JACC Vol. 27, No. 3
March 1, 1996:528–35

Potential Mechanisms Promoting Restenosis in Diabetic Patients

DORON ARONSON, MD, ZACHARY BLOOMGARDEN, MD, ELLIOT J. RAYFIELD, MD

New York, New York

Diabetes is associated with greater restenosis rates after successful balloon angioplasty. The metabolic alterations that occur as a result of hyperglycemia or hyperinsulinemia can accelerate many of the pathophysiologic processes that lead to restenosis. Diabetes results in endothelial dysfunction and accelerated platelet deposition, which increase the propensity to thrombosis. Several growth factors known to promote the restenosis process are overexpressed in the presence of hyperglycemia. Advanced glycosylation promotes inflammatory cell recruitment and smooth muscle cell proliferation. Many of the potential mechanisms promoting restenosis in diabetic patients can be ameliorated by improved metabolic control.

(J Am Coll Cardiol 1996;27:528–35)

Restenosis limits the long-term beneficial effects of percutaneous transluminal coronary angioplasty and related procedures (1). The importance of diabetes as a consistent clinical predictor for restenosis after angioplasty has been demonstrated in several studies. The initial report from the National Heart, Lung, and Blood Institute Angioplasty Registry (2) indicated that the angiographic restenosis rate in diabetic patients was 47% compared with 32% in nondiabetic patients. Subsequent studies have reported restenosis rates of 49% to 71% among diabetic patients (3–9).

New angioplasty devices failed to make any major impact on the restenosis rate among diabetic patients. Diabetes is associated with a twofold increase in recurrent clinical events after directional coronary atherectomy (10). Likewise, diabetic patients have higher restenosis rates after stent placement (11) and after excimer laser angioplasty (12).

Restenosis is viewed as an intraluminal growth process after an arterial injury (see below), and risk factors for restenosis are likely to be risk factors for this growth process. In contrast to diabetes, other traditional risk factors for atherosclerosis, such as male gender, hypertension, hypercholesterolemia and continued smoking after angioplasty, have been reported as risk factors only inconsistently (1,3,7,8). In attempting to predict restenosis from clinical variables, Weintraub et al. (3) concluded that "the problem is that each of the clinical variables is a correlate without a clear relation to the underlying pathophysiological process." The intent of this review is to examine some of the putative mechanisms involved in the restenosis process in light of pathophysiologic events currently known to occur in the diabetic state.

From the Division of Endocrinology and Metabolism, Department of Medicine, Mount Sinai Medical Center, New York, New York 10029.

Manuscript received May 8, 1995; revised manuscript received September 13, 1995, accepted September 29, 1995.

Address for correspondence: Dr. Doron Aronson, Metabolism Section, Joslin Diabetes Center, One Joslin Place, Boston, Massachusetts 02215.

Pathophysiologic Mechanisms of Restenosis in Relation to Diabetes

The complex pathophysiologic events leading to restenosis after balloon injury involve endothelial denudation; platelet deposition with mural thrombosis; vascular smooth muscle cell proliferation and migration; and extracellular matrix synthesis (13–17). Intimal smooth muscle cell hyperplasia is the predominant histologic finding in restenotic lesions (18). A fundamental element in the development of intimal hyperplasia is the transformation of smooth muscle cells from a contractile to a proliferative, secretory phenotype. The restenosis process is initiated when balloon inflation causes endothelial denudation and deep vessel injury. The exposure of subendothelial elements initiates platelet adhesion and activation. Activated platelets at the site of injury secrete growth factors that release smooth muscle cells from growth inhibition and induce their proliferation and subsequent migration from the media to the intima (15,17). Smooth muscle cell proliferation continues beyond the phase of platelet deposition (14). Activated smooth muscle cells themselves secrete growth factors that can act on surrounding cells and help to sustain proliferation and migration (19). The proliferative response becomes quiescent several months after intervention.

A second fundamental element of restenosis is the production and secretion of extracellular matrix by smooth muscle cells that have migrated into the injured intimal zone (17). The neointima is generally hypocellular, composed predominantly of extracellular matrix material that forms the bulk of neointimal growth (13,16).

Although vessel recoil may also contribute to loss of lumen, the markedly increased restenosis rate seen in diabetic patients after stent placement (11) underscores the role of enhanced smooth muscle cell proliferation as the major mechanism for restenosis in these patients, because coronary artery stenting provides a rigid endovascular lattice that prevents both elastic recoil and vascular spasm at the treated site (11).

0735-1097/96/$15.00
0735-1097(95)00496-3

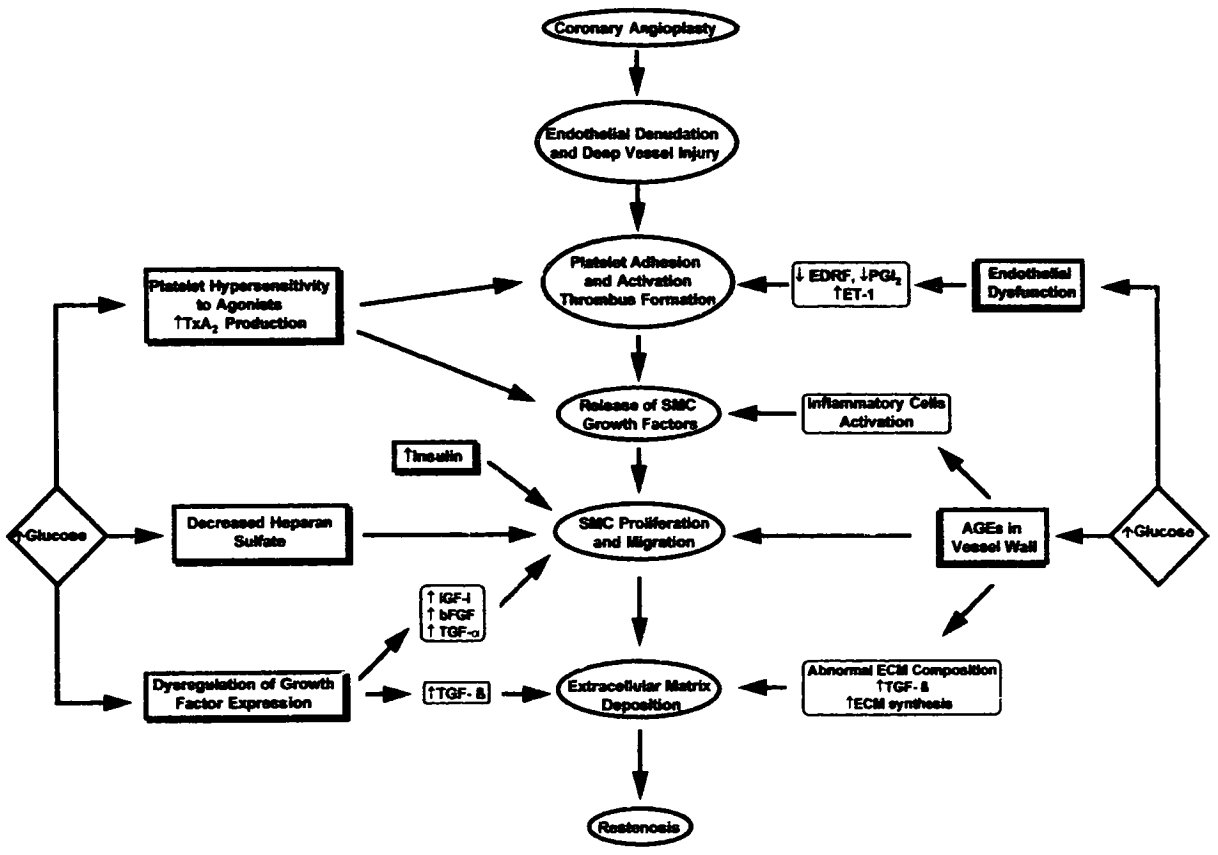

Figure 1. Proposed model for accelerated vascular lesion formation in diabetes. AGEs = advanced glycosylation end products; bFGF = basic fibroblast growth factor; ECM = extracellular matrix. EDRF = endothelium-derived relaxing factor; ET-1 = endothelin-1; IGF-I = insulin-like growth factor-1; PGI_2 = prostacyclin; TGF-α = transforming growth factor-alpha; TGF-β = transforming growth factor-beta; TxA_2 = thromboxane A_2.

In the diabetic state, several mechanisms combine to promote the various processes that constitute the biology of the restenosis process (Fig. 1). In the following section, these mechanisms are discussed.

Endothelial Dysfunction

The removal of the endothelial lining by balloon injury and the endothelial dysfunction that persists during endothelial regeneration both contribute to the restenosis process by promoting thrombosis, vasoconstriction and smooth muscle cell growth. The amount of endothelial denudation appears to correlate with the degree of later neointimal thickness (20). Furthermore, endothelial layer regeneration after vascular injury is critical in determining the eventual lesion formation (15,21). Indeed, intimal hyperplasia is greater in areas where endothelial regeneration occurred last (14).

The integrity and function of the endothelial cell layer are profoundly altered in diabetic animals and humans (Table 1). The best-characterized endothelial abnormality is impaired endothelium-dependent relaxation (22–24). Impaired endothelium-dependent relaxation can be induced by short exposure (several hours) to high glucose concentration (22,25) and occurs in different vascular beds including the coronary arteries (26).

Diabetes can impair endothelium-dependent relaxation by at least two mechanisms: 1) Advanced glycosylation end products (see later) have been shown to rapidly inactivate endothelium-derived relaxing factor in vitro through a direct

Table 1. Effects of Endothelial Dysfunction in Diabetes Mellitus on Restenosis

Diabetes-Induced Endothelial Dysfunction	Possible Promoting Effects on Restenosis
Inactivation of EDRF	Vasoconstriction; loss of antiproliferative activity of EDRF; increased platelet adhesion and aggregation
Reduced PGI_2 synthesis	Vasoconstriction; increased platelet aggregation
Increased ET-1 production	Vasoconstriction; increased SMC proliferation
Impaired endothelial regeneration	Prolonged exposure of SMC to blood-borne mitogens; prolonged interaction of platelet with vessel wall

EDRF = endotheliam-derived relaxing factor; ET-1 = endothelin-1; PGI_2 = prostacyclin; SMC = smooth muscle cell.

chemical reaction (27,28). 2) Increased generation of oxygen free radicals, which occurs in diabetes (22,29), also inactivates endothelium-derived relaxing factor before it can exert its action on smooth muscle cells (25,30). Vasospasm at the dilated coronary artery segment occurs commonly and may contribute to the early reduction in gain and promote clot formation (31). However, the loss of endothelium-derived relaxing factor has a profound effect on the arterial wall beyond the tendency to vasospasm because it inhibits both platelet aggregation and smooth muscle cell proliferation (32–34).

Prostacyclin is another endothelial vasodilator that also inhibits platelet aggregation and adhesion to the endothelium (34). Diabetes-induced alterations in prostaglandin metabolism result in a reversible decrease in prostacyclin production by endothelial cells (35,36).

Endothelin-1 is a potent natural vasoconstrictor synthesized and secreted from endothelial cells; it is also a mitogen for smooth muscle cells (32). Plasma endothelin-1 concentrations are significantly increased in diabetic patients (37). Physiologic concentrations of insulin enhance the transcription rate and secretion of endothelin-1 mRNA in endothelial cells (38,39). Hence, the hyperinsulinemic state that characterizes type II diabetes may result in a continual stimulus for endothelin-1 production and secretion.

In addition to the impaired function of endothelial cells, diabetes affects their migration and proliferation. Human vascular endothelial cell replication in culture is inhibited in the presence of high glucose concentrations (40,41). In spontaneously diabetic rats, the regeneration of the endothelium after catheter deendothelialization is slower than control rats, resulting in prolonged interaction of platelets with the denuded vessel and, subsequently, in greater neointimal proliferation (42).

The impaired ability of endothelial cells to regenerate after balloon injury along with the functional alterations in local production of vasodilators, antiaggregants and antiproliferative molecules that occur in diabetes are likely to have a considerable effect on the restenosis process by decreasing reendothelialization, increasing the propensity to thrombosis and reducing the capacity of endothelial cells to produce the appropriate growth inhibitors for smooth muscle cells.

Platelet Aggregation and Thrombus Formation

The earliest finding after balloon dilation is platelet deposition along the denuded surface, often with subsequent thrombus formation. The importance of thrombus formation in the restenosis process is emphasized by the observation that severe thrombocytopenia induced by antiplatelet antibodies inhibits neointimal accumulation after vascular injury (43). Similarly, antibodies directed against the platelet IIb/IIIa receptor integrin have been shown to significantly decrease the clinical restenosis rate (44).

Platelets that adhere and aggregate at sites of endothelial disruption release several prothrombotic, vasoconstrictive and growth-promoting mediators (Table 2) that stimulate neointimal growth (15,45,46) and have sustained biological effects on myointimal hyperplasia long after platelet deposition and thrombosis have resolved (31).

In diabetic patients, elevated fractions of activated platelets circulate in the absence of clinically detectable vascular lesions (47). In addition, platelets from diabetic subjects exhibit an enhanced adhesiveness, and hyperaggregability in response to various agonists, including epinephrine, collagen, arachidonic acid and thrombin (48–50). Platelet extracts from diabetic patients have been shown to have significantly greater growth-promoting potential for smooth muscle cells in culture than those from control subjects. However, after intensive insulin therapy, the platelet growth activity of these patients significantly declined and became similar to control levels (51).

Thromboxane A_2, a potent platelet activator and vasoconstrictor, is synthesized in platelets during platelet activation. Increased thromboxane A_2 concentrations at sites of endothelial injury facilitate platelet aggregation and contribute to the neointimal proliferative response (52). Enhanced activity of the platelet arachidonic acid pathway with increased thromboxane A_2 synthesis occurs in diabetic subjects (53). There is a significant correlation between thromboxane A_2 production and fasting plasma glucose or hemoglobin A_{1C}, and normal thromboxane A_2 production can be restored by strict glycemic control (49,54).

The abnormal platelet function in diabetes is reflected in platelet interaction with deendothelialized vessels after balloon injury. Platelet accumulation on the injured aorta of diabetic rats is prolonged compared with control rats (42), resulting in a thicker intima with a greater number of layers of smooth muscle cells in diabetic rats (42).

Other abnormalities in the coagulation system in diabetic patients that enhance platelet aggregation and thrombus formation include elevated fibrinogen levels (55,56), increased Factor VII levels in response to hyperglycemia (56,57) and a decrease in the biological activity of antithrombin III as a result of nonenzymatic glycosylation of the lysine residue that binds it to its natural cofactor, heparin (56). In addition, a characteristic feature of insulin resistance and hyperinsulinemia is reduced plasma fibrinolytic activity caused by increased plasminogen activator inhibitor I activity (58,59). In vitro studies (60) have shown that proinsulin, a precursor of insulin, augments plasminogen activator inhibitor I gene expression in hepatocytes, resulting in an increased synthesis by the liver, which is the primary source of this molecule in plasma.

In summary, alterations in hemostatic mechanisms in the diabetic state can lead to further recruitment of platelets and mural thrombus formation through hypersensitivity of platelets to agonists at sites of vessel injury, decreased effectiveness of the inhibited thrombolytic system and elevated clotting factor levels.

Table 2. Growth Factors Involved in Pathogenesis of Restenosis*

Growth Factor and Source	Potential Role in Restenosis	Effect of Diabetes
PDGF		
Platelet alpha-granules; SMCs; endothelium	"Competence factor" for SMCs	SMCs express more PDGF beta-receptor mRNA; AGE–monocyte interaction results in PDGF release
IGF-1		
SMCs; endothelium	"Progression factor" for PDGF-mediated mesenchymal cell growth; synergistic with PDGF	High insulin levels stimulate the IGF-1 receptor; insulin enhances IGF-1 expression
bFGF		
SMCs; endothelium	Powerful mitogenic activity for SMCs and ECs; anti-bFGF antibodies inhibit SMC DNA synthesis after balloon angioplasty	High glucose concentrations increase bFGF mRNA levels
TGF-beta†		
Platelet-alpha granules; endothelium; SMCs	Modulates extracellular matrix production; potent chemotactic factor for fibroblasts and monocytes	Overexpressed in hyperglycemia and in presence of AGEs
EDRF		
Endothelium	Loss of EDRF induces platelet aggregation, vasoconstriction and allows SMC proliferation	Inactivated by AGEs and oxygen free radicals that accumulate at accelerated rate in diabetes
ET		
Endothelium	Mitogen for SMCs	Enhanced secretion in hyperinsulinemic states
HS		
Endothelium; SMCs	Inhibitor of SMC proliferation	Decreased synthesis; increased turnover

*Data from references 13–17,32,45,62–67,76,77,79,81,82. †Has both growth-promoting and growth-inhibitory properties. AGE = advanced glycosylation end product; bFGF = basic fibroblast growth factor; EC = endothelial cell; EDRF = endothelium-derived relaxing factor; ET-1 = endothelin-1; HS = heparan sulfate; IGF-1 = insulin-like growth factor-1; PDGF = platelet-derived growth factor; SMC = smooth muscle cell; TGF-beta = transforming growth factor-beta.

Dysregulation of Growth Factor Expression

The metabolic alterations associated with diabetes can promote restenosis through unique alterations in local growth factor production and action, which in turn may induce proliferation of smooth muscle cells and extracellular matrix synthesis (Table 2). Alterations in growth factor expression have been implicated in the pathogenesis of proliferative diabetic retinopathy as well as in the mesangial cell proliferation and excessive matrix deposition that characterize diabetic nephropathy (61,62). Because many of these mitogenic mediators are overexpressed by vascular smooth muscle cells and endothelial cells in diabetic patients, it is reasonable to assume that they contribute to restenosis.

Platelet-Derived Growth Factor and Insulin-Like Growth Factor-1

Platelet-derived growth factor is a "competence factor" for smooth muscle cells in that it enables the cell to move from the quiescent (i.e., contractile) phenotype into the active phase of replication (63). Progression into actual replication requires a second class of growth factors, termed "progression factors," which trigger "competence" factor-primed cells to proliferate. One of the progression factors for platelet-derived growth factor–mediated cell growth is insulin-like growth factor-1 (64). Higher concentrations of insulin-like growth factor-1 have been demonstrated in smooth muscle cells of the synthetic phenotype from restenotic human coronary atherectomy plaques compared with smooth muscle cells of the contractile phenotype (65).

Smooth muscle cells from diabetic rats grow faster than normal smooth muscle cells in response to platelet-derived growth factor (66) and after balloon catheter injury (67). These cells express more platelet-derived growth factor-beta–receptor mRNA, which is typically expressed on the contractile phenotype of smooth muscle cells (66,67). Thus, vascular smooth muscle cells may be more sensitive to the growth stimulatory action of platelet-derived growth factor in the presence of diabetes.

Alterations in insulin-like growth factor-1 regulation that lead to increased expression and elevated tissue level of this growth factor have been implicated in the pathogenesis of renal hypertrophy in diabetic nephropathy (61,68). Similarly, insulin-like growth factor-1 may be involved in the pathogen-

JACC Vol. 27, No. 3
March 1, 1996:528–35

esis of accelerated diabetic retinopathy (69), as patients with diabetic retinopathy have elevated insulin-like growth factor-1 levels in the vitreous humor (70). The role of insulin-like growth factor-1 in the development of macrovascular lesions is less clear.

Insulin as a Growth Factor for Vascular Smooth Muscle Cells

Physiologic concentrations of insulin are known to stimulate proliferation of cultured smooth muscle cells and fibroblasts (71,72). Although insulin itself is a poor mitogen (73), it can potentiate the expression of the more potent mitogen insulin-like growth factor-1 (74,75). Thus, in the presence of insulin resistance, where the metabolic action of insulin is ineffective, the proliferative response to hyperinsulinemia may still occur.

Transforming Growth Factor-Beta

Transforming growth factor-beta is the most important growth factor regulating the extracellular matrix production that characterizes intimal hyperplasia in its advanced stages (13,76,77). In the rat carotid artery injury model, administration of neutralizing antitransforming growth factor-beta antibodies reduces matrix accumulation in intimal lesions (78). Transforming growth factor-beta expression has been investigated in diabetes in relation to diabetic nephropathy because one of its dominant features is the expansion of extracellular matrix in the mesangial areas. In animal models of diabetes, the expression of transforming growth factor-beta in the kidney increases within a few days of the appearance of hyperglycemia (62,79), in association with active production of matrix components in the glomeruli (62). The increase in transforming growth factor-beta mRNA and protein in diabetic rats can be attenuated with insulin treatment (62). Recently, increased transforming growth factor-beta mRNA and protein were demonstrated in kidneys of patients with advanced diabetic nephropathy (62).

The expansion of the extracellular matrix in diabetic nephropathy bears many similarities to the extracellular matrix accumulation that results from arterial injury. In this context, it should be emphasized that mesangial cells act as specialized contractile smooth muscle cells that produce extracellular matrix components (80). Termination of extracellular matrix deposition is essential to avoid excessive neointimal growth after balloon catheter injury. Thus, failure to regulate or terminate transforming growth factor-beta expression in the presence of diabetes may potentially lead to excessive matrix deposition with greater encroachment on the arterial lumen.

Other Growth Factors

Hyperglycemia affects the expression of several other growth factors such as basic fibroblast growth factor and transforming growth factor-alpha (81). Smooth muscle cells exposed to high glucose concentrations increase their basic fibroblast growth factor mRNA levels (81). Basic fibroblast growth factor is a potent mitogen for smooth muscle cells and may be involved in restenosis, because rats treated with blocking antibodies to basic fibroblast growth factor have decreased smooth muscle cell proliferation after balloon catheter injury (82). Transforming growth factor-alpha is known to be expressed in smooth muscle and endothelial cells (45,81). Thus, when overexpressed in the presence of hyperglycemia, it may promote restenosis.

Increased myointimal proliferation and matrix deposition in diabetic patients may be a consequence of altered production of local or circulating growth factors and/or modulations in the response to these factors. The cellular events that lead to altered regulation of growth factor expression in diabetes are largely unknown. Regulation of growth factor expression by glucose seems to occur at the transcriptional level and may be mediated by one of its intracellular metabolites (81). Regardless of the mechanism involved, the presence of diabetes can selectively alter gene expression in smooth muscle cells, leading to dysregulation of growth factors that are known mediators of the restenosis process.

Abnormal Extracellular Matrix Composition—Role of Heparan Sulfate

The extracellular matrix regulates cell migration, proliferation and matrix production by means of cytoskeletal signals and by posttranslational control of growth factors (83). An important factor in the release from growth inhibition following balloon injury is the loss of inhibitory control of the surrounding proteoglycan matrix. Matrix-associated heparan sulfate is a potent inhibitor of smooth muscle cell proliferation and plays an important role in the regulation of smooth muscle cell growth in injured arteries (13,17,84). After balloon injury, endothelial denudation, disruption of the proteoglycan matrix of the medial layers and activated platelet release of endoglycosidases that cleave heparan sulfate from the surface of smooth muscle cells all lead to the loss of the inhibitory effect of heparan sulfate. In addition, the removal of heparan sulfate renders cells receptive to growth factors and contributes to their phenotypic modulation (13,14,17).

Hyperglycemia induces an increase in selected matrix gene transcription that persists for weeks after restoration of normoglycemia in vivo (85). This results in an increased synthesis of extracellular matrix components such as collagen type IV, fibronectin and laminin. Abnormalities in the synthesis and metabolism of heparan sulfate have been repeatedly reported in association with both experimental and human diabetes (79,86,87). The density of heparan sulfate has been shown to be significantly reduced in the glomerular basement membrane of patients with diabetic nephropathy (79,86,87). Hyperglycemia causes a decrease in the de novo synthesis of heparan sulfate (88), probably because of decreased activity of the

enzyme *N*-deacetylase, which plays a key role in its biosynthesis (89). Interestingly, the administration of protamine as part of commonly used insulin preparations exacerbates smooth muscle cell proliferative lesions after balloon injury in rats and interferes with the growth inhibitory effects of heparin in culture and in vivo (90).

In summary, diminution of matrix-bound heparan sulfate can result in loss of tonic growth inhibition and facilitate smooth muscle cell proliferation. Hyperglycemia-induced augmentation in matrix component production may increase neointimal volume (Fig. 1).

Role of Advanced Glycosylation End Products in Restenosis

Advanced glycosylation end products are a heterogeneous class of nonenzymatically glycosylated adducts of proteins or lipids that accumulate in vascular tissues with aging and at an accelerated rate in diabetes. The degree of nonenzymatic glycosylation is determined mainly by the glucose concentration and time of exposure (91–94). Advanced glycosylation end products are abundant in most tissues and fluids and, through the induction of cytokines and growth-promoting mediators, may participate in tissue remodeling (91–94). Advanced glycosylation is implicated in the initiation and acceleration of multiple organ damage in diabetic patients, including macrovascular disease, nephropathy, and neuropathy (91–95), and may also promote the restenosis process.

Advanced glycosylation end products interact with vessel wall cellular components through a specific receptor system present on various cell types, including monocytes, endothelial cells and smooth muscle cells (94,96,97). Monocyte receptor-mediated interaction with advanced glycosylation end products results in the production of mediators such as tumor necrosis factor-alpha, platelet-derived growth factor and insulin-like growth factor-1 (98–100).

Monocytes and lymphocytes are known to migrate into the thrombus that forms in the balloon injury site. This cellular infiltrate may be an abundant source of growth factors and chemoreactant substances, facilitating and sustaining further cellular recruitment and smooth muscle cell growth (15–17). The presence of advanced glycosylation end products in the exposed vessel wall would be expected to promote the migration of inflammatory cells into the lesion with the subsequent release of growth-promoting cytokines. Furthermore, specific binding of glycosylated proteins by cultured rat smooth muscle cells is associated with increased cellular proliferation (93,94) that is likely to be cytokine or growth factor mediated.

Finally, advanced glycosylation end products influence the expression of selected extracellular matrix genes (e.g., collagen type IV, laminin) as well as transforming growth factor-beta (101). Advanced glycosylation also alters the functional properties of several important matrix constituents. Glycosylation of matrix components such as collagen IV, laminin and vitronectin will decrease binding of anionic heparan sulfate, leading to greater turnover of heparan sulfate (92,102). Glycosylation of the extracellular matrix also alters the normal interactions of transmembrane integrin receptors with their specific matrix ligands. For example, modification of the cell-binding domains of type IV collagen causes decreased endothelial cell adhesion (92,102).

Summary. Advanced glycosylation end products can mediate inflammatory cell recruitment and activation, stimulation of smooth muscle cell proliferation and abnormal matrix production, all of which can promote the restenosis process.

Conclusions

Diabetes influences various cellular events involved in the vessel response to injury (Fig. 1). The same mechanisms can potentially play a role in the intimal proliferation that causes luminal loss in the first years after bypass surgery with venous conduit (103).

An important question is whether the restenosis rate can be reduced in diabetic patients. Pharmacologic manipulations for the prevention of restenosis are based on insights into the pathophysiologic mechanisms of restenosis and include growth factor inhibitors (e.g., trapidil) (17), new antithrombotic agents (44), antiinflammatory agents and gene therapy (14,17). However, it may be possible to use simpler measures in diabetic patients. Many of the potential mechanisms promoting restenosis in diabetic patients are related to elevated glucose or insulin levels, or both. Moreover, the majority of these abnormalities are reversible on improved glycemic control. Therefore, we anticipate that rigorous glycemic control may reduce the restenosis rate in diabetic patients. However, some of the alteration induced by the metabolic abnormalities of the diabetic state may not be readily reversible. For example, hyperglycemia-induced gene transcription may persist for weeks after restoration of normoglycemia in vivo (85). This phenomenon has been termed hyperglycemic memory and may reflect irreversible intracellular and extracellular effects of hyperglycemia (85,102). In addition, normoglycemia is frequently achieved at the price of peripheral hyperinsulinemia. Clinical trials are needed to evaluate the impact of tight glycemic control on restenosis rates among diabetic patients.

References

1. Landau C, Lange RA, Hillis DL. Percutaneous transluminal coronary angioplasty. N Engl J Med 1994;330:981–93.
2. Holmes DR Jr, Vietstra RE, Smith HC, et al. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA Registry of the National Heart, Lung, and Blood Institute. Am J Cardiol 1984;53:77C–81C.
3. Weintraub WS, Kosinski AS, Brown CL, King SB. Can restenosis after coronary angioplasty be predicted from clinical variables. J Am Coll Cardiol 1993;21:6–14.
4. Vandormael MG, Deligonul U, Kern MJ, et al. Multilesion coronary angioplasty: clinical and angiographic outcome. J Am Coll Cardiol 1987; 10:246–52.
5. Quigley PJ, Hlatky MA, Hinohara T, et al. Repeat percutaneous transluminal coronary angioplasty and predictors of recurrent restenosis. Am J Cardiol 1989;63:409–13.
6. Lambert M, Bonan R, Côté G, et al. Multiple coronary angioplasty: a model

to discriminate systemic and procedural factors related to restenosis. J Am Coll Cardiol 1988;12:310–4.
7. Galan KM, Hollman JL. Recurrence of stenoses after coronary angioplasty. Heart Lung 1986;15:585–7.
8. Rensing BJ, Hermans RM, Vos J, et al. Luminal narrowing after percutaneous transluminal coronary angioplasty. Circulation 1993;88:975–85.
9. Bach R, Jung F, Kohsiek I, et al. Factors affecting the restenosis rate after percutaneous transluminal coronary angioplasty. Thromb Hemostas 1994; 74: Suppl 1:S55–77.
10. Popma JJ, Mintz GS, Satler LF, et al. Clinical and angiographic outcome after directional coronary atherectomy. Am J Cardiol 1993;72:55E–64E.
11. Carrozza JP, Kuntz RE, Fishman RF, Baim DS. Restenosis after arterial injury caused by coronary stenting in patients with diabetes mellitus. Ann Intern Med 1993;118:344–9.
12. Rabbani LE, Edelman ER, Ganz P, Selwyn AP, Loscalzo J, Bitti JA. Relation of restenosis after excimer laser angioplasty to fasting insulin levels. Am J Cardiol 1994;73:323–7.
13. Forrester JS, Fishbein M, Halfant R, Fagin A. A paradigm for restenosis based of cell biology: clues for the development of new preventive therapies. J Am Coll Cardiol 1991;17:758–69.
14. Ip JH, Fuster V, Israel D, Badimon L, Badimon J, Chesebro JH. The role of platelets, thrombin, and hyperplasia in restenosis after coronary angiography. J Am Coll Cardiol 1991;17:77B–88B.
15. Casscells W. Migration of smooth muscle and endothelial cells: critical events in restenosis. Circulation 1992;86:723–9.
16. Schwartz RS, Holmes DR, Topol EJ. The restenosis paradigm revisited: an alternative proposal for cellular mechanisms. J Am Coll Cardiol 1992;20: 1284–93.
17. Anderson HV. Restenosis after coronary angioplasty. Dis Month 1993;39: 613–70.
18. Safian RD, Gelbfish JS, Erny RE, Schnitt SJ, Schmidt DA, Baim DS. Coronary atherectomy: clinical, angiographic, and histological findings and observations regarding potential mechanisms. Circulation 1990;82:69–79.
19. Libby P, Schwartz D, Brogi E, Tanaka H, Clinton SK. A cascade model for restenosis. A special case of atherosclerosis progression. Circulation 1992; Suppl III:III-47–52.
20. Liu MW, Roubin GS, King SB. Restenosis after coronary angioplasty: potential biologic determinants and role of intimal hyperplasia. Circulation 1989;79:1374–84.
21. Gibbons GH, Dzau VJ. The emerging concept of vascular remodeling. N Engl J Med 1994;330:1431–8.
22. Tesfamariam B. Free radicals in diabetic endothelial cell dysfunction. Free Radic Biol Med 1994;16:383–91.
23. Johnstone MT, Creager SJ, Scales KM, Cusco JA, Lee BK, Creager MA. Impaired endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. Circulation 1993;88:2510–6.
24. Cohen RA. Dysfunction of vascular endothelium in diabetes mellitus. Circulation 1993;87: Suppl V:V-67–76.
25. Tesfamariam B, Cohen RA. Free radicals mediate endothelial cell dysfunction caused by elevated glucose. Am J Physiol 1992;263:H321–6.
26. Nitenberg A, Valensi P, Sachs R, Dali M, Aptecar E, Attali J-R. Impairment of coronary vascular reserve and ACh-induced coronary vasodilation in diabetic patients aniographically normal coronary arteries and normal left ventricular systolic function. Diabetes 1993;42:1017–25.
27. Bucala R, Tracey KJ, Cerami A. Advanced glycosylation products quench nitric oxide and mediate defective endothelium-dependent vasodilation in experimental diabetes. J Clin Invest 1991;87:432–8.
28. Hogan MA, Bucala R. Advanced glycosylation endproducts block the antiproliferative effect of nitric oxide. J Clin Invest 1992;90:1110–5.
29. Williamson JR, Chang K, Frangos M, et al. Hyperglycemic pseudohypoxia and diabetic complications. Diabetes 1993;42:801–13.
30. Diederich D, Skopec J, Diederich A, Dai F-X. Endothelial dysfunction in mesenteric resistance arteries of diabetic rats: role of free radicals. Am J Physiol 1994;266:H1153–61.
31. Chesebro JH, Lam JYT, Badimon L, Fuster V. Restenosis after arterial angioplasty: a hemorrheologic response to injury. Am J Cardiol 1987;60: 10B–6B.
32. Fuster V, Badimon L, Badimon J, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 1992;326:310–8.
33. Scott-Burden T, Vanhoutte PM. The endothelium as a regulator of vascular smooth muscle proliferation. Circulation 1993;87: Suppl V:V-51–5.
34. Ware JA, Heistad DD. Platelet–endothelium interactions. N Engl J Med 1993;328:628–35.
35. Inoguchi T, Umeda F, Ono H, Junisaki M, Watanabe J, Nawata H. Abnormality in prostacyclin stimulatory activity in sera from diabetics. Metabolism 1989;38:837–42.
36. Umeda F, Inoguchi T, Nawata H. Reduced stimulatory activity on prostacyclin production by cultured endothelium cells in serum from aged diabetic patients. Atherosclerosis 1989;75:61–6.
37. Takahashi K, Ghatei MA, Lam HC, Bloom SR. Elevated plasma endothelin in patients with diabetes mellitus. Diabetologia 1990;33:306–10.
38. Oliver FJ, de la Rubia G, Feener EP, et al. Stimulation of endothelin-1 gene expression by insulin in endothelial cells. J Biol Chem 1991;266:23251–6.
39. Ferri C, Pittoni V, Piccoli A, et al. Insulin stimulates endothelin-1 secretion from human endothelial cells and modulates its circulating levels in vivo. J Clin Endocrinol Metab 1995;80:829–35.
40. Lorenzi M, Cagliero E, Toledo S. Glucose toxicity for human endothelial cells in culture. Delayed replication, disturbed cell cycle, and accelerated death. Diabetes 1985;34:621–7.
41. Lin S-J, Hong C-Y, Chang M-S, Chiang N, Chien S. Increased aortic endothelial cell death and enhanced transendothelial macromolecular transport in streptozotocin-diabetic rats. Diabetologia 1993;36:926–30.
42. Winocour PD, Richardson M, Kinlough-Rathbone RL. Continued platelet interaction with de-endothelialized aortae associated with slower re-endothelialization and more extensive intimal hyperplasia in spontaneously diabetic BB Wistar rats. Int J Exp Pathol 1993;74:603–13.
43. Fingerle J, Johnson R, Clowes AW, Majesky MW, Reidy MA. Role of platelet in smooth muscle proliferation an migration after vascular injury in rat carotid artery. Proc Natl Acad Sci USA 1989;86:8412–6.
44. Topol EJ, Califf RM, Weisman HF, et al. Randomized trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at 6 months. Lancet 1994;343:881–6.
45. Ross R. The pathogenesis of atherosclerosis: a prospective review for the 1990s. Nature 1993;362:801–9.
46. Popma JJ, Topol EJ. Factors influencing restenosis after coronary angioplasty. Am J Med 1990;88:1-16N–24N.
47. Tschöpe D, Esser J, Schwippert B, et al. Large platelets circulate in an activated state in diabetes mellitus. Semin Thromb Haemostas 1991;17: 433–9.
48. Winocour PD. Platelet abnormalities in diabetes mellitus. Diabetes 1992;41 Suppl 2:26–31.
49. Ishii H, Umeda F, Nawata H. Platelet function in diabetes mellitus. Diabetes Metab Rev 1992;8:53–66.
50. El Khawand C, Jamart J, Donckier J, et al. Hemostasis variables in type I diabetic patients without demonstrable vascular disease. Diabetes Care 1993;16:1137–45.
51. Sugimoto H, Franks DJ, Lecavalier L, Chiasson JL, Hamet P. Therapeutic modulation of growth-promoting activity in platelets from diabetics. Diabetes 1987;36:667–72.
52. Willerson JT, Yao S-K, McNatt J, et al. Frequency and severity of cyclic flow alternations and platelet aggregation predict the severity of neointimal proliferation following experimental coronary stenosis and endothelial injury. Proc Natl Acad Sci USA 1991;88:10624–8.
53. Davì G, Catalano I, Averna M, et al. Thromboxane biosynthesis and platelets function in type II diabetes mellitus. N Engl J Med 1990;322:1769–74.
54. Mayfield RK, Halushka PV, Wohltmann HS, Lopez-Virella M, Chambers JK, Loadholt CB. Platelet function during continuous insulin infusion treatment in insulin-dependent diabetic patients. Diabetes 1985;34:1127–33.
55. De Feo P, Gaisano MG, Haymond MW. Differential effects of insulin deficiency on albumin and fibrinogen synthesis in humans. J Clin Invest 1991;88:833–40.
56. Ceriello A. Coagulation activation in diabetes mellitus: a role of hyperglycemia and therapeutic prospects. Diabetologia 1993;36:1119–25.
57. Ceriello A, Giugliano D, Quatraro A, Dello Russo P, Torella R. Blood glucose may condition factor VII levels in diabetic and normal subjects. Diabetologia 1988;31:889–91.
58. Juhan-Vague I, Alessi M, Vague P. Increased plasma plasminogen activator

inhibitor I levels. A possible link between insulin resistance and atherothrombosis. Diabetologia 1991;34:475–62.
59. McGill JB, Schneider CL, Arfken CL, Lucore CL, Sobel BE. Factors responsible for impaired fibrinolysis in obese subjects and NIDDM patients. Diabetes 1994;43:104–9.
60. Nordet TK, Schneider DJ, Sobel BE. Augmentation of the synthesis of plasminogen activator inhibitor type-I by precursors of insulin. A potential risk factor for vascular disease. Circulation 1994;89:321–30.
61. Hammerman MR, Miller SB. The growth hormone insulin-like growth factor axis in kidney revisited. Am J Physiol 1993;265:F1–14.
62. Yamamoto T, Nakamura T, Noble NA, Ruoslahti E, Border WA. Expression of transforming growth factor β is elevated in human and experimental diabetic nephropathy. Proc Natl Acad Sci USA 1993;90:1814–8.
63. Walker LN, Bowen-Pope DF, Ross R, Reidy MA. Production of platelet-like growth factor-like molecules by cultured arterial smooth muscle cells accompanies proliferation after arterial injury. Proc Natl Acad Sci USA 1986;83:7311–5.
64. Stiles CD, Capone GT, Scher CDE, Antoniades NH, Van Wyk JJ, Pledger WJ. Dual control of cell growth by somatomedins and platelet-derived growth factor. Proc Natl Acad Sci USA 1979;76:1279–82.
65. Grant MB, Wargovich TJ, Ellis EA, Caballero S, Monsour M, Pepine CJ. Localization of insulin-like growth factor I and inhibition of coronary SMC growth by somatostatin analogues in human coronary smooth muscle cells. A potential treatment for restenosis? Circulation 1994;89:1511–7.
66. Kawano M, Koshikawa T, Kanzaki T, Morisaki N, Saito Y, Yoshida S. Diabetes mellitus induces accelerated growth of aortic smooth muscle cells: association with overexpression of PDGF β-receptors. Eur J Clin Invest 1993;23:84–90.
67. Kanzaki T, Shinomiya M, Ueda S, Morisaki N, Saito Y, Yoshida S. Enhanced arterial intimal thickening after balloon catheter injury in diabetic animals accompanied by PDGF β-receptor overexpression of aortic media. Eur J Clin Invest 1994;24:377–81.
68. Flyvbjerg A, Thorlacius-Ussing O, Nørras R, Ingerslev J, Ørskov H. Kidney tissue somatomedin C and initial renal growth in diabetic and uninephrectomized rats. Diabetologia 1988;31:310–4.
69. Merimee TJ, Zapf J, Froesch ER. Insulin-like growth factors. Studies in diabetics with and without retinopathy. N Engl J Med 1983;309:527–30.
70. Meyer-Schwickerath R, Pfeiffer A, Blum WF, et al. Vitreous levels of the insulin-like growth factors I and II, and the insulin-like growth factor binding proteins 2 and 3, increase in neovascular eye disease: studies in nondiabetic and diabetic subjects. J Clin Invest 1993;92:2620–5.
71. Stout RW, Bierman EL, Ross R. Effect of insulin on the proliferation of cultured primate arterial smooth muscle cell. Circ Res 1975;36:319–27.
72. Pfefile B, Ditschuneit H. Effects of insulin on growth of cultured human arterial smooth muscle cells. Diabetologia 1981;20:155–8.
73. Bornfeldt KE, Raines EW, Nakano T, Graves TN, Krebs EG, Ross R. Insulin-like growth factors-I and platelet-derived growth factors-BB induce direct migration of human smooth muscle cells via signaling pathways that are distinct from those of proliferation. J Clin Invest 1994;93:1266–74.
74. Murphy LJ, Ghahary A, Chakrabarti AS. Insulin regulation of IGF-I expression in rat aorta. Diabetes 1990;39:657–62.
75. Banskota NK, Taub R, Zellner K, King JL. Insulin, insulin-like growth factor I and platelet-derived growth factor interact additively in the induction of protooncogene c-myc and cellular proliferation in cultured bovine aortic smooth muscle cells. Mol Endocrinol 1989;3:1183–90.
76. Nabel EG, Shum L, Pompili VJ, et al. Direct transfer of transforming growth factor β1 gene into arteries stimulates fibrocellular hyperplasia. Proc Natl Acad Sci USA 1993;90:10759–63.
77. Wilcox JN. Molecular biology: insight into the causes and prevention of restenosis after arterial intervention. Am J Cardiol 1993;72:88E–95E.
78. Wolf YG, Rasmussen LM, Ruoslahti E. Antibodies against transforming growth factor-β1 suppress intimal hyperplasia in a rat model. J Clin Invest 1994;93:1172–8.
79. Ziyadeh FN. The extracellular matrix in diabetic nephropathy. Am J Kidney Dis 1993;22:736–44.
80. Davies M. The mesangial cell: a tissue culture view. Kidney Int 1994;45:320–7.
81. McClain DA, Paterson AJ, Ross MD, Wei X. Glucose and glucosamine regulate growth factors gene expression in vascular smooth muscle cells. Proc Natl Acad Sci USA 1992;89:8150–4.
82. Lindner V, Reidy MA. Proliferation of smooth muscle cells after vascular injury is inhibited by antibody against fibroblast growth factor. Proc Natl Acad Sci USA 1991;88:3739–43.
83. Casscells W, Engler D, Willerson JT. Mechanisms of restenosis. Tex Heart Inst J 1994;21:68–77.
84. Clowes AW, Karnovsky MJ. Suppression by heparin of smooth muscle cell proliferation in injured arteries. Nature 1977;265:625–6.
85. Roy S, Sala R, Cagliero E, Lorenzi M. Overexpression of fibronectin induced by diabetes or high glucose: phenomenon with a memory. Proc Natl Acad Sci USA 1990;87:404–8.
86. Kanwer YS, Roseazweig LJ, Linker A, Jakubowski ML. Decreased de novo synthesis of glomerular proteoglycans in diabetes. Proc Natl Acad Sci USA 1983;80:2272–5.
87. Vernier RL, Steffes MW, Sisson-Ross S, Mauer M. Heparan sulfate proteoglycan in the glomerular basement membrane in type 1 diabetes. Kidney Int 1992;41:1070–80.
88. Kanwar Y, Yoshinaga Y, Liu Z, Wallner E, Carone F. Biosynthetic regulation of proteoglycans by aldohexoses and ATP. Proc Natl Acad Sci USA 1992;89:8621–5.
89. Unger E, Pettersson I, Eriksson UJ, Lindhal U, Kjellen L. Decreased activity of heparan sulfate modifying enzyme glucosaminyl N-deacetylase in hepaocytes from streptozotocin-diabetic rats. J Biol Chem 1991;226:9671–4.
90. Edelman ER, Pukac LA, Karnovsky M. Protamine and protamine-insulin exacerbate the vascular response to injury. J Clin Invest 1993;91:2308–13.
91. Brownlee M, Cerami A, Vlassara H. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. N Engl J Med 1988;318:1315–21.
92. Brownlee M. Glycation and diabetic complications. Diabetes: 1994;43:836–41.
93. Vlassara H. Receptor-mediated interactions of advanced glycosylation end products with cellular components within diabetic tissues. Diabetes 1992;41 Suppl 2:52–6.
94. Vlassara H, Bucala R, Striker L. Pathogenic effects of advanced glycosylation: biochemical, biologic and clinical implications for diabetes and aging. Lab Invest 1994;70:138–51.
95. Nakamura Y, Horii Y, Nishino T, et al. Immunohistochemical localization of advanced glycosylation endproducts in coronary atheroma and cardiac tissue in diabetes mellitus. Am J Pathol 1993;143:1649–56.
96. Schmidt AM, Hori O, Brett J, Yan SD, Wautier J-L, Stern D. Cellular receptors for advanced glycation end products. Implications for induction of oxidant stress and cellular dysfunction in the pathogenesis of vascular lesions. Arterioscler Thromb 1994;14:1521–8.
97. Brett J, Schmidt A-M, Yan S-D, et al. Survey of the distribution of a newly characterized receptor for advanced glycosylation end products in tissues. Am J Pathol 1993;143:1699–1712.
98. Vlassara H, Brownlee M, Manogue KR, Dinarello C, Pasagian A. Cachectin/TNF and IL-1 induced by glucose modified proteins: role in normal tissue remodeling. Science 1988;240:1546–8.
99. Kirstein M, Brett J, Radoff S, Ogawa S, Stern D, Vlassara H. Advanced protein glycosylation induces selective transendothelial human monocyte chemotaxis and secretion of PDGF: role in vascular diseases of diabetes and aging. Proc Natl Acad Sci USA 1990;87:9010–4.
100. Kirstein M, Aston C, Hintz R, Vlassara H. Receptor-specific induction of insulin like growth factor 1 (IGF-1) in human monocytes by advanced glycosylation endproduct-modified proteins. J Clin Invest 1992;90:439–46.
101. Yang CW, Vlassara H, Peten PE, He CJ, Striker GE, Striker LJ. Advanced glycation end products up-regulate gene expression found in diabetic glomerular disease. Proc Natl Acad Sci USA 1994;91:9436–40.
102. Ruderman NB, Williamson JR, Brownlee M. Glucose and diabetic vascular disease. FASEB J 1992;6:2905–14.
103. Davies MG, Kim JH, Klyachkin ML, et al. Diabetes mellitus and experimental vein graft structure and function. J Vasc Surg 1994;19:1031–43.