The Proinflammatory and Hypercoagulable State of Diabetes Mellitus

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The diabetic population is at high risk for development of cardiovascular disease (CVD), cerebrovascular disease, and peripheral vascular disease. Approximately 80% of these patients die from a thrombotic cause, with CVD complications being involved in 75% of those. The mechanisms involved in the development of coronary artery disease (CAD) in the diabetic population are multifactorial, including hyperglycemia, hyperlipidemia, hypertension, and insulin resistance, ultimately leading to endothelial dysfunction and accelerated atherogenesis. Thus, diabetes has become a CAD risk equivalent. Early and aggressive intervention in treating risk factors may reduce the risk of developing diabetes and may prevent CVD in patients with established diabetes.
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Key words: Diabetes • Insulin resistance syndrome • Cardiovascular disease • Hypercoagulability

The diabetic population is at high risk for development of cardiovascular disease (CVD), cerebrovascular disease, and peripheral vascular disease. It has been reported that up to 80% of patients with diabetes die from a thrombotic cause, with 75% of these patients dying from CVD complications.[1] Epidemiologic data from the Framingham Study indicates a two- to threefold increase in atherosclerotic disease in the diabetic population. Importantly, diabetic patients without a history of myocardial infarction have been shown to have

a risk of infarction similar to nondiabetic patients with a history of prior myocardial infarction. As the prevalence of diabetes in the general population increases, the study of mechanisms underlying development of CVD in diabetics is ever important as they have a strong predisposition to the development of coronary artery disease (CAD) and suffer from increased morbidity and mortality as compared with nondiabetic patients. Thus, diabetes has become an atherosclerosis risk equivalent.

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The mechanisms involved in the development and progression of CAD in the diabetic population are multifactorial. Hyperglycemia, hyperlipidemia, and insulin resistance associated with diabetes all play a role in the pathogenesis of CAD.[1-9] Insulin resistance is basically an impaired physiologic response to the normal actions of insulin. Insulin resistance has been found to play a critical role in the development of CVD, and recent evidence suggests that it parallels the progression of atherosclerosis. It is important to note, however, that the atherosclerotic process begins in high-risk patients well before diabetes becomes established.

This article reviews the latest research and literature exploring the link between diabetes and CAD.

Risk of CAD Across Diabetic Groups

A higher risk of CAD occurs in the prediabetic state of impaired glucose tolerance (two- to threefold), in the metabolic syndrome as defined by the National Cholesterol Education Program (twofold risk), and in type 2 diabetes (fourfold risk).[3] The metabolic syndrome, defined by a cluster of risk factors including hypertension, central obesity, and dyslipidemia with or without hyperglycemia, seems to be associated with increased risk of macrovascular disease. In one study, a population of individuals aged 43-84 years was evaluated from 1988-1990 and again 5 years later. The risk of incident CVD 5 years later increased with the number of the components present; 2.5% of those with 1 component developed CVD, whereas 14.9% of those with 4 or more components developed CVD.[6]

Compared with nondiabetic individuals, patients with diabetes carry a greatly increased risk not only for sustaining CVD events but also for poorer outcomes associated with CAD. Although early mortality due to acute myocardial infarction (AMI) in the general population has been dramatically reduced, AMI-related mortality rates remain significantly greater for patients with diabetes versus those without diabetes (Figure 1).[7] A person with diabetes is more likely than his/her nondiabetic counterpart to die before reaching the hospital if a heart attack occurs outside the hospital.[8] Additionally, diabetic patients are about twice as likely as nondiabetic patients to die during hospitalization in the first year after a first AMI.[7] Diabetes is a significant predictor of perioperative cardiovascular morbidity and mortality as well, but few studies have evaluated methods to modify this risk. Current evidence indicates that aggressive management of diabetes may substantially decrease the adverse consequences of myocardial ischemia and infarction. In a recent prospective analysis of 336 consecutive patients admitted with AMI, 1-year mortality was 9% for patients with AMI and normal admission blood glucose values. In contrast, patients with hyperglycemia on admission demonstrated substantial increases ($P < .005$) in mortality.[10] The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial found a nearly linear relationship between blood glucose concentration on admission and long-term mortality.[11]

Disturbingly, research indicates that diabetic traits are associated

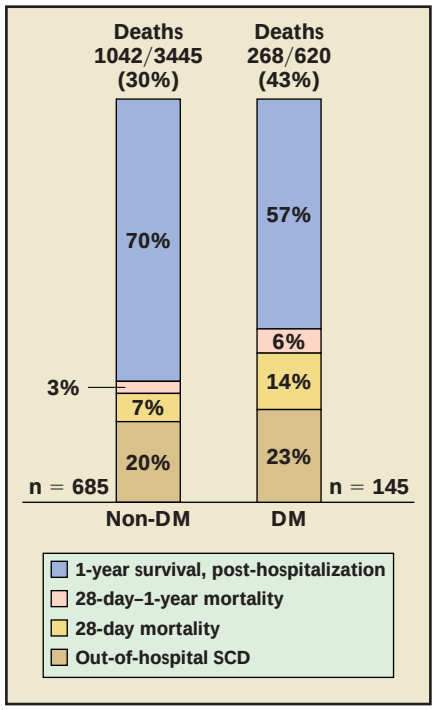

Figure 1. *Mortality associated with first myocardial infarction by diabetes status. Data are the percentages of mortality and survival for patients with diabetes mellitus (DM) and without DM (non-DM) in Finland between 1988 and 1992, adjusted for age and geographic area. Out-of-hospital deaths were based on review of death certificates and data extracted from medical records. SCD, sudden cardiac death. Reproduced with permission from Nesto RW.*[7]

with the accelerated development of atherosclerotic lesions and plaques. In a study by McGill and colleagues,[9] atherosclerosis in the right coronary artery was examined postmortem in youthful individuals (N = 1532), ranging in age from 15 to 34 years, who died of external causes. Fatty streaks were found in a greater percentage of the intimal surface of the right coronary artery in individuals with hyperglycemia (based on glycosylated hemoglobin [HbA_{1c}] value) than in individuals without hyperglycemia.[9] Moreover, the hyperglycemic right coronary arteries were three times more likely to have macroscopic raised lesions. It has also been proposed that body weight in young individuals is positively correlated with the accelerated development of atherosclerosis.[12]

The results of several studies suggest that atherosclerosis develops before the onset of clinical diabetes. In many epidemiologic studies, including the San Antonio Heart Study, an increased number of cardiovascular risk factors were found in patients before the onset of type 2 diabetes—particularly high plasma levels of triglycerides, low plasma levels of high-density lipoprotein (HDL) cholesterol, and elevated systolic blood pressure.[13] A second analysis of the San Antonio Heart Study indicated that an atherogenic pattern of changes in the prediabetic state is primarily seen in insulin-resistant patients.[14]

Inflammation

Several mechanisms may explain the relation between chronic inflammation and insulin resistance, including hypersecretion of proinflammatory cytokines (eg, interleukin [IL]-6, tumor necrosis factor [TNF]-α) from adipose tissue, which exerts major stimulatory effects on the synthesis of acute-phase proteins (APPs).[4,15] In addition, there may be enhanced expression of inflammatory proteins by the counteracting physiologic effect of insulin on hepatic APP synthesis as a result of decreased insulin sensitivity.[16]

Hepatocytes respond to many of the factors via their cell surface receptors. According to one theory, the inflammatory mediators fall into four major categories: 1) IL-6–type cytokines, of which IL-6 is the major representative; 2) IL-1–type cytokines (including IL-1α, IL-1β, TNF-α, and TNF-β); 3) glucocorticoids; and 4) growth factors (including insulin).[17] The cytokines would act as primary stimulators of APP gene expression, whereas the glucocorticoids and growth factors function more as modulators of cytokine action.[18] Several molecular mediators (eg, cellular adhesion molecules, cytokines) and inflammatory proteins (eg, fibrinogen, C-reactive protein [CRP]) comprise the acute-phase response.

Adipokines/Cytokines

Adipose tissue is a key producer of inflammatory cytokines (so-called adipokines), among which TNF-α and IL-6 are major pathophysiologic mediators of diabetes and the metabolic syndrome, including APPs such as CRP. In this way, the obesity component of the metabolic syndrome may be a contributor to inflammatory response, resulting in a chronic up-regulation of IL-6 production. Cytokines are intercellular signaling polypeptides, which have multiple functions in the autocrine and paracrine pathways. They act as important humoral regulators in immunoregulation, hematopoiesis, and the inflammatory cascade. In fact, cytokines may be more immediate in the underlying inflammatory process than fibrinogen or CRP. Volpato and associates[19] have already identified a relationship between IL-6 levels and clinical outcomes in patients with CVD. The lack of significant insulin action, as found in type 2 diabetes or insulin deficiency, is unable to block TNF-α, IL-1, and IL-6 actions, leading to a prolonged acute-phase reaction. Higher serum concentrations of CRP, fibrinogen, α_1-acid glycoprotein, amyloid A, sialic acid, and orosomucoid have been described in patients with type 2 diabetes mellitus as well.[20] Other cytokines in insulin resistance include a recently discovered centrally operating cytokine, IL-10, with strong anti-inflammatory properties by antagonizing IL-6 and TNF-α.[21]

IL-6

In humans, IL-6 activities range from acute-phase response to tissue factor expression by monocytes. It is estimated that one third of total circulating concentrations of IL-6 originate from adipose tissue. But other sources are also potentially important. Glucose-stimulated IL-6 production by human peripheral blood monocytes has been demonstrated, and it could be of significance in patients with type 2 diabetes. Although TNF-α functions locally at the level of the adipocyte in a paracrine fashion, IL-6 circulates in plasma at high concentrations. In this sense, IL-6 may represent a hormonal factor that induces muscle insulin resistance.[18]

Interleukin-6 has been implicated in the development of CAD through a number of metabolic, endothelial, and procoagulant mechanisms. Chronic up-regulation of IL-6 may predispose a patient to atherosclerosis. Huber and coworkers[22] demonstrated that chronic injections of small amounts of IL-6 in mice resulted in a two- to fivefold increase in lesion size. Endothelial and smooth muscle cells produce IL-6 and IL-6 gene transcripts that are expressed in human atherosclerotic

lesions. IL-6 not only strongly predicts increased CVD risk in established diabetes but also raises the risk of developing type 2 diabetes.[23] In a study of postmenopausal women on hormone therapy for 1 year, Rosano and colleagues[24] recently found that IL-6 was actually a stronger predictor of CVD events than elevated CRP.

TNF-α

Tumor necrosis factor-α is expressed by adipose tissue, and the plasma concentration of TNF-α is increased in obese humans. Plasma TNF-α concentration is also related to insulin resistance, and it falls with dietary restriction and weight loss. TNF-α blocks the action of insulin, and the induction of insulin resistance is mediated through its ability to produce serine phosphorylation of insulin receptor substrate 1, decreasing the tyrosine kinase activity of the insulin receptor.[25] TNF-α also decreases collagen synthesis and increases matrix metalloproteinase activity in vitro, perhaps leading to plaque rupture.[26] In fact, human atherosclerotic lesions have been found to contain TNF-α mRNA.[27] Early accumulation of monocytes and lymphocytes in the aortic intima with cytokine release may be essential in the development of the disease. Another proposed mechanism is the accumulation of cholesteryl esters in macrophages that are exposed to low-density lipoprotein (LDL), leading to increased synthesis and release of TNF-α.[28]

CRP

C-reactive protein is the classic APP and is a sensitive marker of inflammation and tissue damage, although it is not directly involved in the coagulation process. CRP is increased during inflammation and is an independent predictor for development of myocardial infarction and other cardiovascular events. In healthy individuals, CRP levels generally remain low and increase only during acute illness. However, in patients with diabetes, CRP levels are higher compared with healthy individuals, possibly contributing to the increased incidence of cardiovascular mortality in this patient population. Elevated CRP levels also have been linked to the development of diabetes.[29]

As a downstream biomarker, CRP provides functional integration of overall upstream cytokine activation. It also exerts direct effects on vascular disease, including the binding and activation of complement. Some studies indicate that high concentrations of plasma CRP elevate levels of cell adhesion molecules and tissue factor, mediate LDL cholesterol uptake by endothelial macrophages, induce recruitment of monocytes into blood vessel walls, and augment levels of monocyte chemoattractant protein-1. CRP classically originates from the liver, but it may also be produced by vascular sources, including cells residing in atherosclerotic plaques. Mice that were made transgenic for human CRP expression developed both prothrombotic and proatherogenic states.[30]

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Patients with the metabolic syndrome also had increased plasma high-sensitivity CRP (hs-CRP) levels in the Women's Health Study.[19,30] In the Insulin Resistant Atherosclerosis Study (IRAS), Festa and associates[15] demonstrated that plasma levels of CRP were strongly correlated with insulin sensitivity in nondiabetic patients. In addition, a linear increase in CRP concentrations was associated with the number of disorders related to the metabolic syndrome.[14,15] A recent statement released by the Centers for Disease Control and Prevention and the American Heart Association concluded that hs-CRP can be measured as an adjunct to the measurement of established risk factors for assessment of the risk of CAD.[31] The report acknowledged, however, that larger prospective studies are necessary to improve the reliability of the evidence. Kushner and Sehgal[32] pointed out that there are currently no data directly linking the reduction of hs-CRP to a reduced risk of atherosclerosis or cardiovascular events. In light of these findings, Mosca[33] and Rackley[34] suggested that although CRP levels may contribute greatly to patient management, these levels are probably not diagnostic on their own. These data might suggest that CRP is more strongly related to plaque vulnerability or thrombotic risk than to atherosclerosis itself.

The association between CRP and CVD partly reflects its strong association with body mass index and with total body-fat mass and waist girth.[15] This is consistent with the idea that part of the atherogenic effect of obesity is via inflammatory pathways.

Fibrinogen

Fibrinogen is an APP whose transcription is stimulated by IL-6 and whose synthesis is suppressed by IL-1β and TNF-α. High levels of fibrinogen are also associated with increased levels of CRP and may be a consequence of inflammatory changes associated with atherosclerosis. Data from the Framingham

Study showed that the risk of developing CAD correlates positively with fibrinogen levels for both men and women.[35] Increasing quartiles of fibrinogen also have been shown to be a significant predictor of peripheral arterial disease. In the Cardiovascular Health Study, fibrinogen was significantly associated with CAD (relative risk [RR], 2.1), stroke, or transient ischemic attack (RR, 1.3), and mortality within 2.5 years of follow-up (RR, 5.8) in men.[36] The elevated fibrinogen levels are often clustered with other major risk factors for atherosclerosis, such as age, lipids, blood pressure, smoking, and diabetes, but show an independent and strong association with CAD.[35,37] A recent study looked at various inflammatory and procoagulation markers and their correlation with metabolic factors. Fibrinogen loaded on the inflammation factor but not on the procoagulation factor, which is consistent with the hypothesis that regulation of fibrinogen concentration is more closely related to inflammation than to coagulation status.[38] In addition, studies have concluded that fibrinogen mainly reflects the severity of underlying disease rather than conferring increased procoagulation status.[39]

CD40/CD40L

Also of interest are CD40 and CD40 ligand (CD40L) proteins, which are a 50-kDa integral membrane protein of the TNF receptor family and a 39-kDa member of the TNF family, respectively. They are coexpressed by several cells involved in atherosclerosis, namely activated T lymphocytes, vascular endothelial cells, smooth muscle cells, and macrophages.[40] Studies examining circulating levels of soluble CD40L (sCD40L) found them to be elevated in patients with unstable angina and moderate hypercholesterolemia, and in individuals with type 1 or 2 diabetes.[40] As diabetic subjects have increased platelet activation and decreased endogenous inhibitors of platelet activity, this could lead to augmented plasma sCD40L concentrations.[41] However, the definitive source(s) of elevated sCD40L in diabetic patients require further investigation.

Peroxisome Proliferator-Activated Receptors

Peroxisome proliferator-activated receptors (PPAR) are transcription factors belonging to the nuclear hormone receptor family. They are ligand-activated and inhibit nuclear factor-κB (NF-κB) activity. This nuclear transcription factor has been widely implicated in proinflammatory actions at the isolated cardiac myocyte level and has been shown to be activated by endothelin, catecholamines, and predominantly angiotensin II. These cytotoxic effects accelerate the progression of congestive heart failure.[42] PPAR-γ is a key actor of adipocyte differentiation. It is expressed at high levels in mature cells and is thought to play a critical role in maintaining the metabolic functions of differentiated adipocytes.[43]

Adiponectin

Adiponectin (ARCP30, ADIpoQ, apM1, or GBP2 8) is a newly discovered 247–amino acid peptide that is predominantly secreted by adipocytes.[44,45] Expression of adiponectin is reduced in obesity, insulin resistance, and type 2 diabetes. Adiponectin is also inversely associated with other traditional cardiovascular risk factors, such as blood pressure, heart rate, and total and LDL cholesterol and triglyceride levels, and is positively related to HDL cholesterol levels.[46] Recent studies suggest that it may have antiatherogenic and anti-inflammatory properties that lower the risk of CAD, although data in humans are lacking.

Process of Atherogenesis

Atherosclerotic plaque development begins with endothelial cell activation, including overexpression of leukocyte adhesion proteins. The normal endothelium resists prolonged leukocyte attachment. But the expression of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), enhances the recruitment of inflammatory cells from the blood. VCAM-1 binds leukocytes (eg, monocytes) found in nascent atheromas. Stimuli such as monocyte chemoattractant protein-1 promote migration of leukocytes into the intima, where macrophage colony-stimulating factor promotes the differentiation of monocytes into macrophages. Macrophages in turn express scavenger receptors that allow them to engulf and modify lipoproteins to form foam cells. These lipid-laden phagocytes secrete a number of inflammatory mediators that amplify inflammation in the vessel wall and may contribute to additional leukocyte accumulation, smooth muscle cell proliferation, and extracellular matrix remodeling. By elaboration of matrix metalloproteinases that degrade the protective collagen structure of the plaque's fibrous cap, macrophages can contribute to plaque vulnerability, to rupture, and to formation of thrombi, which may precipitate acute coronary events. Simultaneously, the inflammatory response inhibits collagen production and stimulates macrophage expression of the potent procoagulant tissue factor, contributing to the prothrombotic environment. Thus, inflammation plays an integral role in the development and progression of atherosclerosis as well as its thrombotic complications.[30]

Various studies have yielded consistent results implicating cytokines and growth factors in the pathophysiology of insulin resistance and atherosclerosis and in their complications. Two notions exist regarding the pathophysiology of this exaggerated acute-phase response. The first contends that the acute-phase response is activated by ongoing intra-arterial inflammation, which involves arterial wall-resident macrophages secreting proinflammatory cytokines in response to multiple stimuli. According to the second view, extravascular stimuli induce a chronic, low-level activation of the acute-phase response. The low-level activators include smoking, mucosal infections, aging, and obesity.[18] The result of both views is the triggering of the inflammatory cascade leading to insulin resistance and atherosclerosis (Figure 2).

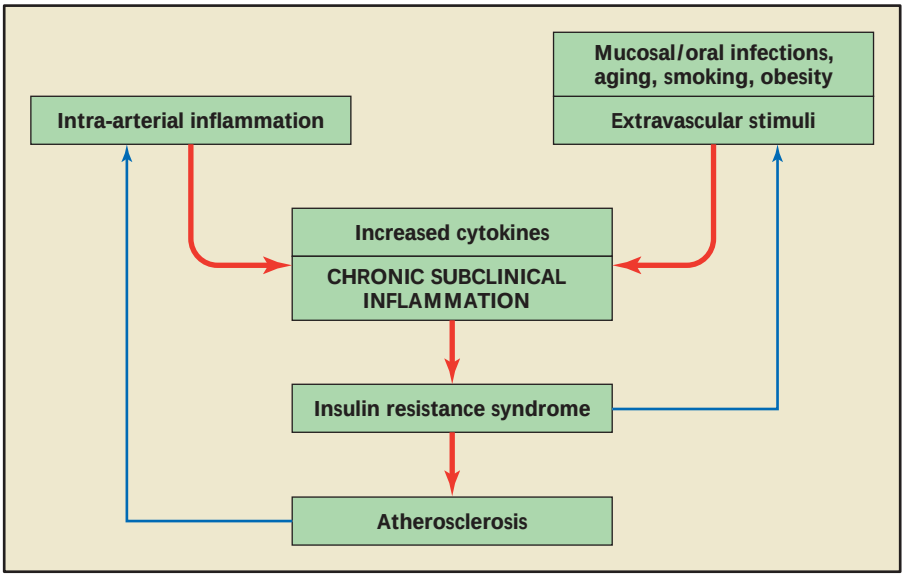
Procoagulation

Multiple abnormalities in platelet function, coagulation, and fibrinolysis have been described in patients who have diabetes. Among these are increased platelet aggregability, an increase in fibrinogen and factor VII levels, and an increase in the concentration of plasminogen activator inhibitor-1 (PAI-1).

The known metabolic CVD risk factors associated with insulin resistance syndrome do not adequately explain the excess CVD risk attributed to this syndrome, and abnormalities in hemostatic variables may contribute to this excess risk. One study used data from the Cardiovascular Health Study and looked at metabolic, procoagulation, and inflammation variables to examine the clustering of the metabolic and hemostatic risk markers. The authors concluded that hemostatic variables may be independently responsible or, because they are highly intercorrelated, may predict disease because they represent a class of variables that reflect a larger underlying disease mechanism.[47]

The endogenous fibrinolytic system represents equilibrium between activators of plasminogen (primarily tissue type plasminogen activator) and inhibitors of these activators (PAI-1). Low-grade coagulation is a continuous process, and thus the fibrinolytic activity is necessary to maintain the fluidity of blood. Impaired fibrinolytic function in diabetes leads to coagulation and thrombosis, a critical process in cardiovascular events. Elevated levels of fasting insulin are also associated with impaired fibrinolysis and hypercoagulability in subjects with normal glucose tolerance.[48] Other factors in diabetic patients include alterations in serum fibrinogen and factors V, II, and VII, increased D dimer, von Willebrand factor (vWF) antigen, α_2-antiplasmin, and decreased antithrombin III.[49] However, many of these abnormalities are nonspecific, and the association of insulin resistance with coagulation abnormalities is less reliable than that with abnormal fibrinolysis. Nevertheless, coagulation abnormalities probably play a role in increasing the frequency and severity of thrombotic events in patients with diabetes.

Figure 2. *Possible pathogenesis of atherosclerosis resulting from chronic inflammation. Adapted with permission from Fernandez-Real JM and Ricart W.*[18]



Platelet Markers

Platelets can bind to the surface of activated endothelial cells and to leukocytes that are already adherent to the vessel wall, mediated by a variety of glycoproteins that are expressed on activated platelets, including P-selectin, platelet endothelial cell adhesion molecule-1, vWF, and β_3-integrins (glycoprotein IIb/IIIa).[50] There is growing agreement that platelets not only are involved in hemostasis and thrombosis but may also modulate acute and chronic inflammatory responses. Platelets release factors that may either inhibit (soluble P-selectin, nitric oxide [NO]) or activate (oxygen radicals, leukotrienes, thromboxane A_2) neutrophils.[51] Platelets may also enhance the recruitment of leukocytes into

inflamed tissue by providing P-selectin adhesion sites and by reducing shear rates in venules through the release of potent vasoconstrictors such as thromboxane A.[51]

Platelets are known to be altered in younger type 1 diabetic subjects, but platelet adhesion protein function in older type 2 diabetic patients with established CAD has not been well described.[52,53] A recent study found that the surface expression of platelet P-selectin was significantly increased in type 2 diabetic cardiac patients compared with nondiabetic cardiac patients. Furthermore, the platelets in diabetic blood demonstrated a hypersensitivity to an acute, in-vitro stimulation with platelet-activating factor, a cytokine produced and released under ischemic conditions. These findings indicate that there is a marked rise in the level of platelet activity in the blood of diabetic patients with established ischemic heart disease. Another group of researchers[54] suggested a primary alteration in the megakaryocytic bone marrow thrombocytopoiesis, releasing hyperreactive platelets into the circulation of diabetes patients in a manner similar to end-stage CVD. Recently, such platelet alterations have been reported even in fetal blood in diabetic pregnancies.[55] This study did not show a response to metabolic improvement, indicating that the inflammatory cell reactions, including platelet activation, remain active.[53]

PAI-1

Plasminogen activator inhibitor-1 antigen and activity are elevated in a wide variety of insulin-resistant subjects, including obese subjects with and without diabetes, as well as in women with polycystic ovarian syndrome. Evolving evidence of the central role of PAI-1 in mediating fibrosis and thrombosis increasingly supports the theory that it is a significant risk factor for macrovascular complications and CVD, particularly in patients with diabetes. Maintenance of hemostasis is mediated through such factors as PAI-1 and tissue plasminogen activator (t-PA). PAI-1 is known to be regulated by the key proinflammatory transcription factors NF-κB and Egr-1. Both TNF-α and insulin have been shown to up-regulate endothelial cell production of PAI-1.[47]

Evolving evidence of the central role of PAI-1 in mediating fibrosis and thrombosis increasingly supports the theory that it is a significant risk factor for macrovascular complications and CVD, particularly in patients with diabetes.

PAI-1 has two important actions in the vessel wall.[29] First, it inhibits the breakdown of fibrin clots, promoting thrombus formation upon rupture of unstable atherosclerotic plaques. PAI-1 interferes with clot dissolution by inhibiting the actions of t-PA. Second, elevated PAI-1 activity, by altering the fibrinolytic balance, also contributes to remodeling of the vascular architecture.[16]

Several clinical studies have demonstrated a strong correlation between circulating PAI-1 levels and cardiovascular events and mortality. Meigs and colleagues[48] examined levels of hemostatic factors in 2962 men and women with (n = 587) or without (n = 2375) glucose intolerance or diabetes who were participating in the Framingham Offspring Study. Serum t-PA and PAI-1 levels were found to be higher with increasing insulin concentrations in both glucose-tolerant and -intolerant patients ($P < .01$ in both groups). Results of the study indicate that elevated levels of fasting insulin are associated with a corresponding increase in markers of hypercoagulability, thus increasing the risk of thrombosis in both glucose-tolerant and -intolerant patients. The greatest elevations in PAI-1 occur when there is a combination of hyperinsulinemia, hyperglycemia, and increased free fatty acids in obese insulin-resistant subjects, and impaired fibrinolysis is closely related to the metabolic syndrome.[56] There is also evidence that PAI-1 content is increased in atherosclerotic lesions of patients with type 2 diabetes.[57] Diabetic patients have increased PAI-1 in the arterial wall, which could decrease local fibrinolysis and elevate thrombus formation, leading to evolution of atherosclerotic plaques.

Other Factors

The traditional risk factors, such as obesity, dyslipidemia, and hypertension, do not fully account for the excess risk for CAD in diabetic patients. Therefore, other nontraditional risk factors may be important in people with diabetes. Although some of these risk factors cluster, others appear to be independent of one other. Although CAD is a complex multifactorial disease and many of these processes are functioning simultaneously, in the interest of simplicity, we will consider each risk factor separately. Many of these risk factors are common for both diabetes and CAD. Some of these nontraditional risk factors have been shown in studies to be altered in the prediabetic state, during which both insulin resistance and inflammation are often present (Figure 3).

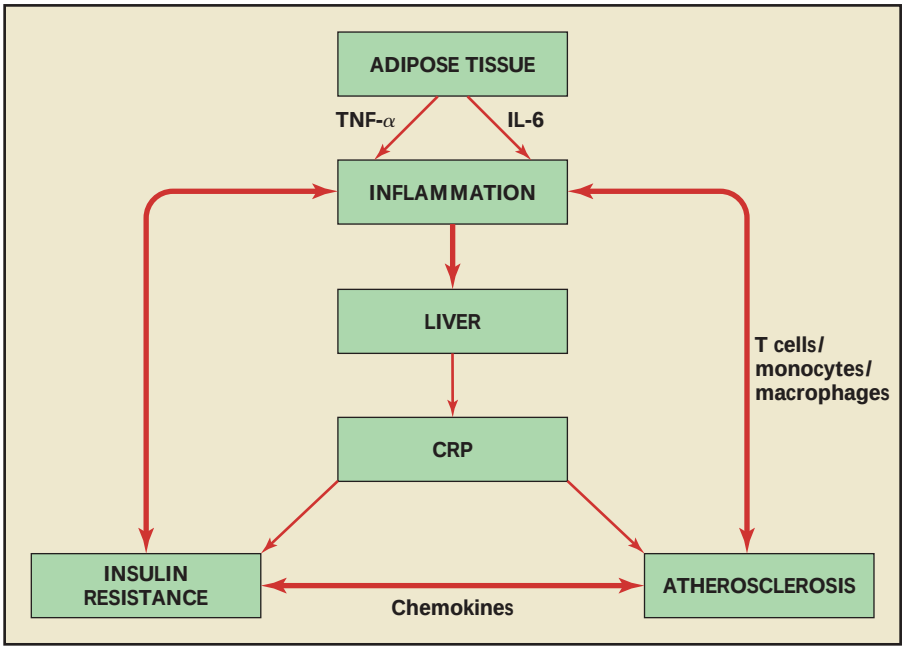


Figure 3. *Interactions between inflammation, insulin resistance, and atherosclerosis. CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α. Adapted with permission from Fonseca V et al.*[58]

Endothelial Dysfunction

The endothelium is a critical determinant of vascular tone, reactivity, inflammation, vascular remodeling, maintenance of vascular patency, and blood fluidity. Many of the functions of the endothelium are maintained through regulatory substances secreted from endothelial cells, which may often have opposing actions. For example, endothelial cells secrete NO and prostacyclin, which are potent vasodilators. The vasodilatory actions are opposed by secretion of potent vasoconstrictors such as endothelin-1. These actions maintain the balance among smooth muscle cell growth, promotion, and inhibition; thrombosis and fibrinolysis; inflammation; and cell adhesion. Other biochemical parameters of endothelial dysfunction include plasma vWF, thrombomodulin, and several adhesion molecules, such as VCAM, intercellular adhesion molecule (ICAM), E-selectin, and P-selectin. Because endothelial injury is an early event in atherogenesis, it has been suggested that abnormal ability to vasodilate may precede the development of structural changes in the vessel wall. This abnormality has been shown in several insulin-resistant states and is present in relatives of patients with type 2 diabetes who have normal glucose tolerance. It has even been proposed that endothelial dysfunction may be a precursor of the insulin resistance or vice versa.[58]

In patients with diabetes or those with impaired glucose tolerance, however, these normal patterns of reactive vasodilation are impaired.[59] Postprandial increases in plasma glucose, LDL cholesterol, and insulin concentrations also cause further vasoconstriction by triggering increased expression and activity of vasoconstrictors, including endothelin-1, angiotensin II, and prostanoids.[60] Endothelin-1 production is likely increased by the presence of advanced glycation end products produced in patients with diabetes in response to hyperglycemia.[61]

Blood Pressure

Although it is well established that essential hypertension is frequently associated with insulin resistance, the impact of this abnormality on blood pressure homeostasis is still a matter of debate. Patients with hypertension often have significantly reduced rates of glucose disposal. However, it is not yet known whether insulin resistance itself gives rise to increased blood pressure.[2] Multiple potential mechanisms by which insulin resistance may cause hypertension include resistance to insulin-mediated vasodilation, impaired endothelial function, sympathetic nervous system overactivity, sodium retention, increased vascular sensitivity to the vasoconstrictor effect of pressor amines, and enhanced growth factor activity leading to proliferation of smooth muscle walls. However, some studies do not support the association of metabolic insulin resistance with essential hypertension.[58] Although several mechanisms may contribute to salt-sensitive hypertension, altered NO metabolism appears to play a major role. The potential link between hypertension and inflammatory mechanisms is summarized in Figure 4.

Multiple potential mechanisms by which insulin resistance may cause hypertension include resistance to insulin-mediated vasodilation, impaired endothelial function, sympathetic nervous system overactivity, sodium retention, increased vascular sensitivity to the vasoconstrictor effect of pressor amines, and enhanced growth factor activity leading to proliferation of smooth muscle walls.

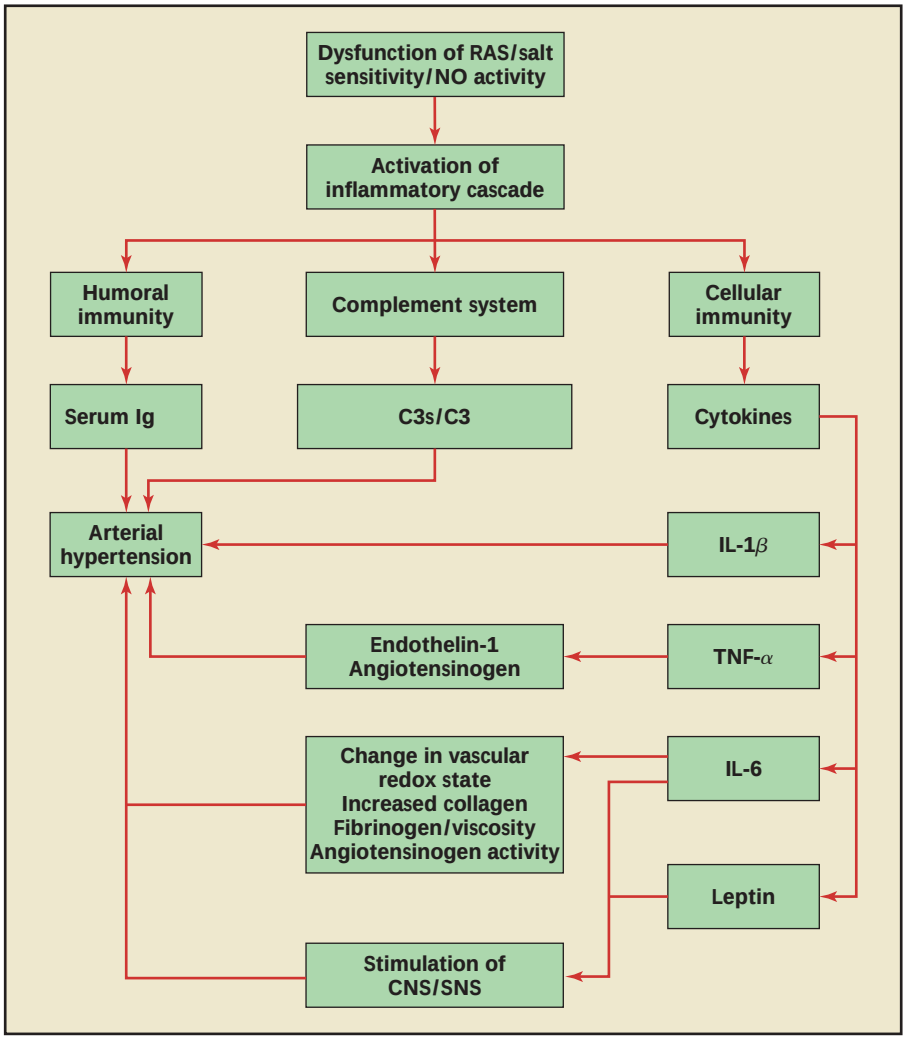


Figure 4. *Proposed mechanisms in the development of hypertension via inflammatory pathways. CNS, central nervous system; Ig, immunoglobulin; IL, interleukin; NO, nitric oxide; RAS, renin-angiotensin system; SNS, sympathetic nervous system; TNF, tumor necrosis factor. Adapted with permission from Fernandez-Real JM and Ricart W.*[18]

Vessel Structure

Several studies have demonstrated abnormal carotid intima-media complex thickness (IMT) in patients with diabetes, suggesting a link between increased carotid IMT and insulin resistance.[61] B-mode ultrasound is a noninvasive method for evaluating carotid IMT, which is an indicator of early atherosclerosis and may serve as a surrogate marker for atherosclerotic events.[62] One possibility is the effect of hyperinsulinemia on growth of vascular smooth muscle cells and extracellular matrix. Increased arterial stiffness is another indicator of early atherosclerosis that has been found with increased frequency in patients with diabetes, possibly a result of glycation of arterial collagen and elastin and accumulation of advanced glycation end products.[63] The calcification of the arterial wall is a simple noninvasive marker of established CAD. Abnormal calcium scores on electron beam computed tomography (EBCT) are common in patients with diabetes, although the significance of such abnormalities in predicting cardiovascular events is unclear. Nevertheless, carotid IMT and EBCT provide valid measures of subclinical atherosclerosis. Interestingly, nondiabetic young relatives of patients with diabetes also have arterial stiffness, suggesting some genetic influence.[64]

Hyperinsulinemia

Prospective studies suggest that hyperinsulinemia may be an important risk factor for ischemic heart disease. In the Quebec Heart Study, high fasting insulin concentrations were an independent predictor of ischemic heart disease.[65] Similarly, hyperinsulinemia was associated with increased all-cause and cardiovascular mortality in Helsinki policemen, independent of other risk factors.[66] However, it is important to recognize that the relationship between insulin resistance and plasma insulin may not be linear, and some studies have been negative. Ethnic background and type of insulin assay may influence the results in these studies. Overall, these studies confirm that insulin resistance with resultant hyperinsulinemia is an independent risk factor for CVD (including CAD and stroke). It remains controversial whether insulin itself is the culprit as the vasodilatory and anti-inflammatory properties should protect against atherosclerosis.[58]

Connection Between Inflammation and Procoagulation

Few studies have actually looked at the possible link between the proinflammatory and prothrombotic states in diabetic patients. However, the work of Ritchie and colleagues[4,5] suggests a possible pathway. Monocytes appear capable of binding fibrin degradation products and subsequently producing IL-6, which goes to the liver and affects the acute-phase

response. This has been proposed to be the mechanism by which fibrinogen consumption is replaced and may be an important link between coagulation and inflammation.[4] This theory may have far-reaching implications in such areas as development of drugs that address the underlying mechanisms for premature CVD in this high-risk population.

As mentioned in detail elsewhere in this article, the proinflammatory features of diabetes promote plaque instability and rupture. As a result of the relative imbalance between collagen synthesis and breakdown, the plaque becomes more susceptible to rupture when exposed to hemodynamic stresses.[60] The prothrombotic state in diabetes is marked not only by hyperaggregability of platelets in the blood but also by the disruption of fibrinolysis within the blood vessel walls and atheromas. Diabetic atheromas may also exhibit increased expression of tissue factor, a substance that acts as a potent procoagulant.[7,67] As mentioned earlier, levels of IL-6 not only are associated with the severity of the conditions but also are very strong predictors of subsequent outcomes. This might be explained by the procoagulant effect of inflammation. CRP, whose secretion is induced by IL-6, may promote thrombosis by activating the complement pathway, and has been shown to induce circulating monocytes to express tissue factor, a potent procoagulant factor.[67] The presence of an inflammatory process characterizes the site of plaque rupture or erosion, and proinflammatory cytokines upregulate the expression of matrix metalloproteinases, which are known to be involved in the vascular remodeling and plaque disruption.[19] Thrombin is another possible link between coagulation and inflammation. When thrombin binds to its receptor, protease-activated receptor-1, on endothelial cells, it induces the expression of P-selectin, E-selectin, VCAM-1, and ICAM-1 through activation of NF-κB.[68]

Therapeutic Options

Until now, the rationale for the treatment of diabetes was directed toward the correction of hyperglycemia, because hyperglycemia is known to be responsible for the symptoms of polyuria and polydipsia in the short term and microangiopathic complications of diabetes in the long term. However, the recent focus is on targeting the proinflammatory state of diabetes. The following section briefly mentions the latest options for treating nontraditional risk factors for CVD in diabetes.

Thiazolidinediones

Ligands to the nuclear receptor PPAR have emerged as important therapeutic options in this setting because they improve insulin resistance and attenuate the proinflammatory, proatherosclerotic environment in obesity and type 2 diabetes. The thiazolidinediones (TZDs), such as rosiglitazone and pioglitazone, 1) activate PPAR-γ; 2) decrease insulin-resistant, proinflammatory cytokines, TNF-α, leptin, PAI-1, IL-6, and circulating hs-CRP levels; and 3) increase plasma adiponectin levels. These actions on adipose adipokine production likely contribute to the insulin-sensitizing effects of the TZDs and to their effects to protect the vasculature.[3] These agents also cause an increase in the anti-inflammatory cytokine IL-10 and decrease reactive oxygen species generation by mononuclear cells.[18] In patients with type 2 diabetes who completed a 26-week randomized, double-blind, placebo-controlled study of rosiglitazone, the reduction in mean hs-CRP was significantly correlated with the change in the estimate of insulin resistance.[69] TZDs have been shown to improve endothelial function, inflammation, and fibrinolysis.[58]

Freed and associates[70] found that the addition of rosiglitazone to sulfonylurea was associated with a 21.8% decrease in PAI-1 antigen level and a 33.8% decrease in PAI-1 activity, compared with increases in both hemostatic markers with sulfonylurea treatment alone. Treatment with troglitazone was shown to also significantly decrease IMT in patients with type 2 diabetes.[71] It is possible that all the above effects of the TZDs are direct cellular effects on the atherosclerotic process that are not linked to their effects on insulin resistance.

Angiotensin-Converting Enzyme Inhibitors

Many clinical trials have documented the effectiveness of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in delaying the development and progression of diabetic nephropathy. In addition, the Micro Hope Trial demonstrated favorable effects on cardiovascular outcomes.[72] ACE inhibition also significantly decreases PAI-1 without altering t-PA. A reduction in the incidence of type 2 diabetes in patients treated with ramipril, an ACE inhibitor with presumed anti-inflammatory effects, has been observed.[73] Thus, it appears that either an ACE inhibitor or an ARB should be included in the treatment regimen for patients with diabetes and hypertension. Current American Diabetes Association guidelines suggest that the practice of choosing an ACE inhibitor as a first-line therapy is reasonable, particularly in older people who have high cardiovascular risk.

Insulin

Insulin is increasingly recognized as an anti-inflammatory molecule. This

general anti-inflammatory activity is supposed to be responsible for the improvements in mortality and morbidity after low doses of insulin are given to patients with AMI and to patients admitted to a surgical intensive care unit.[74] In the United Kingdom Prospective Diabetes Study (UKPDS), the risk of AMI was directly related to fasting blood glucose and HbA_{1c} concentrations.[75] Furthermore, intensive insulin treatment instituted within hours of admission after AMI significantly decreased long-term mortality compared with a less aggressive management approach. A decrease in mortality as well as morbidity resulting from infection was also observed in patients with diabetes who were treated with a continuous infusion of insulin to maintain blood glucose concentration $<$ 200 mg/dL after cardiac surgery.[76] Aggressive insulin treatment (ie, maintenance of blood glucose concentrations between 80 and 110 mg/dL with insulin) significantly decreased in-hospital deaths from 26% to 17% in critically ill patients (13% had a history of diabetes) admitted to the intensive care unit (60% were cardiac surgical patients) compared with conventional therapy (ie, maintenance of blood glucose concentration between 180 and 200 mg/dL).[77] Few patients developed hypoglycemia requiring treatment, and none developed hemodynamic instability or neurologic complications. These remarkable results suggest that aggressive control of blood glucose concentrations with insulin may provide substantial improvements in outcome.

Antiplatelets

Salicylates have been described to improve insulin action in vitro and in vivo in animal models.[78] High doses of salicylate and inactivation of IκB kinase-β prevent fat-induced insulin resistance in skeletal muscle by blocking fat-induced defects in insulin signaling and action. In humans, high-dose aspirin treatment resulted in an approximately 25% reduction in fasting plasma glucose, associated with an approximately 15% reduction in CRP and total cholesterol, an approximately 50% reduction in triglycerides, and an approximately 30% reduction in insulin clearance. Aspirin treatment also resulted in an approximately 20% reduction in basal rates of hepatic glucose production and an approximately 20% improvement in insulin-stimulated peripheral glucose uptake.[79]

Recent studies have examined whether nonaspirin inhibitors of platelet aggregation have added benefit in diabetic patients. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, a post hoc analysis of the diabetic subgroup revealed that clopidogrel reduced a composite CAD end point 12% more than did aspirin, an effect that was greater than that observed in nondiabetic subjects; in addition, clopidogrel caused less bleeding.[80] These data suggest that more-potent antiplatelet therapy is of particular benefit in diabetic patients with vascular disease, and given the observed synergistic effects of dual clopidogrel and aspirin therapy, diabetic patients may have added benefit from the combination.

Revascularization

Patients with diabetes respond less favorably to percutaneous coronary interventions (PCI) and surgery compared with nondiabetic patients, which has led to the initiation of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. Historically, revascularization has been shown to improve survival over medical therapy alone in selected high-risk patients. In the Bypass Angioplasty Revascularization Investigation 1 (BARI 1) study, patients with diabetes had higher mortality rates compared with those without diabetes despite revascularization in each group. The increased rates of restenosis in patients with diabetes is likely caused by intimal hyperplasia.[81]

The primary objective of the BARI 2D trial is to simultaneously test with the use of a 2×2 factorial design two clinically discrete hypotheses regarding the efficacy of treatment in patients with type 2 diabetes and stable CAD who may be candidates for coronary revascularization. The first concern is the value of early use of coronary revascularization procedures, and the second is the value of using an insulin-sensitizing agent versus an insulin-providing therapy. Another hypothesis being tested in the trial concerns treatment of the CAD itself. The two strategies being compared are intensive pharmacologic management of CAD and intensive pharmacologic management plus initial coronary revascularization by either PCI or coronary bypass grafting (CABG). The target for glycemic control in both groups is reduction of HbA_{1C} concentrations to $\leq$ 7.0%. The primary end point is 5-year mortality, with a major secondary combined end point of death, Q wave myocardial infarction, or stroke. This 5-year prospective study is expected to be a landmark trial in the management of patients with type 2 diabetes and CAD.[81,82]

Future Considerations

Clinicians and clinical investigators are increasingly using newer measures of both insulin resistance and CAD risk. Most are useful research tools but not practical for clinical use. The most widely accepted measure of insulin resistance is the so-called euglycemic-hyperinsulinemic

clamp. A number of mathematical models have been developed to estimate insulin resistance, and most use both fasting insulin and glucose concentrations. Such measures, including the homeostatic model assessment have been used in epidemiologic studies.[83] Several laboratory measures, such as fasting and stimulated plasma insulin, C-peptide, homocysteine, CRP, fibrinogen, and PAI-1, have also been suggested as surrogate measures for insulin resistance. However, results are often difficult to interpret. Ultimately, the diagnosis of insulin resistance syndrome remains a clinical one.

It is also essential to determine whether treatment to enhance insulin sensitivity improves cardiovascular survival. The current success of PCI and CABG suggests that early application of these procedures may reduce mortality and myocardial infarction rates in diabetic patients. Similarly, it is crucial to determine whether insulin sensitizers may improve cardiovascular mortality among patients with type 2 diabetes. There are other ongoing studies that are focusing on these issues—including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Veterans Affairs Diabetes Trial (VADT).[82] ■

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Main Points

- The thiazolidinediones (TZDs), such as rosiglitazone and pioglitazone, 1) activate PPAR-γ; 2) decrease insulin-resistant, proinflammatory cytokines, TNF-α, leptin, PAI-1, IL-6, and circulating hs-CRP levels; and 3) increase plasma adiponectin levels.
- A higher risk of coronary artery disease occurs in the prediabetic state of impaired glucose tolerance (two- to threefold), in the metabolic syndrome as defined by the National Cholesterol Education Program (twofold risk), and in type 2 diabetes (fourfold risk).
- Several mechanisms may explain the relation between chronic inflammation and insulin resistance, including hypersecretion of proinflammatory cytokines (eg, IL-6, TNF-α) from adipose tissue, which exerts major stimulatory effects on the synthesis of acute-phase proteins.
- It appears that either an ACE inhibitor or an ARB should be included in the treatment regimen for patients with diabetes and hypertension.
- Coagulation abnormalities probably play a role in increasing the frequency and severity of thrombotic events in patients with diabetes.
- Some of the nontraditional risk factors for coronary artery disease in diabetes have been shown in studies to be altered in the prediabetic state, during which both insulin resistance and inflammation are often present.
- Aggressive control of blood glucose concentrations with insulin may provide substantial improvements in outcome.
- Until now, the rationale for the treatment of diabetes was directed toward the correction of hyperglycemia; however, the recent focus is on targeting the proinflammatory state of diabetes.
- The current success of percutaneous coronary intervention and coronary artery bypass grafting suggests that early application of these procedures may reduce mortality and myocardial infarction rates in diabetic patients.

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