Published in final edited form as:
J Mol Cell Cardiol. 2012 April ; 52(4): 840–847. doi:10.1016/j.yjmcc.2011.08.018.

Influence of obesity and metabolic dysfunction on the endothelial control in the coronary circulation

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Abstract

Diseases of the coronary circulation remain the leading cause of death in Western society despite impressive advances in diagnosis, pharmacotherapy and post-event management. Part of this statistic likely stems from a parallel increase in the prevalence of obesity and metabolic dysfunction, both significant risk factors for coronary disease. Obesity and diabetes pose unique challenges for the heart and their impact on the coronary vasculature remain incompletely understood. The vascular endothelium is a major interface between arterial function and the physical and chemical components of blood flow. Proper function of the endothelium is necessary to preserve hemostasis, maintain vascular tone and limit the extent of vascular diseases such as atherosclerosis. Given its central role in vascular health, endothelial dysfunction has been the source of considerable research interest in diabetes and obesity. In the current review, we will examine the pathologic impact of obesity and diabetes on coronary function and the extent to which these two factors impact endothelial function.

Diseases of the coronary circulation remain the leading cause of death in Western society despite impressive advances in diagnosis, pharmacotherapy and post-event management. Part of this statistic likely stems from a parallel increase in the prevalence of obesity and metabolic dysfunction, significant risk factors for coronary disease. Obesity and diabetes pose unique challenges for the heart. For example, obesity increases cardiac output to service a large corpus, increasing the denominator of the perfusion/function relationship. While hyperlipidemia is well-recognized as a coronary risk factor, diabetes is characterized more as a triglyceride dyslipidemia and differs from the traditional hypercholesterolemia of the lean patient with atherosclerosis. How these and other factors impact the vasculature remains incompletely understood.

The vascular endothelium is a major interface between arterial function and the physical and chemical components of blood flow. Proper function of the endothelium is necessary to preserve hemostasis, maintain vascular tone and limit the extent of vascular diseases such as atherosclerosis. Given its central role in vascular health, endothelial dysfunction has been the source of considerable research interest in diabetes and obesity. In the current review, we

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Disclosures: I hereby confirm that any and all potential conflicts of interest have been fully and properly disclosed in the manuscript as outlined.

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Obesity, diabetes and coronary disease in the human population

Obesity in clinical terms has been defined by a series of indices, the most common of which is the Body Mass Index or BMI. Increasing BMI is associated with increasing cardiovascular risk when the value exceeds 25, especially in women [1]. In addition to the well-described increase in the incidence of diabetes, additional evidence suggests that components of the metabolic syndrome such as insulin resistance and dyslipidemia are equally important. Indeed, data from the NHANES III Study indicate that coronary disease is much more prevalent in individuals with metabolic syndrome whether diabetes is present or not (Figure 1) [2].

The heart of the obese, diabetic individual faces a number of unique challenges. Most notable among these is an increase in cardiac output to service the larger body mass of the obese patient [3]. The increase in cardiac output is multi-factorial, reflecting an increase in venous return from the body's larger blood volume [4] combined with a sympathoactivation that is prevalent in the obese population [5]. Elevations in cardiac output increases cardiac oxygen consumption [6] and thus the need for perfusion is increased.

In parallel to this increased demand, the deleterious effects of the obese state tend to drive down perfusion due to increasing incidence of atherosclerosis and microvascular disease [7]. Flow restriction via large artery stenosis and/or loss of microvascular vasomotor function contribute to reduced perfusion, and obesity and diabetes impact each of these in human populations. The paradigm of increasing demand combined with threats to perfusion underlies the central clinical dilemma in the cardiac health of obese and metabolically compromised patients.

Atherosclerosis

The effects of diabetes on atherosclerosis are well known and have been subject to extensive review [8, 9]. Data from the MRFIT study suggest that incidence of coronary atherosclerosis may be as high as 4-fold compared to non-diabetic patients [10] and the diabetic patient often presents with a progressive and complex form of atherosclerosis. It has been suggested that diabetics may be refractory to Glagov remodeling [11, 12], a vascular adaptation to the presence of a lesion that preserves lumen patency in the early stages of disease [13]. The loss of this effect contributes to premature encroachment on the lumen by the lesion and accelerates ischemic risk. The mechanisms by which diabetes limits Glagov remodeling are unclear and some controversy exists regarding diabetic risk [14]. Similar defects thwart revascularization therapy as diabetics are often more prone to restenosis of arterial bypass grafts and intrusion of lesion into coronary stents [15, 16]. Finally, diabetes may impair the formation of collateral arteries, undermining in the hearts intrinsic protections against chronic ischemia [17]. While precise links between coronary disease and frank diabetes remain to be fully elucidated, the diabetic milieu presents a toxic state of elevated lipids, disproportionate levels of triglycerides, high glucose, activation of inflammatory cells and oxidant stress [18, 19]. Indeed, when so many injurious factors are present, it may be virtually impossible to tease out specific sources of injury that contribute to atherosclerosis.

An important avenue of intervention may be a more aggressive management of the obese and pre-diabetic patient population. Mounting evidence suggests that, even in the absence of frank diabetes, metabolic dysfunction can be identified as a predictor of atherosclerosis [20, 21]. As early as 1970, Kayshap et al [22] determined that in "asymptomatic diabetics", individuals without observable diabetes but evidence of glucose intolerance, those with

ischemic heart disease demonstrated more severe metabolic alterations when challenged with oral glucose or tobutamide. The authors concluded that these deficits might lay the ground work for atherosclerosis even before the effects of frank diabetes were evident. Over the intervening decades, this concept has been refined from “exaggerated insulin production” [23] to the modern concept of insulin resistance or metabolic syndrome used today [24–26]. Consistent with the observations of the NHANES Study[2], obesity is also a positive and independent risk factor for pro-atherosclerotic conditions traditionally attributed to diabetes, such as rates of restenosis after stenting [15, 27]. Obese individuals commonly have an atherogenic lipid profile with disproportionate levels of plasma triglycerides and low HDL[28]. Keaney et al documented that oxidant stress, a major suspect in diabetic vasculopathy, correlated with increased body mass independently of diabetes [29]. Finally obesity is associated with a heightened state of inflammation with elevated levels of pro-inflammatory cytokines such as TNF-alpha and interleukin-6 [30]. Thus, many of the “usual suspects” in atherogenesis are present and potentially causal in the pre-diabetic patient as well as those with later stage disease.

Microvascular disease

While much of the functional impact of coronary disease is secondary to atherosclerotic stenosis, microvascular disease is also an important contributor [31–33]. Impaired vasomotor tone limits the ability of the heart to adapt to a stenosis by autoregulatory dilation [34] and in some cases, limits coronary reserve or produces ischemia even in the absence of significant plaque burden [35–37]. Moreover, diabetics have a greater incidence of silent ischemia [38], a precursor condition to infarction in which the microcirculation likely plays a greater role [39–41]

As with atherosclerosis, the impact of diabetes on the human coronary circulation is well-known and profound. Diabetic microvascular disease in the coronary circulation is characterized by a reduced vasodilator tone[37, 42], inappropriate vasoconstriction [43] and detrimental structural remodeling to stiffer vessels with smaller lumina [44]. The impairments in vasodilator function include decrements in endothelium-dependent dilation [43] as well smooth muscle dilation to hypoxia [45] or adenosine [46].

While deleterious effects of diabetes are well-documented, microvascular data from obese, pre- or non-diabetic humans are significantly less abundant. This stems in part from the relatively recent increase in the prevalence of obesity, even more recent recognition that obesity may itself be a risk factor for cardiovascular disease and the fact that most obese patients undergoing cardiac procedures (where material for study is largely derived) usually have more advanced disease than obesity alone.

Nevertheless, some basic observations indicate that obesity itself has impact on the coronary circulation. Recent work from Kiviniemi et al [47] indicates that in healthy young adult men, coronary flow reserve varied inversely with waist-to-hip ratio, suggesting that accumulation of visceral fat has a detrimental impact on the coronary vasculature (Figure 2). Furthermore, Dagres and colleagues found that insulin resistance was a predictor of reductions in coronary flow reserve in obese individuals [46]. Mechanistic studies from intact coronary arterioles remains limited, though some evidence of endothelial dysfunction has been reported [48].

Taken together, the above evidence makes a convincing case that obesity and diabetes have profound negative consequences for the coronary circulation. The current review will examine the effects of obesity and metabolic disease on endothelial and smooth muscle cells, the two predominant cell types in the vasculature. Insight into smooth muscle defects is offered in the sister article to this one by Berwick et al [49]. Insights into endothelial cell

defects will be offered from a broad understanding of effects of obesity and diabetes on vascular endothelium in general with specific discussion of the coronary circulation following.

Obesity, diabetes and the vascular endothelium

Endothelial control of vascular tone

Represented by a monolayer of cells which lines the entire vascular system, the vascular endothelium constitutes the interface between the circulating blood and the vascular wall but also serves as an important autocrine and paracrine organ that regulates vascular function. The endothelium is a dynamic organ sensitive to mechanical forces exerted by the flowing blood (shear stress) and to chemical signals and secretes a wide range of vasoactive and trophic factors that regulate vascular tone, cell adhesion, platelet function, plasmatic coagulation, vascular smooth muscle cell proliferation, and vessel wall inflammation. The importance of the endothelium was first recognized for its effects on vascular tone more than 30 years ago when Furchgott and Zawadsky demonstrated elegantly that vascular relaxation depends on a vasodilator substance released by the endothelium [50]. The endothelium-derived relaxing factor, as they called it, was subsequently identified to be nitric oxide (NO). NO is released in response to an increase in shear stress but is also secreted in response to signaling molecules such as bradykinin, adenosine, vascular endothelial growth factor and insulin. NO is generated by the conversion of L-arginine to L-citruline by the endothelial NO synthase (eNOS or NOS3), in the presence of co-factors such as tetrahydrobiopterin (BH4) [51]. Once released, NO diffuses across the endothelial cells into the adjacent smooth muscle cells where it activates the soluble guanylate cyclase and induces cGMP-mediated vascular relaxation[52].

Although NO is the main vasodilator substance released by the endothelium, endothelium-dependent control of vascular tone also involves NO-independent mechanisms. Endothelial cells could lead to vascular relaxation through the secretion of endothelium-derived hyperpolarizing factors (EDHF) able to mediate hyperpolarization of smooth muscle cells. EDHF is released under endothelial stimulation by agonists such as bradykinin and acetylcholine [53]. EDHF increases potassium conductance and facilitates the propagation of hyperpolarization of smooth muscle cells to maintain the vasodilator tone. The nature of EDHF and its involvement in the control of vascular relaxation are partially understood and differ between vascular beds [54].

In the endothelium, the conversion of arachidonic acid (AA) by the cyclooxygenases leads to the formation of prostacyclins (PGI2, PGE2) and thromboxane A2 (TxA2) that respectively relax and constrict vascular smooth muscle cells. Cyclooxygenases are present in 2 isoforms in the endothelium, a constitutive form, COX-1 and an inducible cyclooxygenase, COX-2. Both isoforms secrete prostanoids and are involved in the endothelium-mediated constriction[55]. COX-derived prostacyclins (PGI2, PGE2) bind the IP receptor at the surface of the smooth muscle cells and activate adenylate cyclase which triggers vascular relaxation by the synthesis of cyclic adenosine monophosphate (cAMP). On the other hand, once generated, TxA2 activates thromboxane-prostanoid (TP) receptors present at the surface of the smooth muscle cells, a phenomenon that will lead to an increase in intracellular Ca2+ levels and trigger vasoconstriction [56].

Additionally, endothelial cells modulate vasomotion by secreting endothelin 1 (ET-1) [57, 58]. Mostly activated by inflammatory cells and interleukin secretion, ET-1 secretion is also downregulated by shear stress, NO and PGI2 [59]. Due to the presence of ET-1 receptor at both the endothelial and smooth muscle cells level, ET-1 presents the particularity to either relax or constrict blood vessels. Activation of the ETB receptor on the endothelium causes

vasodilation via the release of NO and PGI2 [60, 61] while ET-1 binding on ETA receptors at the smooth muscle cell level increases intracellular Ca2+ and triggers vasoconstriction.

Finally, endothelial cells can control vasomotion is by facilitating the conversion of angiotensin I to angiotensin II [62]. Secreted at the endothelial surface, angiotensin II could either induce vasodilation through the activation AT2 receptor expressed in endothelial cells [63] or constriction via binding AT1 receptors at the surface of the smooth muscle cells.

Common mechanisms of dysfunction (superoxide and inflammation)

Endothelial dysfunction could be defined as an inadequate vasodilation and/or paradoxical vasoconstriction in response to stimuli that release nitric oxide (NO). This improper response of the endothelial cells could be explained in most cases by a decreased bioavailability of the vasodilator NO and/or in some cases by an increase in the production of constrictor factors by the endothelium. NO bioavailability represents the balance between the amounts of NO produced by eNOS and the amount of active NO scavenged by reactive oxygen species (ROS), particularly superoxide anion (•O2−).

An important consideration in the study of endothelial dysfunction is progression. While studying the effects of a gradual increase in insulin resistance in obese mice, we demonstrated that the endothelial function of obese and lean mice is progressively and gradually reduced with the addition of risk factors such as type 2 diabetes and aging[64]. This progressively impedes the ability of the vessels to respond functionally and structurally to chronic changes in blood flow and ischemic injury[65].

ROS have been shown to reduce NO bioavailability through several mechanisms. By reacting directly with NO, ROS form peroxynitrite (•ONOO−). This will have for consequence to directly reduce NO bioavailability but also to alter eNOS functioning and to lead to eNOS uncoupling. When uncoupled, instead of releasing NO, eNOS produces ROS [66, 67]. Depletion of the eNOS substrate L-arginine [68] or ROS-mediated oxidation of the eNOS cofactor, tetrahydrobiopterin (BH4) are the main mechanisms responsible for eNOS uncoupling [69]. ROS-mediated eNOS uncoupling is a major source of NO reduction, however, ROS can also directly affect NO release by inhibiting the dimethylarginine dimethylaminohydrolase (DDAH) enzyme that converts the endogenous eNOS inhibitor called asymmetric dimethylarginine (ADMA). Inhibition of DDAH causes ADMA accumulation and suppression of NO secretion [70].

While reduction in NO bioavailability plays a key role in the reduced ability of the vessels to relax in response to dilator stimuli, an exaggerated secretion of constrictor agents is also involved in this dysfunction. In the presence of high ROS levels, peroxynitrite inhibits the prostacyclin synthase reducing PGI2 release. This induces a shift in the arachidonic acid metabolism to the PGI2 precursor PGH2 and other TP receptor agonists such as TXA2 promoting a constrictive phenotype [71].

In mammalian cells potential enzymatic sources of ROS include the mitochondrial electron transport chain, xanthine oxidase, cyclooxygenase, lipoxygenase, NO synthase, heme oxygenase, peroxidases and NADH oxidases. However, in the vasculature, the NAD(P)H oxidases represent the primary source of ROS. In endothelial cells, NAD(P)H oxidase isoforms are expressed in the endoplasmic reticulum, and in the perinuclear membranes generating ROS as modulators of redox sensitive signaling pathways [72, 73]. NAD(P)H oxidase is functionally active in all cells within the vascular wall (endothelial, vascular smooth muscle cells, fibroblasts). NAD(P)H oxidase is a multi-complex catalyzer that possesses a membrane component formed by the association of two transmembrane proteins p22phox and gp91phox (termed NOX2 or its homologues NOX1,3-5) and a cytoplasmic

component represented by the proteins p47phox, p67phox and the small proteins Rac-1 and Rac-2 that play a key role in NAD(P)H oxidase activation. Upon activation, p47phox is phosphorylated, and the cytosolic subunits form a complex that translocates to the membrane in which it associates with cytochrome b558 (heterodimeric flavoprotein formed by the association of p22phox and gp91phox), to assemble the active oxidase, which transfers electrons from the substrate to O2 forming •O2[74, 75]. Produced at the molecular level, ROS act as signaling molecules to influence diverse signal transduction pathways, such as oxidation of reactive cysteine residues. However, when generated in excess ROS causes the vascular dysfunction described above.

Risk factors driving endothelial function

At the interface between the circulating blood and the vascular wall, the endothelium is highly exposed and the first organ submitted to changes in physical forces and chemical signals, making it highly susceptible to alterations. Endothelial dysfunction represents the earliest abnormality in the development of vascular diseases and is associated with a number of traditional risks factors including diabetes mellitus, hypercholesterolemia, hypertension, insulin resistance, advanced age and obesity [76]. Obesity is one of the most relevant health issues of the last decades, and represents one of the highest risk factor for the development of endothelial dysfunction. The authors of the Framingham Heart Study established an independent relationship between body mass index and blunted brachial artery flow-mediated dilation [77] that was further confirmed by several studies highlighting the deleterious effects of abdominal fat deposition on the endothelial function [78–80]. Using animals models of obesity and type 2 diabetes, obesity, from its early stage to the development of frank type 2 diabetes induces a progressive and gradual decrease in endothelial function [65, 81–85].

Obesity is a multi-factorial and complex disease that is associated with metabolic (insulin resistance, hyperglycemia, hypercholesterolemia, dyslipidemia, hyperleptinemia), and hemodynamic dysfunction (hypertension) but also recognized as an inflammatory disease. While the endothelial dysfunction observed in obesity and type II diabetes could mainly be explained by a single factor represented by a decrease in NO availability, the origins of this dysfunction are multiple. However, they do not involve a decrease in eNOS expression. Indeed eNOS expression was either reported not to be affected by insulin resistance and obesity [65, 86] or to be increased in pathological states associated with oxidative stress [87, 88]. Reduced NO bioavailability due to excess ROS generation becomes then the major source of endothelial dysfunction in obesity and diabetes. The complexity and the multi-factorial aspect of metabolic disease explain the multiple sources involved in ROS generation.

A key player in excessive ROS generation associated with obesity and diabetes is NADPH oxidase [89]. Endothelial cells isolated form obese individuals have been reported to exhibit an increased NADPH oxidase expression [90]. However, obesity per se is probably not the factor triggering NADPH overexpression but insulin resistance and its consequent metabolic disturbances likely represent the main source. The arguments to support this postulate are provided by a recent study from Ali et al analyzing the vascular consequences of correcting insulin sensitivity in obese mice. Insulin sensitivity was restored in obese mice via the deletion of the molecular restrain of the insulin signaling pathway, the protein tyrosine phosphatase 1B. In this study, we demonstrated that despite obesity, insulin sensitive mice present a normal endothelial function and lower levels of oxidative stress and NADPH subunits expression in the microcirculation, compared to obese insulin resistant animals [81]. This clearly highlights the role of insulin resistance in the endothelial dysfunction associated with obesity and more precisely its importance in excessive ROS generation.

The metabolic disturbances associated with insulin resistance are certainly the main cause of increased oxidative stress observed with obesity. Insulin resistance is characterized by a decreased ability of insulin to promote glucose uptake in skeletal muscle and adipose tissue and to suppress hepatic glucose output which combined with impaired beta cells function increases circulating blood glucose [91]. As reported by several studies hyperglycemia has been shown to be involved in NADPH-derived ROS generation. Indeed, treatment of human [92] or mouse microvascular endothelial cells [87] with high glucose increases NADPH oxidase expression and levels of oxidative stress. Under hyperglycemic conditions advanced glycation end-products (AGE) are also formed and stimulate NADPH activity. Furthermore, AGE scavenging with soluble form receptor for AGE induced a partial restoration of the endothelial function of obese diabetic mice that was associated with a reduced NADPH oxidase expression [93]. According to these authors [94, 95] and others [96, 97] AGEs promote NADPH oxidase-derived ROS secretion through an inflammatory process involving the NF-κB and TNF-α signaling pathway, highlighting the role of inflammation in the vascular dysfunction associated with obesity.

By affecting mitochondrial metabolism, hyperglycemia generates an increase in mitochondrial-derived superoxide production increasing diacylglycerol (DAG) formation. DAG activates protein kinase C isoforms and more specifically PKC-β that is implicated in the regulation and activation of membrane associated NADPH oxidase regulatory subunits p22phox, p47phox and p67phox in the vessels of diabetic patients. In the latter patients, PKC inhibition has been reported to reduce superoxide generation [89].

With insulin resistance, DAG levels could also be increased independently of mitochondrial-generated ROS. Under hyperglycemic conditions, elevated glucose levels also increase the glycolytic pathway flux and leads to an elevation in the levels of intracellular glyceraldehyde-3-phosphate. This in turn can stimulate increases in the de novo synthesis of DAG and activate PKC [98–100]. Upon activation, PKCs inhibit the activity of the PI3 kinase/Akt signaling pathway thereby limiting the subsequent phosphorylation of eNOS and NO release in response to insulin. In addition PKC activation mediates the overexpression of adhesion molecules such as ICAM-1, VCAM-1 and E-selectin and enhances vascular contractility by increasing ET-1 release [101].

Finally, hyperglycemia is involved in the up-regulation of angiotensin 2 secretion associated with obesity and diabetes [102]. Angiotensin II promotes NADPH-induced ROS release [103] and ET-1 stimulation and/or release, which counteract NO activities and impair endothelial function.

While insulin resistance is characterized by high circulating glucose levels, it also involves high circulating lipid levels resulting from the reduced sensitivity of the adipose to the metabolic effects of insulin. Dyslipidemia and more specifically hypercholesterolemia was the first pathological condition associated with an impaired endothelium dependent relaxation. In hypercholesterolemic rabbits and monkeys vasorelaxation to acetylcholine was almost absent or changed into vasoconstriction [104, 105]. Similar observations were made in patients with coronary artery diseases [106, 107]. Once again ROS are the main player in the endothelial dysfunction. However contrary to high glucose levels that increase ROS through NADPH oxidase activation, hypertriglyceridemia-derived ROS appears to induce a xanthine oxidase-mediated ROS release in the endothelial cells [108, 109].

Increased ROS in response to high glucose and high lipids levels also activate NF-kB, which further stimulates production of other proinflammatory cytokines including TNF-α and IL-6 and C reactive protein [110, 111] that will further impair the endothelial function by further activating NADPH oxidase [112].

Taken together, these data suggest that obesity and insulin resistance produce an oxidant injury to the endothelium that reduces NO-mediated dilation (Figure 3). The exact metabolic components and the role of accessory processes such as inflammation remain to be determined.

Unique characteristics of the coronary circulation

As discussed above, the plasma milieu of the diabetic and obese individual has pervasive effects on the vascular endothelium across virtually all beds studied to date, by largely similar mechanisms. Interestingly, studies from animal models find that while many diabetic models demonstrate endothelial injury in the coronary circulation, models of obesity are much less likely to have similar defects. Knudson et al [113] observed normal vasodilator responses to acetylcholine in obese, pre-diabetic dogs, Zhang et al [114] made similar observations in young db/db mice and parallel results have been obtained in young adult obese Zucker Rats [115–117].

As metabolic disease worsens toward diabetes, the impact on the coronary circulation is unambiguous. In the Ossabaw swine model of the metabolic syndrome, endothelial dilation is markedly reduced to bradykinin [118] and TRPV1 channel activation [119], effects that may be attributed to factors released from periadventitial fat. As shown in other beds [120, 121], the loss of endothelial dilation in the coronary circulation is progressive as shown in older Zucker rats [115] and db/db mice [114]. Moreover, the progressive injury may reflect the accumulation of differing insults rather than simple escalation of metabolic variables as the impact of cytokine blockade varies over the course of progression. TNF-α, for example, makes a larger contribution to the total impairment in 12 week old db/db mice vs. 24 week olds. This observation correlated with an ability of TNF-α antagonism to reduce superoxide in younger animals but the antagonism was much less potent in older animals, suggesting that other factors contribute to the oxidant injury driving endothelial dysfunction in obesity and metabolic disease [114].

The apparent limitation in endothelial injury in the coronary circulation begs the question: why? Perhaps the simplest answer is that unlike many organs in obese individuals, the heart must work significantly harder to maintain effective cardiac output to larger individuals. Increases in cardiac output correlate with increased myocardial oxygen consumption in obese but otherwise healthy adults [6]. The increased work would, at least initially, produce increased flow and increased shear stress which is well documented to influence coronary tone in vivo [122, 123]. Evidence for the concept is found in the Zucker rat model of obesity, in which metabolic injury is relatively minor at younger ages but cardiac output is significantly increased [116]. Vasodilation to acetylcholine is normal in the septal arteries from these animals or even augmented at supra-normal levels of stimulation. The concept of a shear-mediated preservation of endothelial function is further supported by studies of aortic vasodilation. An increase in cardiac output translates to an increase in aortic flow and shear stress and the earliest studies of aortic dilation in the Zucker rat demonstrated an increased dilator capacity to endothelial stimulation [124]. Taken together, it seems plausible that an increase in shear may offset the deleterious defects to endothelial function caused by metabolic changes early in obesity.

The mechanisms by which endothelial tone is protected or preserved are incompletely understood. Work from Katakam et al suggests an increase in NO generation, as evidenced by more potent buffering of endothelin-mediated vasoconstriction by NO [125]. In studies using a high-fat model of obesity (one of the mildest metabolic models), Jebelovszki et al observed an increased sensitivity to NO which was attributed to an increase in soluble guanylate cyclase activity [126]. Finally, it should be considered that eventual impairment in

endothelial signaling might be supplemented by other dilators. Indeed, Szerafin et al determined in human coronary arteries that metabolic disease increases vasodilation to cyclooxygenase products, providing an alternative NO-independent mechanism to preserve vasodilator capacity and cardiac perfusion [127].

Summary

Taken together, the literature reviewed above indicates that diabetes and obesity have progressive deleterious effects on the endothelial lining. An emerging consensus indicates that the primary injury is oxidant-mediated corruption of nitric oxide signaling, with oxidation being driven in large part by a pro-inflammatory tissue environment. The primary risk factor associated with endothelial function appears to be primarily the insulin resistant state, possibly secondary to pro-inflammatory advanced glycation end products or changes in lipid status. The coronary circulation appears to be afforded a measure of protection early on in the progression of metabolic disease, most likely due to hemodynamic changes associated with increased cardiac output. Ultimately, the balance shifts in favor of metabolic disease, leaving the heart vulnerable to ischemic heart disease.

Acknowledgments

The authors wish to acknowledge Michelle Davis of Michelle Davis Studios (http://www.mdavisstudios.com) for art for Figure 3.

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Highlights

- Obesity and diabetes are major risk factors for coronary endothelial dysfunction.
- Insulin Resistance is the major risk factor for this endothelial dysfunction
- Oxidation and inflammation are the primary mechanisms of endothelial dysfunction.
- The coronary circulation may be more slowly injured due to effects of increased cardiac work.

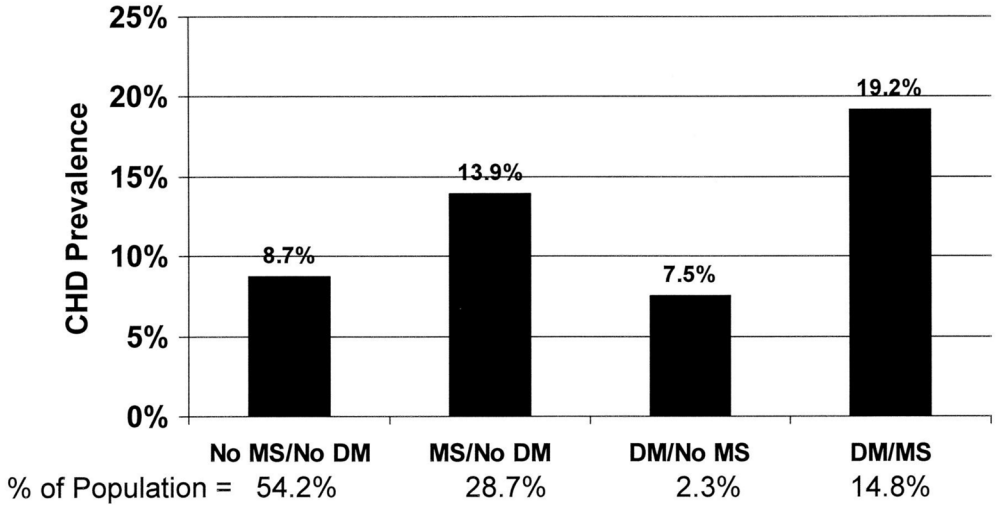

Figure 1.
Effects of obesity and diabetes on the prevalence of coronary heart disease in adults. From Alexander et al, 2003 [2]. Reproduced with permission.

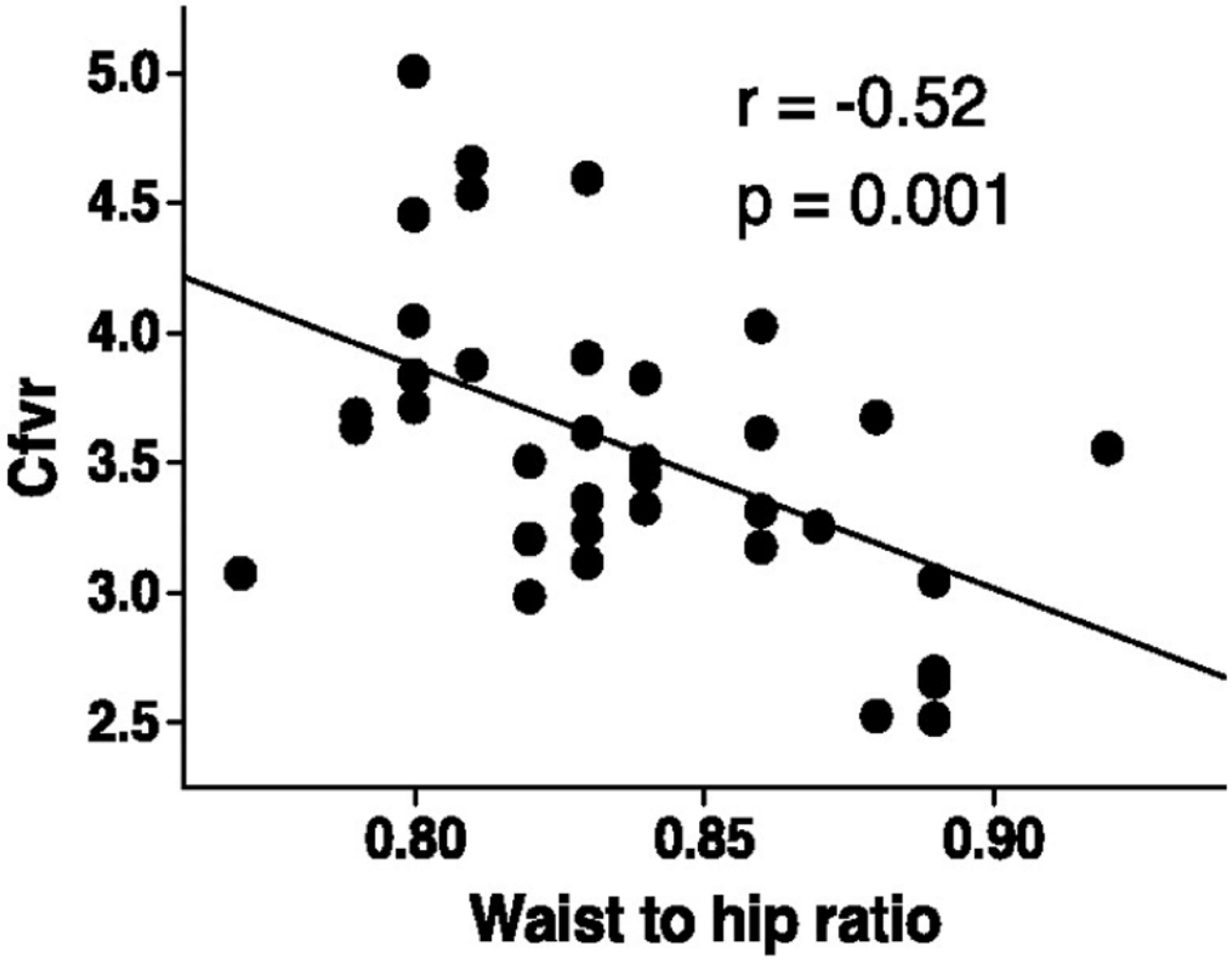

Figure 2.
Effects of obesity on coronary flow velocity reserve in health young men. From Kiviniemi et al, 2008 [47]. Reproduced with permission.

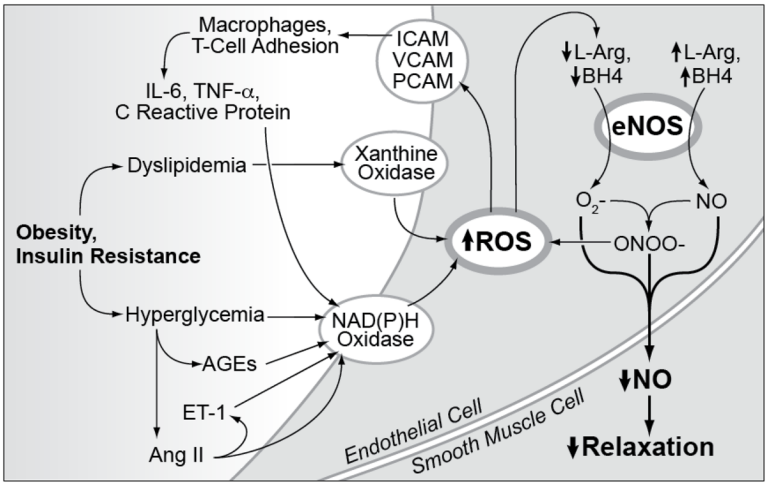

Figure 3.
The impact of obesity and insulin resistance on endothelial NO production and action.