Endothelial Dysfunction, Inflammation, and Insulin Resistance: A Focus on Subjects at Risk for Type 2 Diabetes

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Subjects with obesity, family history of type 2 diabetes, polycystic ovary syndrome, previous gestational diabetes, dyslipidemia, hypertension, impaired glucose tolerance or impaired fasting glucose, and those with metabolic syndrome are at risk for the development of type 2 diabetes. Some of them are also at risk for cardiovascular disease. Some underlying abnormalities such as insulin resistance, endothelial dysfunction, and low-grade chronic inflammation are frequently present and closely associated in all these groups. The flow of substrates, hormones, and cytokines from visceral fat to skeletal muscle and to the endothelial cells, along with some genetic abnormalities that lead to impaired insulin action in the peripheral tissues and to impaired insulin-stimulated nitric oxide production in endothelial cells, may play a role in establishing these shared metabolic and vascular derangements. Weight loss, thiazolidinediones, and metformin improve vascular function in subjects at risk for type 2 diabetes and may prove to reduce cardiovascular events in these individuals.

Introduction

Coronary heart disease represents the main cause of death in people with diabetes. Whereas chronic hyperglycemia may directly participate in the development of atherosclerosis [1], significant damage to the vasculature results from the common presence of well-known cardiovascular risk factors, such as hypertension, dyslipidemia, altered fibrinolysis, and obesity, all components of the insulin resistance or metabolic syndrome [2]. Because this syndrome is usually present before the development of diabetes, it follows that a significant contribution to the risk for cardiovascular disease in subjects with diabetes is established before the appearance of hyperglycemia [3].

The hallmark of the insulin resistance or metabolic syndrome is the existence of a decreased effect of insulin to regulate metabolic processes (insulin resistance) and, therefore, a significant amount of work has focused on understanding its relationship to the development of atherosclerosis and cardiovascular disease. Individuals with hyperinsulinemia, a reflection of insulin resistance, have a higher risk of developing macrovascular disease after controlling for the most common traditional cardiovascular risk factors [4,5]. The mechanisms that link insulin resistance and vascular disease are multiple and complex.

The study of human endothelial function in health and disease has allowed us to increase our understanding on how vascular disease develops in people with diabetes and insulin resistance. Endothelial dysfunction is considered a key element in the development of atherosclerosis and is associated with insulin resistance and obesity [1,6,7•]. Because endothelial dysfunction usually precedes the development of type 2 diabetes, the study of vascular function in individuals at risk for the disease is an intuitively appropriate area to understand the mechanisms behind its development as well as the strategies to improve it. The purpose of this article is to present updated clinical information on the presence of endothelial dysfunction, inflammation, and insulin resistance in well-identified groups at risk for type 2 diabetes. Mechanisms that link these metabolic and vascular abnormalities, as well the effect that some pharmacologic and nonpharmacologic interventions that reduce human insulin resistance have on endothelial function in these groups, are also reviewed.

Insulin Resistance in the Development of Type 2 Diabetes

Most individuals who advance toward the development of type 2 diabetes experience progressive deterioration of glucose tolerance over time. They generally progress from a state of normoglycemia to impaired glucose tolerance (IGT) and finally to overt diabetes. Insulin resistance, defined as the inability of insulin to promote glucose uptake in peripheral

Table 1. The presence of IR, ED, and low-grade chronic INFL in various groups at risk for type 2 DM*

Group at risk for DM	IR	Impaired vascular reactivity	Endothelial activation	Low-grade chronic INFL
Obesity	Yes	Yes	Yes	Yes
FH of DM	Some	Yes	Yes	Yes
PCOS	Some	Yes/no	NA	Yes
Prior GDM	Some	Yes/no	NA	NA
IGT	Yes	Yes	Yes	Yes
IFG	Some	Yes	NA	NA
Dyslipidemia	Some	Yes	Yes	Yes
Hypertension	Some	Yes	Yes	Yes
Metabolic syndrome	Yes	Yes	Yes	Yes

*Impaired vascular reactivity represents endothelium-dependent vasodilation in the coronary arteries or peripheral circulation. Endothelial activation has been considered if elevation of circulating adhesion molecules has been reported. Low-grade chronic INFL is represented by elevated highly sensitive C-reactive protein circulating levels. Yes/no indicates positive and negative results in the literature.
DM—diabetes mellitus; ED—endothelial dysfunction; FH—family history; GDM—gestational diabetes mellitus; IFG—impaired fasting glucose; IGT—impaired glucose tolerance; INFL—inflammation; IR—insulin resistance; NA—not available; PCOS—polycystic ovary syndrome.

tissues such as skeletal muscle and adipose tissue, is usually present for many years before the development of any abnormality in glucose levels [8]. It can be identified in very young populations at high risk for type 2 diabetes [9]. Insulin resistance is overall a good predictor of the risk of incident type 2 diabetes, although it is particularly valuable in those individuals with additional risk factors for diabetes, such as those with family history of the disease [10]. In most individuals with insulin resistance, a state of compensatory hyperinsulinemia is achieved by increasing insulin production. However, due to poorly understood genetic and environmental factors, β cells are not capable of maintaining an adequate amount of insulin to prevent hyperglycemia in some individuals [8].

Main Groups at Risk for Type 2 Diabetes

The main groups considered at increased risk for type 2 diabetes are the following: first-degree relatives of patients with type 2 diabetes, overweight and obese individuals (mostly those with central or abdominal obesity), some people with hypertension, those with dyslipidemia manifested by high triglycerides and low high-density lipoprotein (HDL) cholesterol, and women with polycystic ovary syndrome (PCOS) [11]. In addition, there are people who have already manifested a decreased ability of the pancreas to overcome the presence of insulin resistance, such as women who have had gestational diabetes and individuals with IGT or impaired fasting glucose (IFG) [11]. These two categories are not completely equivalent and may reflect some subtle differences in the underlying pathophysiology of the disease. Individuals with the metabolic or insulin resistance syndrome are at increased risk for type 2 diabetes because they exhibit many of the categories already described, such as central obesity, hypertension, dyslipidemia, or hyperglycemia [12]. Table 1 shows the main groups at risk for type 2 diabetes, along with some of their metabolic and vascular abnormalities.

Endothelial Dysfunction and Chronic Low-grade or Subclinical Inflammation

In recent years, endothelial function has gained increasing attention in understanding vascular health and disease. The arterial endothelium comprises the inner layer of the vessel, sitting on a basement membrane and in close structural and functional contact with the underlying vascular smooth muscle cells. The endothelium exerts autocrine, paracrine, and endocrine functions. It plays a vital role in vascular homeostasis, regulating vascular tone, vascular smooth muscle cell proliferation, and transendothelial leukocyte migration, as well as thrombosis and thrombolysis. In response to various mechanical and chemical stimuli, endothelial cells synthesize and release a large number of vasoactive substances, growth modulators, and other factors that mediate these functions [13]. Endothelial dysfunction can be defined as the partial or complete loss of balance between naturally occurring opposing vascular states, such as constriction and dilation, proinflammation and anti-inflammation, growth promotion and growth inhibition, and coagulation and fibrinolysis. Low-grade chronic inflammation at the level of the vessel wall mediates all stages of atherosclerosis and is a reflection of endothelial dysfunction [14••].

Endothelial dysfunction and low-grade chronic inflammation are the result of the deleterious effects that cardiovascular risk factors produce on the vascular wall, primarily by activating a number of pro-oxidative events, manifested by the increased production of reactive oxygen species, such as superoxide, that ultimately lead to a decrease in nitric oxide production or action, and activation of the local renin-angiotensin system, as well as endothelial release of transcriptional and growth factors, proinflammatory cytokines, chemoattractant substances, and adhesion molecules. Thus, endothelial dysfunction and low-grade chronic inflammation are regarded as pivotal events in atherogenesis [1,14••].

Evaluation of Human Endothelial Function

Endothelial function can be assessed by measures of the balance between the naturally opposing vascular states already defined. The most common approaches are the evaluation of vascular reactivity and blood flow to assess the balance between constriction and dilation, the measurement of markers of inflammation such as highly sensitive C-reactive protein (hs-CRP) to assess the balance between proinflammation and anti-inflammation, and the measurement of tissue plasminogen activator (tPA), plasminogen activator inhibitor-1 (PAI-1), fibrinogen, or thrombomodulin to assess the balance between coagulation and fibrinolysis. The measurement of adhesion molecules, such as soluble vascular cellular adhesion molecule (sVCAM), soluble intercellular adhesion molecule (sICAM), and E- and P-selectin, is a means to evaluate "endothelial activation," an early inflammatory state whereby circulating monocytes and macrophages are attracted to the vascular wall after a mechanical or biochemical insult. Circulating concentrations of fat-derived substrates (free fatty acids), hormones (adiponectin), and cytokines (tumor necrosis factor-α [TNF-α], interleukin-1 [IL-1], and interleukin-6 [IL-6]), which play a role in vascular function and inflammation, can also be used to assess vascular health and disease. There are other factors that can translate endothelial dysfunction or inflammation, such as endothelin-1 (ET-1), von Willebrand factor, and measures of nitric oxide metabolism, among others.

Vascular reactivity and blood flow can be assessed through invasive and noninvasive techniques, such as arterial catheterization, venous occlusion plethysmography, laser Doppler flowmetry, ultrasound, and positron emission tomography scanning. Vascular reactivity mainly assesses the nitric oxide pathway, highly important in vascular health and various disease states. The infusion of acetylcholine or methacholine in the coronary or peripheral circulation is frequently used to stimulate the endothelium to produce nitric oxide (endothelium-dependent vasodilation), whereas sodium nitroprusside is used to directly stimulate vascular smooth muscle cells (endothelium-independent vasodilation). "Shear stress" is the term used to define the mechanical force that increased blood flow exerts on the endothelium during reactive hyperemia in the brachial artery ultrasound technique (endothelium or flow-mediated dilation). In this method, sublingual nitroglycerin is used to stimulate the vascular smooth muscle cells (endothelium-independent vasodilation) [15,16•].

Several measures of endothelial dysfunction and inflammation have been shown to precede the development of cardiovascular disease, such as impaired vascular reactivity in the coronary circulation or the brachial artery, elevated levels of adhesion molecules, PAI-1, and more recently, increased hs-CRP levels [17–21]. Interestingly, some of these markers of endothelial activation and inflammation are also very good predictors of incident type 2 diabetes [22].

The clinician however, should keep in mind that all these biochemical and functional measures of endothelial dysfunction and inflammation are primarily used in clinical research settings. Thus, their use in routine clinical practice has not been well defined yet.

Vascular Dysfunction and Insulin Resistance in Subjects at Risk for Type 2 Diabetes

Obesity

Obesity is a major risk factor for type 2 diabetes and is closely associated with insulin resistance and endothelial dysfunction [6,7•]. This association is present in all age groups, including children [23]. Chronic subclinical or low-grade inflammation has also been frequently reported as part of the obesity or insulin resistance syndrome [24]. Endothelial dysfunction is particularly related to visceral obesity [25]. The mechanisms linking obesity, insulin resistance, and endothelial dysfunction are multiple and complex [7•]. An increased flow of substrates, cytokines, and hormones from the insulin-resistant adipose tissue (primarily visceral fat) to skeletal muscle, liver, and the endothelium plays a crucial role in affecting glucose metabolism and vascular function. Free fatty acids lead to decreased insulin action in liver and skeletal muscle, through mechanisms that may affect the intracellular insulin signaling cascade and are also associated with impaired vascular reactivity [26,27]. TNF-α reduces insulin action in skeletal muscle and may also have some direct effects in the vasculature [28,29].

The adipocytokines IL-1 and IL-6 are increased in obesity and insulin resistance and have been closely linked to endothelial dysfunction and subclinical inflammation [30]. IL-6 is a potent stimulus for the production of C-reactive protein (CRP) in the liver, which in turn may have some direct deleterious effects in the vascular wall [30,31]. Leptin has effects on energy expenditure, satiety, and neuroendocrine function. In theory, it may improve insulin sensitivity by an indirect mechanism related to decreased satiety and body weight regulation, and in a more direct way by affecting insulin signaling in muscle [32]. Interestingly, it may also have some direct vasodilatory effects [33]. Resistin, another fat-derived hormone, was found to be linked to obesity and insulin resistance in animal models; however, its role in human obesity is not clear [34]. It is not known whether resistin may also have some vascular actions. Conversely, adiponectin, frequently reduced in human obesity, improves insulin sensitivity by enhancing intracellular insulin signaling and has some direct vasodilatory and anti-inflammatory effects [35,36]. Therefore, various mechanisms that alter insulin action and endothelial function are frequently present and closely linked in the obese individual (Fig. 1).

Family history of type 2 diabetes

Our group reported impaired vascular reactivity in the brachial artery and in the skin microcirculation, as well as

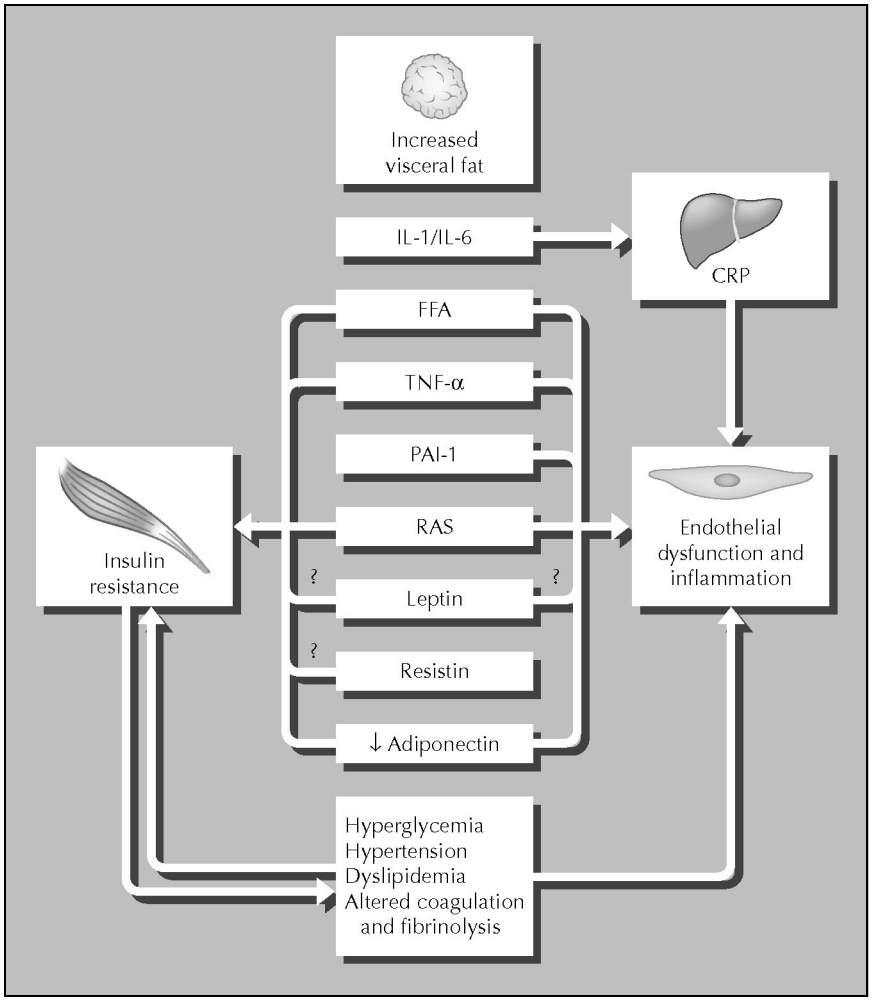

Figure 1. Mechanisms that link obesity (increased visceral fat), insulin resistance, and endothelial dysfunction or inflammation. Subjects at risk for type 2 diabetes are frequently overweight and have insulin resistance. Most of these groups have also been found with endothelial dysfunction and inflammation. CRP—C-reactive protein; FFA—free fatty acid; IL—interleukin; PAI-1—plasminogen activator inhibitor-1; RAS—renin-angiotensin system; TNF-α—tumor necrosis factor-α.

increased concentrations of sVCAM-1 and ET-1 in subjects with normal glucose tolerance and history of type 2 diabetes in one or both parents [37]. This group of individuals had a normal glucose tolerance test and blood pressure levels and their lipids and body mass index (BMI) were not statistically different from those in the control group. Our findings raised the question of whether the abnormalities found in vascular function were related to developing not yet clinically evident metabolic abnormalities related to insulin resistance or to some potential genetically determined intrinsic vascular defects.

Balletshofer *et al.* [38] reported that only those that had demonstrable insulin resistance had decreased endothelium or flow-mediated vasodilation in the brachial artery. However, more recently, Goldfine *et al.* [39] reported that even the most insulin-sensitive offspring of both parents with type 2 diabetes had impaired endothelium-dependent vasodilation in the brachial artery. The populations in the three studies are not comparable. However, these recent findings suggest that some vascular genetic factors may be operative in these individuals because it has been reported in other groups at risk for vascular disease [40]. Increased plasma levels of CRP have also been reported in women with a family history of diabetes [41]. More studies are required to define the precise contribution of genetically determined intrinsic vascular abnormalities and those secondary to metabolic insulin resistance to endothelial dysfunction in this group at risk for type 2 diabetes.

Polycystic ovary syndrome

Polycystic ovary syndrome is a well-identified component of the insulin resistance syndrome. It is important to remember that not all women with PCOS are insulin resistant and not all women with insulin resistance have PCOS. Paradisi *et al.* [42] found that women with PCOS have decreased leg blood flow responses (impaired endothelium-dependent vasodilation) in response to graded intrafemoral artery infusions of methacholine chloride in association with insulin resistance. Conversely, Mather *et al.* [43] found no difference in vascular reactivity in the brachial artery in another group of women with PCOS in comparison with age-matched control subjects. These discrepant results may be explained by differences in the study methodology and populations.

Polycystic ovary syndrome has also been linked to subclinical inflammation [44]. Talbott *et al.* [45] reported increased intima-media wall thickness (IMT) in the carotid artery in women with PCOS above 45 years of age in

comparison with control subjects. These changes were statistically associated with obesity and fat distribution. They did not find a difference in IMT between groups in women 30 to 44 years of age. These findings suggest that certain duration of obesity or insulin resistance and their associated abnormalities is necessary before some measures of atherosclerosis can be identified in this group.

Previous gestational diabetes

Women with a history of gestational diabetes represent a high-risk group for the development of type 2 diabetes [11]. Anastasiou *et al.* [46] reported reduced flow-mediated dilatation in the brachial artery in obese (BMI > 27) and nonobese women (BMI < 27) with normal glucose tolerance and previous gestational diabetes. Some of the nonobese women can be considered overweight according to current criteria (BMI > 25). This group had elevated uric acid levels, possibly related to insulin resistance. Thus, subtle insulin resistance may account for these interesting findings. However, Hannemann *et al.* [47] reported no difference in vascular reactivity in the skin and in the brachial artery in another group of women with normal glucose tolerance and previous gestational diabetes [47]. The number of people included in the latter study was small and may explain the observed results. In addition, subtle differences in the methodology may also contribute to these discrepant results..

In a study to assess the effect of weight loss on endothelial function, Bergholm *et al.* [48] found that moderate weight loss (8%) in obese (mean BMI of 32) women with a history of gestational diabetes did not improve endothelium-dependent vasodilation in the brachial artery, whereas low-density lipoprotein cholesterol reduction did. These interesting findings suggest that other mechanisms independent from obesity or insulin resistance may be responsible for the vascular abnormalities in women with prior gestational diabetes or that a more profound weight loss is necessary in this group. Vitamin C has also been found to have a beneficial effect on endothelial function in this group, suggesting that oxidative stress may be an important underlying mechanism in this group [49].

Impaired glucose tolerance and impaired fasting glucose

Impaired glucose tolerance and IFG represent two important high-risk groups for type 2 diabetes [11]. Multiple studies have been conducted to assess various metabolic and vascular abnormalities in people with IGT, as well as effective nonpharmacologic and pharmacologic interventions to reduce the progression to type 2 diabetes and in some to cardiovascular disease. The studies that have reported some results are the Diabetes Prevention Program (DPP), the Finish Diabetes Prevention study, the Da Qing study, the Malmo study, the Stop-NIDDM (Study to Prevent non–insulin-dependent diabetes) trial, the Sibutramine study, and the TRIPOD (Troglitazone in Prevention of Diabetes) study. There are several additional ongoing prevention trials testing various pharmacologic interventions.

Many of the finished studies have reported abnormalities in various markers of endothelial activation, coagulation, and inflammation in subjects with IGT. For instance, the DPP, which included more than 3000 individuals, found increased levels of hs-CRP, fibrinogen, and tPA at baseline [50••]. Our group also reported that people with IGT have impaired endothelium-dependent vasodilation in the brachial artery, as well as elevated levels of sICAM and ET-1 [37].

Esposito *et al.* [51] recently reported elevated levels of IL-6 and TNF-α at baseline and a pronounced increase in response to an intravenous infusion of glucose in people with IGT. Their findings suggest that acute hyperglycemia can also contribute to the vascular abnormalities through an oxidative mechanism in people with IGT. Individuals with IFG have not been as extensively studied, although abnormalities in vascular function have also been reported in this group [52].

Dyslipidemia and hypertension

Individuals with insulin resistance often share the presence of hypertension and dyslipidemia, manifested as high triglycerides and low HDL cholesterol. Each of these abnormalities are considered risk factors for type 2 diabetes and cardiovascular disease. Hypertriglyceridemia and low HDL cholesterol have been independently associated with endothelial dysfunction and inflammation [53].

Hypertensive individuals, who often have insulin resistance and are at increased risk for type 2 diabetes, have been frequently reported with endothelial dysfunction, even in the absence of increased weight [54]. These findings suggest that mechanisms independent from obesity link hypertension with endothelial dysfunction.

Metabolic syndrome

Individuals with the metabolic syndrome manifest several of the categories at risk for type 2 diabetes already described [12]. Because subjects with the metabolic syndrome include by definition the presence of obesity, dyslipidemia, hypertension, or hyperglycemia, it is not surprising that they have been reported not only with impaired vascular reactivity and increased levels of some markers of endothelial activation and inflammation, but also with increased rates of cardiovascular and cerebrovascular disease [12,55].

Common Explanatory Mechanisms

As previously shown, all typical groups at risk for type 2 diabetes frequently have insulin resistance, endothelial dysfunction, and low-grade chronic inflammation (Table 1). Several mechanisms can explain the presence of these metabolic and vascular abnormalities. Many of these groups are overweight or obese and have increased insulin-

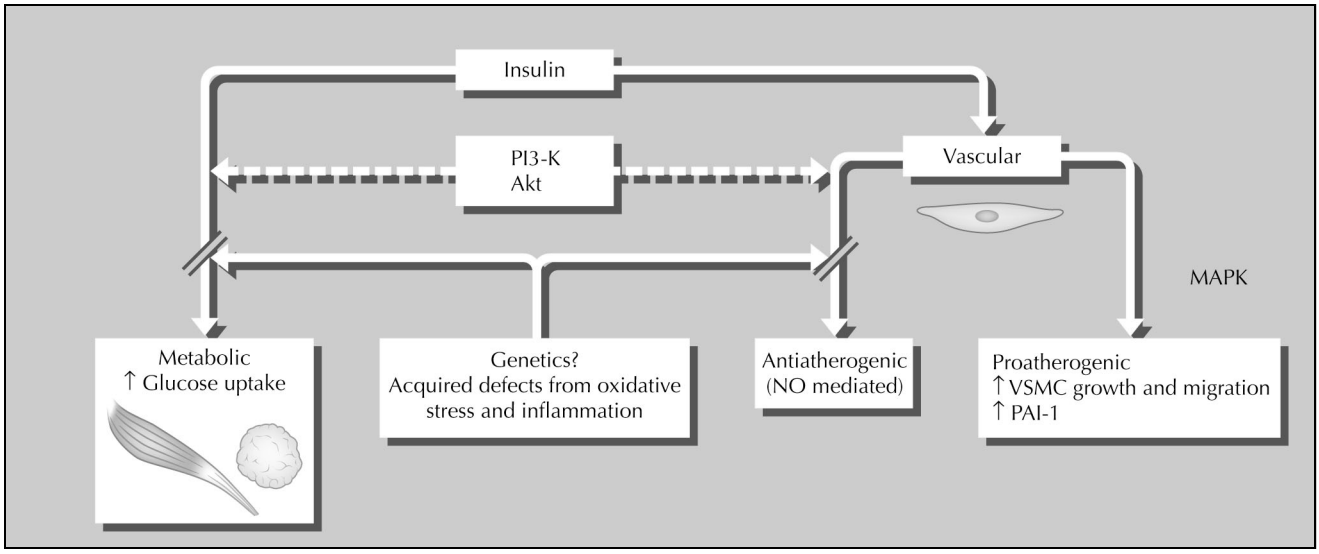

Figure 2. Possible shared genetically determined or acquired defects in phosphatidylinositol 3-kinase (PI3-K) or Akt activity in skeletal muscle, fat cells, and endothelial cells in subjects with insulin resistance. These defects lead to decreased insulin-mediated glucose uptake in peripheral tissues and decreased insulin-mediated nitric oxide (NO) production in endothelial cells. In this construct, the proatherogenic effects of insulin on vascular smooth muscle cell (VSMC) growth and migration and on plasminogen activator inhibitor-1 (PAI-1) levels would be preserved through the mitogen-activated protein kinase (MAPK) pathway.

resistant visceral fat and, therefore, an excess of substrates, hormones, and adipocytokines flowing to skeletal muscle, and the vascular wall, as already reviewed in the section regarding obesity in this article (Fig. 1). In addition, some of these individuals exhibit hypertension or dyslipidemia, known cardiovascular risk factors that are associated with endothelial dysfunction and inflammation. A third and intriguing possibility is a more direct association between metabolic insulin resistance and endothelial dysfunction and inflammation. Perhaps some genetic or acquired abnormalities in insulin action in skeletal muscle, fat, and endothelial cells are shared in a certain group of individuals. Insulin is known to stimulate nitric oxide production in endothelial cells and glucose uptake in muscle and fat tissue through the phosphatidylinositol 3-kinase (PI3-K) and Akt pathway [56,57]. In contrast, other effects of insulin action on the vasculature, including the stimulation of migration and growth of smooth muscle cells and the production of PAI-1, are mediated through the mitogen-activated protein kinase (MAPK) pathway [58]. Perhaps some individuals at risk for type 2 diabetes have some shared defects in the PI3-K pathway in skeletal muscle, fat, and endothelial cells, with an intact MAPK pathway, as has been described in Zucker rats, a well-known animal model of insulin resistance (Fig. 2) [59].

Interventions

Several interventions have been shown to improve endothelial function, such as angiotensin-converting enzyme inhibitors, statins, calcium channel blockers, estrogens, vitamin E, protein kinase C β inhibitors, angiotensin II receptor blockers, L-arginine, and fibrates [58,60,61]. In addition, weight loss, metformin, and thiazolidinediones (TZDs), common therapeutic options in the obese or insulin-resistant individual with type 2 diabetes, have shown some benefits on vascular function. Our group recently reported that diet and exercise, leading to a mean loss of 6.6% of body weight in obese individuals with normal glucose tolerance, IGT, and type 2 diabetes, resulted in a significant improvement in flow-mediated dilation in the brachial artery and a reduction in sICAM and PAI-1 levels [62].

The intensive lifestyle modification arm of the DPP, combining a balanced dietary regimen as well as exercise conducive to a mean loss of 5% of body weight, resulted in a significant reduction in hs-CRP, fibrinogen, and tPA in individuals with IGT [50••]. A recent study suggests that dietary changes leading to weight loss have a higher impact than exercise alone on markers of inflammation, including hs-CRP, TNF-α, and IL-6 [63]. As expected, vascular function sees the highest benefit when diet and exercise are combined, as shown in a recent study in obese children [64]. Another recent study showed that a reduction in glucose levels is the most important factor associated with an improvement in endothelial function in obese individuals following a very low caloric diet [65].

From the pharmacologic stand point, the use of TZDs has become a very attractive option to improve insulin resistance, endothelial function, and decrease inflammation. TZDs activate nuclear peroxisome proliferator-activated receptors (PPARs), having their main effect on PPAR-γ. TZDs lead to an improvement in vascular function through three mechanisms: 1) via a direct effect on adipose tissue, TZDs modify the circulating levels of fat-derived substrates and cytokines that affect endothelial function. Specifically, TZDs lead to a reduction of free fatty acids,

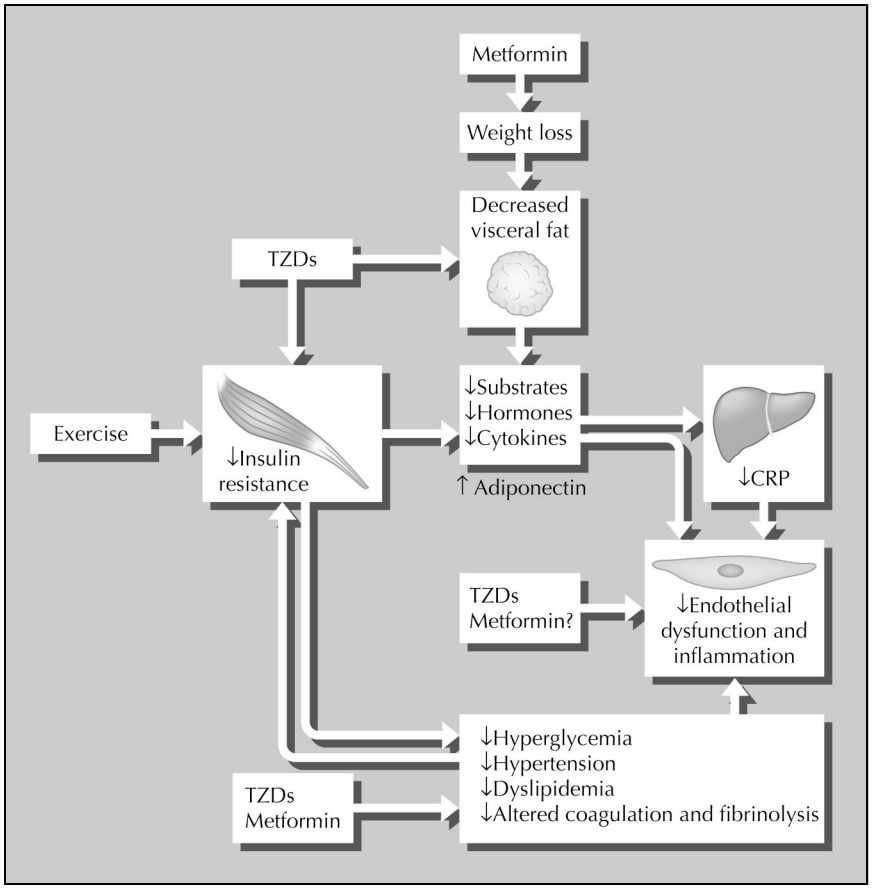

Figure 3. Mechanisms by which weight loss, exercise, thiazolidinediones (TZDs), and metformin decrease endothelial dysfunction and inflammation. Weight loss leads to a decrease in the total amount of fat, including visceral fat. Exercise improves insulin sensitivity directly. TZDs reduce the amount of visceral fat, leading to improved insulin sensitivity and endothelial function. A less potent direct effect on skeletal muscle is also present. They improve known cardiovascular risk factors and also have direct effects on vascular function. Metformin improves weight, glycemia, and other cardiovascular risk factors. It may also have a direct modest effect on vascular function. CRP—C-reactive protein.

TNF-α, IL-1, and IL-6. The IL-6 decrease leads to a reduced formation of CRP in the liver. In addition, PPAR-γ stimulation leads to an increase in adiponectin levels; 2) amelioration of known cardiovascular risk factors such as dyslipidemia, glycemia, and a modest effect on blood pressure; and 3) direct effects on the vascular wall.

Peroxisome proliferator-activated receptor-γ is expressed on all major cells of the vasculature, including endothelial cells, vascular smooth muscle cells, and monocytes and macrophages. In vitro and animal studies have shown that TZDs inhibit the expression of adhesion molecules, vascular smooth muscle cells proliferation and migration, foam cell formation, metalloproteinase-9 formation, and inflammation [66•,67]. Human studies have seen the translation of these effects into an improvement of vascular function. For instance, our group reported that troglitazone improved flow-mediated dilation in the brachial artery in association with a reduction of insulin resistance in a group of subjects with early type 2 diabetes [68]. Pioglitazone and rosiglitazone have also demonstrated beneficial effects on vascular reactivity, as well as on the levels of some markers of endothelial activation, inflammation, and IMT in the carotid artery [69]. Several studies are being conducted to assess the effects of TZDs on cardiovascular events in subjects with type 2 diabetes and in those with IGT.

Metformin is a biguanide that primarily reduces hepatic glucose output with a secondary, apparently indirect effect on decreasing peripheral insulin resistance. Metformin has beneficial effects on lipids, glucose, blood pressure, and weight. In the DPP, metformin also showed a significant reduction in hs-CRP and tPA in people with IGT, although less effectively than lifestyle modification [50••]. In the obese nondiabetic subjects included in the BIGPRO-1 (Biguanides and the Prevention of the Risk of Obesity) study, metformin led to a reduction in PAI-1 levels in an association with weight loss [70]. We recently found that metformin improved plasma levels of sVCAM, sICAM, and von Willebrand factor in Hispanic persons with IGT, whereas it had no significant effect on hs-CRP and TNF-α [71]. Interestingly, the beneficial effects on the markers of endothelial activation were independent from any effect on weight. These findings suggest that metformin may have some direct effects on vascular function, although more studies are needed to address this possibility. Mechanisms by which lifestyle modification, TZDs, and metformin improve vascular function are presented in Figure 3.

Conclusions

Insulin resistance, endothelial dysfunction, and low-grade chronic inflammation are frequently present in individuals at risk for type 2 diabetes. Subjects with obesity, family history of type 2 diabetes, PCOS, previous gestational diabetes, dyslipidemia, hypertension, IGT/IFG, or the

metabolic syndrome frequently share metabolic insulin resistance and endothelial dysfunction manifested by impaired endothelium-dependent vasodilation in the coronary or peripheral circulation, as well as an elevation of some adhesion molecules as markers of endothelial activation, and elevation of hs-CRP as a marker of inflammation, among other vascular abnormalities. All these metabolic and vascular derangements may be due to the presence of various substrates, hormones, and cytokines that flow from insulin-resistant visceral adipose tissue to affect insulin action in muscle and fat as well as nitric oxide production in endothelial cells. In addition, oxidative stress as the result of the presence of well-known cardiovascular risk factors in some of these groups can also participate in the genesis of vascular abnormalities. Some genetic factors that lead to the development of both an impairment of insulin-stimulated glucose uptake as well as insulin-stimulated nitric oxide production in endothelial cells may also play a role. Various strategies that improve insulin resistance, such as dietary changes and exercise leading to weight loss, as well as the use of medications such as TZDs and metformin, have been shown to improve vascular function in some groups at risk for type 2 diabetes. Whether these interventions can lead to a reduction of cardiovascular events in some of these groups, primarily in those with IGT, is not known yet and is currently under investigation.

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