
170. Lorenz M, Wessler S, Follmann E, Michaelis W, Dusterhoft T, Baumann G, et al. A constituent of green tea, epigallocatechin-3-gallate, activates endothelial nitric oxide synthase by a phosphatidylinositol-3-OH-kinase-, cAMP-dependent protein kinase-, and Akt-dependent pathway and leads to endothelial-dependent vasorelaxation. *The Journal of biological chemistry*. 2004; 279(7):6190–6195. [PubMed: 14645258]
171. Kim JA, Formoso G, Li Y, Potenza MA, Marasciulo FL, Montagnani M, et al. Epigallocatechin gallate, a green tea polyphenol, mediates NO-dependent vasodilation using signaling pathways in vascular endothelium requiring reactive oxygen species and Fyn. *The Journal of biological chemistry*. 2007; 282(18):13736–13745. [PubMed: 17363366]
172. Potenza MA, Marasciulo FL, Tarquinio M, Tiravanti E, Colantuono G, Federici A, et al. EGCG, a green tea polyphenol, improves endothelial function and insulin sensitivity, reduces blood pressure, and protects against myocardial I/R injury in SHR. *American journal of physiology. Endocrinology and metabolism*. 2007; 292(5):E1378–1387. [PubMed: 17227956]
173. Kim W, Jeong MH, Cho SH, Yun JH, Chae HJ, Ahn YK, et al. Effect of green tea consumption on endothelial function and circulating endothelial progenitor cells in chronic smokers. *Circulation journal : official journal of the Japanese Circulation Society*. 2006; 70(8):1052–1057. [PubMed: 16864941]
174. Alexopoulos N, Vlachopoulos C, Aznaouridis K, Baou K, Vasiliadou C, Pietri P, et al. The acute effect of green tea consumption on endothelial function in healthy individuals. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*. 2008; 15(3):300–305.
175. Miller RJ, Jackson KG, Dadd T, Mayes AE, Brown AL, Minihane AM. The impact of the catechol-O-methyltransferase genotype on the acute responsiveness of vascular reactivity to a green tea extract. *The British journal of nutrition*. 2011; 105(8):1138–1144. [PubMed: 21144097]
176. Formoso G, Chen H, Kim JA, Montagnani M, Consoli A, Quon MJ. Dehydroepiandrosterone mimics acute actions of insulin to stimulate production of both nitric oxide and endothelin 1 via distinct phosphatidylinositol 3-kinase- and mitogen-activated protein kinase-dependent pathways in vascular endothelium. *Molecular endocrinology*. 2006; 20(5):1153–1163. [PubMed: 16373398]

177. Kawano H, Yasue H, Kitagawa A, Hirai N, Yoshida T, Soejima H, et al. Dehydroepiandrosterone supplementation improves endothelial function and insulin sensitivity in men. *The Journal of clinical endocrinology and metabolism*. 2003; 88(7):3190–3195. [PubMed: 12843164]
178. Mieczkowska J, Mosiewicz J, Sak J, Grzybowski A, Terlecki P, Barud W, et al. Effects of cigarette smoking, metabolic syndrome and dehydroepiandrosterone deficiency on intima-media thickness and endothelial function in hypertensive postmenopausal women. *Medical science monitor : international medical journal of experimental and clinical research*. 2012; 18(4):CR225–234. [PubMed: 22460094]
179. Dagre A, Lekakis J, Mihas C, Protogerou A, Thalassinou L, Tryfonopoulos D, et al. Association of dehydroepiandrosterone-sulfate with endothelial function in young women with polycystic ovary syndrome. *European journal of endocrinology / European Federation of Endocrine Societies*. 2006; 154(6):883–890. [PubMed: 16728549]
180. Novakovic A, Gojkovic-Bukarica L, Peric M, Nežić D, Djukanovic B, Markovic-Lipkovski J, et al. The mechanism of endothelium-independent relaxation induced by the wine polyphenol resveratrol in human internal mammary artery. *Journal of pharmacological sciences*. 2006; 101(1):85–90. [PubMed: 16682785]
181. Wallerath T, Deckert G, Ternes T, Anderson H, Li H, Witte K, et al. Resveratrol, a polyphenolic phytoalexin present in red wine, enhances expression and activity of endothelial nitric oxide synthase. *Circulation*. 2002; 106(13):1652–1658. [PubMed: 12270858]
182. Lopez-Sepulveda R, Gomez-Guzman M, Zarzuelo MJ, Romero M, Sanchez M, Quintela AM, et al. Red wine polyphenols prevent endothelial dysfunction induced by endothelin-1 in rat aorta: role of NADPH oxidase. *Clinical science*. 2011; 120(8):321–333. [PubMed: 20977430]
183. Nicholson SK, Tucker GA, Brameld JM. Physiological concentrations of dietary polyphenols regulate vascular endothelial cell expression of genes important in cardiovascular health. *The British journal of nutrition*. 2010; 103(10):1398–1403. [PubMed: 20021702]
184. Fujitaka K, Otani H, Jo F, Jo H, Nomura E, Iwasaki M, et al. Modified resveratrol Longevinex improves endothelial function in adults with metabolic syndrome receiving standard treatment. *Nutrition research*. 2011; 31(11):842–847. [PubMed: 22118755]
185. Wong RH, Howe PR, Buckley JD, Coates AM, Kunz I, Berry NM. Acute resveratrol supplementation improves flow-mediated dilatation in overweight/obese individuals with mildly elevated blood pressure. *Nutrition, metabolism, and cardiovascular diseases : NMCD*. 2011; 21(11):851–856.
186. Shantikumar S, Caporali A, Emanuelli C. Role of microRNAs in diabetes and its cardiovascular complications. *Cardiovascular research*. 2012; 93(4):583–593. [PubMed: 22065734]
187. Zhang MX, Ou H, Shen YH, Wang J, Coselli J, Wang XL. Regulation of endothelial nitric oxide synthase by small RNA. *Proceedings of the National Academy of Sciences of the United States of America*. 2005; 102(47):16967–16972. [PubMed: 16284254]
188. Dickhout JG, Hossain GS, Pozza LM, Zhou J, Lhotak S, Austin RC. Peroxynitrite causes endoplasmic reticulum stress and apoptosis in human vascular endothelium: implications in atherogenesis. *Arteriosclerosis, thrombosis, and vascular biology*. 2005; 25(12):2623–2629.
189. Sheikh-Ali M, Sultan S, Alamir AR, Haas MJ, Mooradian AD. Hyperglycemia-induced endoplasmic reticulum stress in endothelial cells. *Nutrition*. 2010; 26(11-12):1146–1150. [PubMed: 20080028]
190. LaRocca TJ, Henson GD, Thorburn A, Sindler AL, Pierce GL, Seals DR. Translational evidence that impaired autophagy contributes to arterial ageing. *The Journal of physiology*. 2012; 590(Pt 14):3305–3316. [PubMed: 22570377]
191. Zhang YL, Cao YJ, Zhang X, Liu HH, Tong T, Xiao GD, et al. The autophagy-lysosome pathway: a novel mechanism involved in the processing of oxidized LDL in human vascular endothelial cells. *Biochemical and biophysical research communications*. 2010; 394(2):377–382. [PubMed: 20223224]
192. Finan B, Yang B, Ottaway N, Stemmer K, Muller TD, Yi CX, et al. Targeted estrogen delivery reverses the metabolic syndrome. *Nature medicine*. 2012; 18(12):1847–1856.

193. Haltia LT, Savontaus E, Vahlberg T, Rinne JO, Kaasinen V. Acute hormonal changes following intravenous glucose challenge in lean and obese human subjects. *Scandinavian journal of clinical and laboratory investigation*. 2010; 70(4):275–280. [PubMed: 20429700]
194. Small CJ, Bloom SR. Gut hormones as peripheral anti obesity targets. *Current drug targets. CNS and neurological disorders*. 2004; 3(5):379–388. [PubMed: 15544446]