

DIABETES MELLITUS IS NOT ONLY A RISK FACTOR BUT A CARDIOVASCULAR DISEASE

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ABSTRACT

Diabetes Mellitus (DM) is a chronic systemic disease characterized by disorders in metabolism of insulin, carbohydrate, fat and protein and impairment of structure and function of blood vessels; the early manifestations are metabolic and the complications result from vascular disease. Vascular changes may precede several years overt DM. Both type 1 and type 2 DM are vulnerable to microvascular and macrovascular complications. The relation of glucose and coronary artery disease is continuous and graded across the range of nondiabetic glucose values, independent of traditional and nontraditional risk factors with no gender difference.

Several epidemiological studies have confirmed excess morbidity/mortality due to cardiovascular disease (CVD) in patients with DM. Proposed mechanisms linking DM to CVD are uniformly targeted to endothelial cell dysfunction.

The rationale to institute primary prevention of vascular damage in patients with DM is compelling to reduce morbidity/mortality. Type 1 or 2 DM are at high risk for CVD: coronary artery disease, stroke, peripheral arterial disease, cardiomyopathy and congestive heart failure. Therefore, it becomes imperative that physicians who take care of clinically diabetic patients or nondiabetics with genetic evidence of diabetes in the family history should search for evidence of impaired glucose tolerance, hyperinsulinemia and lipidemia. Treating a patient with impaired glucose tolerance and overt DM must be a "shared responsibility" among specialists of vascular beds involved.

The intimately incriminating connection between DM and CVD is real. The vascular manifestation of DM affect more vascular beds than any other disease. None of the presently known risk factors inflicts more morbidity and mortality in the cardiovascular system than DM. Indeed, DM is not only a major risk factor for CVD but in reality DM is CVD that destroys the vascular beds of several target organs.

Keywords: Diabetes mellitus, cardiovascular disease, insulin resistance

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INTRODUCTION

In 1999 the American Diabetes Association, the National Heart, Lung and Blood Institute, the Juvenile Diabetes Foundation International, the National Institute of Diabetes and Digestive and Kidney Diseases and the American Heart Association issued a Joint Editorial Statement indicting diabetes mellitus (DM) as a major risk factor for cardiovascular disease (CVD).¹ In the last 3 decades of the 20th century several epidemiology studies have confirmed excess morbidity and mortality due to CVD (Table I) in patients with DM.²⁻¹⁰ All these studies suggest strongly DM as a major risk factor for CVD. In addition, other risk factors for CVD¹¹ are frequently associated with DM (Table II).

Recent survey among physicians conducted by the "make the link" project of the American College of Cardiology and the American Diabetes Association linking DM with coronary artery disease and stroke found DM as the highest risk factor for CVD, higher than traditional risk factors of smoking, hypertension, hypercholesterolemia or obesity.¹² Further, DM is associated with more extensive atherosclerosis affecting blood vessels in the eyes, brain, heart, kidneys and peripheral arteries in the neck, aorta and lower extremities. These vascular changes appear several years before overt DM is manifest.¹² Indeed more than just another risk factor for CVD, DM can be conceptualized and correctly called CVD.

This review will describe the vascular changes in DM, the mechanisms connecting DM to vascular disease and guidelines for primary prevention of cardiovascular complications in the context that DM is CVD.

Table I. Age* Adjusted Incidence** of Cardiovascular Events According To Sex in Diabetic and Nondiabetic Subjects

Arterial disease events	Men		Women	
	Diabetic	Nondiabetic	Diabetic	Nondiabetic
Cardiovascular	4.7	1.9	6.2	1.7
Claudication	12.6	3.3	8.4	1.3
Coronary	24.8	14.9	17.8	6.9

Adapted from data of Kannel WB, McGee DL. JAMA 1978;241:2035-38
*Framingham cohort with age range 45-74 yr; **Incidence/100 patient years.

Table II. Prevalence of Atherogenic Factors in Diabetes Mellitus

Factor	Type I with IRF	Type II
Hypertension	+++	++
Hypercholesterolemia	+++	++
Hypertriglycemia	+++	+++
Remnant	+++	++
Low HDL	+++	++
Hyperinsulinemia	++	++
Obesity	0	+++

+indicates increase prevalence; IRF-impaired renal function; 0-normal prevalence

Adapted from data of Ruderman NB, Haudenschild C. Prog Cardiovasc Dis 1984;26:373

Definition

As early as 1967 Waife¹³ defined DM as a chronic systemic disease characterized by disorders in metabolism of insulin, carbohydrate, fat and protein and impairment of structure and function of blood vessels (Table III). According to Waife¹³ the early signs and symptoms of DM are metabolic but its complications are due to vascular disease. The 2 types of DM presently recognized are called type 1 and type 2 (Table IV).¹⁴ Type 1 DM is due to immunologic destruction of pancreatic B cells and commonly results in microvascular complications of retinopathy, neuropathy and nephropathy and collectively called microangiopathy in 1955 by Ditzel and Rooth¹⁵ (Figure 1). Type 2 DM is most common in adult life. The metabolic cause has been identified as due to the combination of impaired insulin-mediated glucose disposal (insulin resistance) and defective insulin secretion by pancreatic B cells.¹⁴ Insulin resistance precedes onset of DM and often accompanied by hypertension, dyslipidemia, prothrombotic state, impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). This cluster of risk factors is called the metabolic syndrome that antedates the emergence of type 2 DM by many years.¹⁶

Vascular changes in diabetes mellitus

1. Diabetic retina

There is an initial dilatation of retinal veins. This is followed by loss of endothelial cells and pericytes of capillaries leading to a cellular capillaries and microaneurysms. There is increased vascular permeability allowing the production of hard yellowish exudates, arteriolar occlusions and soft (cotton wool) exudates. Retinitis proliferans is characterized by progressive neovascularization

and glial formation with normalization of blood flow.

According to McMillan¹⁷ diabetic microangiopathy starts with altered local blood flow with dilatation of the small veins, periodic arteriolar vasoconstriction, sclerosis of arterioles, veins and capillaries resulting in progressive microcirculatory decompensation (Table V).

2. Diabetic kidney

Arteriolosclerosis begins in the afferent glomerular arteriole and followed by diffuse glomerulosclerosis. The latter leads to hypertension. Diffuse glomerulosclerosis may be accompanied with nodular glomerulosclerosis producing renal insufficiency. Renin production is depressed but sensitivity to angiotensin II is increased. The glomerular basement membrane thickens and glomerular filtration rate is increased. The evolution of diabetic nephropathy was described by Mogensen¹⁸ in 5 stages in 1987 (Table VI).

3. Diabetic peripheral nerve

With onset of diabetic autonomic dysfunction depressed motor conduction velocity becomes manifest. There is segmental demyelination due to Schwann cell deterioration. Symmetric sensory polyneuropathy with loss of deep tendon reflexes is common in long-term DM.

4. Diabetic extremity

Atherosclerosis obliterans of arteries in one or both lower extremities produce ischemic changes leading to ulceration, gangrene and diabetic foot.

5. Diabetic skin

Cutaneous manifestations of diabetic microangiopathy are usually associated with retinopathy, neuropathy and nephropathy. The classic skin lesions are the asymptomatic atrophic brown areas in the leg called necrobiosis lipidica diabetorum seen in long-term DM.

6. Diabetic heart and strokes

Coronary artery disease affects large and small coronary arteries. Painless myocardial infarction and angina with normal coronary angiogram

are not uncommon in diabetic patients. Type 2 DM have more diffuse coronary atherosclerosis and greater prevalence of stenosis of any grade by angiographic study.¹⁹ Necropsy study of coronary arteries in type 2 DM by Waller and co-workers²⁰ showed identical number of significant obstructive atherosclerotic plaques in the 3 epicardial coronaries in patients with DM without clinical coronary artery disease, DM with coronary artery disease and control subjects with coronary artery disease without DM (Table VII).

Atherosclerotic carotid and vertebral arterial systems and cerebral vessels may lead to thrombotic strokes. Microaneurysms in the basal ganglia and subcortical region called Charcot-Bouchard aneurysms cause hemorrhagic stroke.²¹

Hypertension and DM frequently occur simultaneously leading to excess morbidity and mortality for cardiovascular events and renal disease (Table VIII). They share the same metabolic features of impaired glucose tolerance and insulin resistance. Likewise the development of complications is related to duration and/or severity of each condition.²²

7. Diabetic cardiomyopathy

This is characterized by diffuse areas of fibrosis and hypertrophy. The arteriolar walls present positive periodic acid Schiff (PAS) material. Diabetic cardiomyopathy was first described by Rubler in 1972²³ associated with duration of DM of 5 years or more and nephropathy.

Table III. Metabolic and Vascular Changes in the Evolution of Diabetes

Diabetic stage	Glucose		Tolerance	Vascular change
	fasting blood sugar	standard glucose tolerance	cortisone glucose tolerance	
Prediabetes	N	N	N	+
Subclinical	N	N	Abnormal	+
Latent	N	Abnormal	Test not needed	++
Overt	Abnormal	Test not needed	Test not needed	+++

Modified from Waife SO, Diabetes Mellitus, 7th ed, Eli Lilly and Co Indianapolis 1967 p.9
 N = normal; + = increasing presence of vascular change.

Table IV. Clinical Manifestations of Diabetes¹⁴

Type 1	- due to immunologic destruction of pancreatic β cells. - commonly produces microvascular complications
Type 2	- most common appearing in adults - metabolic cause is due to - combination of impaired insulin-mediated glucose disposal (insulin resistance) and defective insulin secretion by pancreatic β -cells. - Insulin resistance precedes onset of DM often accompanied by metabolic syndrome/hypertension, dyslipidemia, prothrombotic state, impaired fasting glucose (IFG) or impaired glucose tolerance (IGR) before overt DM.

Table V. Evolution of Diabetic Microangiopathy¹⁷

1. altered local blood flow
2. progressive reversible dilatation of small veins
3. periodic arteriolar vasoconstriction
4. sclerosis of the walls of arterioles, small veins and capillaries
5. slowly progressive microcirculatory decompensation

Table VI. Stages in Diabetic Nephropathy¹⁸

Stage I	Hypertrophy and hyperfiltration increase in size and weight of kidneys, glomerular volume and capillary lumen.
Stage II	Silent nephropathy thickening of glomerular basement membrane and expansion of mesangial matrix.
Stage III	Incipient nephropathy microalbuminuria and generalized endothelial dysfunction.
Stage IV	Overt nephropathy modular or diffuse glomerulosclerosis.
Stage V	Renal insufficiency interstitial tissue is enlarged by edema and fibrosis; decline in creatinine clearance.

Adapted from Mogensen CE. Contemp Issues Nephrol 1989;20:19-49

Table VII. Coronary Arteries in Type 2 Diabetes and in Coronary Artery Disease at Necropsy

Arteries (>75% stenosis)	DM-CAD (n=65) %	DM+CAD (n=164) %	CAD-DM (n=183) %
LAD			
proximal	77	80	76
distal	72	84	81
LCx			
proximal	82	87	85
distal	77	81	76
RCA			
proximal	75	88	76
distal	78	84	83
LMCA	7	23	11

Adapted from data of Waller BF, et al Am J Med 1980;69:498-506
 DM-CAD, diabetes mellitus without coronary artery disease; DM+CAD, diabetes mellitus and coronary artery disease; CAD-DM, coronary artery disease without diabetes mellitus; LAD-left anterior descending; LCx-left circumflex; RCA-right coronary artery; LMCA-left main coronary artery

Table VIII. Close Association of Diabetes and Hypertension²²

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1. Leading causes of end-stage renal disease.
 2. Occur simultaneously often leading to excess morbidity and mortality for cardiovascular events and renal disease.
 3. Share metabolic features of impaired glucose tolerance and insulin resistance.
 4. Risk of developing complication is related to duration and/or severity of each condition.
 5. Strategies of treatment go beyond blood pressure and sugar control with focus on prevention/reduction of target organ damage.
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Mechanisms of cardiovascular damage

Proposed mechanisms linking DM to CVD are uniformly targeted to produce endothelial damage and dysfunction. Three principal substances have been identified to play major roles in producing endothelial dysfunction. They are: heparin sulfate (HS),²⁴ glucose,²⁵⁻²⁸ and insulin.²⁹⁻³² Loss of HS, glucose scavenging of nitric oxide (NO) and insulin resistance impair endothelial function separately or in concert.

The normal vascular endothelium acts as autocrine and paracrine organ releasing substances that regulates vascular tone, thrombosis and fibrinolysis, permeability and smooth muscle growth as well as extracellular matrix composition. Endothelial cell function is finely orchestrated by the integrity of the L-arginine-eNOS-NO system.²⁸⁻³³ Hence, normal production and/or availability of NO is essential in regulating various substances generated and released by the endothelial cell through its autocrine and paracrine functions. Damage of vascular endothelium from inappropriate sulphation of heparin sulfate and loss of anionic sites or increased synthesis and secretion of PAI-1 by glucose and insulin stimulation lead to impaired NO production and/or availability.

The writing group II tasked to formulate the executive summary of the American Heart Association sponsored Conference on Prevention VI: Diabetes and Cardiovascular Disease on January 18 to 20, 2001 in Orlando, Florida defined 5 mechanisms relating to pathogenesis of atherosclerosis in DM.³⁴ They are: 1) metabolic factor arising from insulin deficiency and insulin resistance producing a state of chronic hyperglycemia; 2) excessive oxidation/glucooxidation due to spontaneous nonenzymatic reaction between glucose, lipids and proteins producing advanced glycosylation end products (AGE); 3) endothelial dysfunction is associated with hyperglycemia, dyslipidemia, insulin resistance, hypertension and atherosclerosis (Table VIII); 4) inflammation is

increased in DM due to excess adipose tissue which is an important source of interleukin-6. Cytokines generate growth factors that stimulate proliferation and migration of vascular smooth muscle cells and induce platelet aggregation; 5) prothrombotic state of DM perpetuating imbalance between prothrombotic mechanisms and antifibrinolytic processes.

In the 1988 Claude Bernard Lecture, Deckert proposed the Steno hypothesis.²⁴ This hypothesis states that albuminuria and vascular changes are due to genetic polymorphism of N-deacetylase causing inappropriate sulphation of HS. Abnormal sulphation of HS leads to loss of anionic charge in extracellular matrix and endothelial membranes and endothelial cell dysfunction. HS is the main glycosaminoglycan of basement membranes of glomeruli, mesangial and endothelial plasma membranes. Tables IX and X describe the properties of HS and the putative mechanism of widespread damage in DM respectively.²⁴ Abnormal sulphation of HS due to genetic polymorphism of N-deacetylase in combination with environmental factor like poor diabetic control leads to angiopathy (Figure 2).

The glucose connection leading to endothelial cell damage is related to the continuous and graded relation across the range of nondiabetic glucose values, independent of traditional and non-traditional risk factors for CVD.²⁵ Blood glucose scavenging of NO from the endothelium produces cellular effects in endothelial cell, pancreatic B cells, macrophages, nervous tissue and skeletal muscle (Table II).²⁶ Vascular effects of hyperglycemia are reversed by L-arginine.²⁸ Hyperglycemia from poor diabetic control reduces bioavailability of NO through the production of AGE (Table XII) and reactive oxygen species (ROS) (Table XIII). It is suggested that the common mechanism of cardiovascular risk factors is oxidative stress. Oxidative stress is a necessary consequence of organisms living in air since 1-5% of inhaled oxygen become ROS.³⁵

Table IX. Properties of Heparin Sulfate²⁴

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1. Heparan sulfate is the main glycosaminoglycan of basement membranes of glomeruli, mesangial and endothelial plasma membranes.
 2. Heparan sulfate after sulphation by N-deacetylase is incorporated in plasma and basement membranes of extracellular matrix and maintains the integrity of the collagen network providing anionic charge.
 3. Heparan sulfate inhibits smooth muscle cell growth.
 4. Heparan sulfate in endothelial membranes is antithrombogenic.
 5. Heparan sulfate inhibits mesangial cell growth.
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Table X. Mechanism of Widespread Vascular Damage in Diabetes²⁴

1. Diabetes affects sulfate metabolism.
2. In diabetic animals inappropriate sulphation of heparan sulfate shows impaired activity of N-deacetylase enzyme.
3. Loss of normal heparan sulfate leads to loss of anionic charge of extracellular and endothelial plasma membrane.
4. Loss of anionic sites leads to albuminuria.
5. Loss of heparan sulfate in the glomerular basement membrane has been demonstrated in nephropathy
6. Loss of heparan sulfate is associated with vascular dysfunction, renal and extrarenal complications.

Table XI. Cellular Effects of Glucose Scavenging Nitric Oxide (NO)^{25,26}

1. Endothelium – endothelial cell dysfunction
2. Pancreatic β cells – defective glucose-stimulated insulin secretion (early phase is NO-dependent).
3. Macrophages – defective response to lipopolysaccharide stimulation
4. Nervous tissue – reduced cGMP generation (preconditioning for diabetic neuropathy?)
5. Skeletal muscle – impaired insulin – stimulated glucose utilization.

Table XII. Hyperglycemia Triggers Endothelial Cell Dysfunction²⁵⁻²⁸

1. Vascular effects of acute hyperglycemia in humans are reversed by L-arginine: evidence for reduced availability of NO during hyperglycemia.^{27,28}
2. Each episode of hyperglycemia however transient leads to temporary decrease of bioavailability of NO and impairs the NO-dependent functions of the endothelium.²⁵
3. Formulation of AGE depends on hyperglycemia. AGE inactivates NO by a receptor-specific (RAGE) pathway.²⁶

Table XIII. Diabetes and Vascular Production of Reactive Oxygen Species (ROS)^{35,44}

1. Hyperglycemia enhances glucose autoxidation and changes in ROS-producing enzymes.
2. ROS stimulates glucose-induced activation of protein-kinase C (PKC) isoforms.
3. ROS activates formation of advanced glycation end products (AGE).
4. ROS stimulates glucose flux and NF- β activation in endothelial cells.

The acute and chronic stages of endothelial cell dysfunction in a diabetic patient are triggered by hyperglycemia.²⁵ The presence of AGE perpetuates the impairment of endothelial function through the induction of PAI-1 gene.^{26,27}

Insulin stimulates the release of endothelin (ET) and NO (Table XIV). Imbalance of ET and NO may be involved in the pathophysiology of hypertension

and atherosclerosis in insulin resistant state with endothelial dysfunction.²⁹⁻³¹ Hyperinsulinemia accompanying insulin resistance increases endothelial ET production and release.³⁰⁻³¹ Insulin resistance is present in patients with impaired glucose tolerance and type 2 DM and hyperinsulinemia precedes type 2 DM. In insulin sensitive state, insulin maintains balance of ET and NO. However, in insulin resistance and hyperinsulinemia there is an imbalance between insulin action on ET and NO producing increased vascular tone and endothelial dysfunction. Insulin resistance and atherosclerosis exist long before clinical disease reveals itself-sharing common history.³⁶⁻⁴⁰ The “common soil” hypothesis of Jarrett³⁶ of DM and atherosclerosis states that these 2 conditions share the same genetic and environmental roots (Table XV).

CVD is as common in newly diagnosed DM as in DM of long duration and patients with IGT have the same rate of CVD as those with overt DM.^{37,38} Insulin resistance appears to be a multisystem disorder (Table XVI) involving genetics, obesity, physical inactivity, aging and metabolic factors like atherogenesis, dyslipidemia, hypertension, glucose intolerance and prothrombotic state.⁴¹

Primary Prevention of Cardiovascular Disease in Diabetics

In DM vascular complications are only partially prevented by tight glyceic control. Diabetics have greater CVD morbidity and mortality.^{3,4,14} Table XVII shows DM alters hemostatic factors.⁴¹ Type 2 DM patients without prior myocardial infarction are at the same risk of coronary events as nondiabetic patients with prior myocardial infarction.^{42,43} A guide to primary prevention of CVD in patients with diabetes in 1999 was recommended by Grundy *et al*¹⁴ for control of risk factors with corresponding goals for optimal results. These include: complete abstinence from smoking, blood pressure and glucose control, use of antiplatelet agents, increase in physical activity and weight control.

Table XIV. Insulin Resistance and Endothelial Dysfunction²⁹⁻³¹

- Insulin stimulates production of NO and endothelin.
- Insulin resistance is present in type 2 DM, obesity and essential hypertension with endothelial dysfunction.
- Endothelial dysfunction is manifested as diminished blood flow response to cholinergic agonists and insulin
- Concurrent improvement in endothelial function and insulin sensitivity with exercise, metformin and troglitazone.

Table XV. Insulin Resistance and Atherosclerosis³⁶⁻⁴⁰

- Insulin resistance and atherosclerosis exist long before the clinical disease reveals itself; they share common history.
- "Common Soil" hypothesis: DM and atherosclerotic CVD share the same genetic and environmental roots.
- Cardiovascular complications are as common in newly diagnosed DM as in DM of long duration.
- Patient with impaired glucose tolerance have the same rate of CVD as those with DM.

Table XVI. Insulin Resistance and the "Metabolic Syndrome"³⁷⁻⁴¹

- Most type 2 DM have insulin resistance.
- Insulin resistance predisposes to CVD and DM
- Insulin resistance appears to be a multisystem disorder involving:
 - genetics, obesity, physical inactivity, aging
 - metabolic factors (atherogenesis, dyslipidemia, hypertension, glucose intolerance, prothrombotic state).

Table XVII. Diabetes and Hemostasis⁴¹

Diabetes alters the following hemostatic factors:

- large platelets; abnormal platelet aggregation
- increased GP IIb/IIIa receptors
- increased activated circulating platelets
- increased adhesion molecules
- impaired fibrinolysis

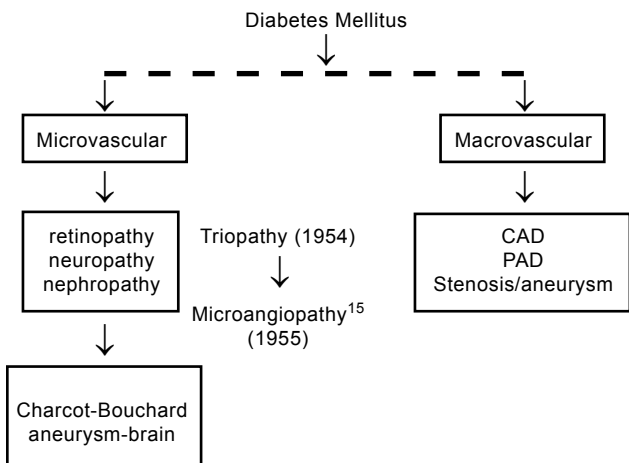


Fig. 1. Vascular Complications of Diabetes Mellitus, CAD-Coronary Artery Disease; PAD-Peripheral Artery Disease

Angiotensin converting enzyme inhibitor (ACEI) has been advocated by Munzel and Keane⁴⁴ as a "magic bullet" against oxidative stress since it targets oxidative stress at its source by inhibiting nicotinamide adenine dinucleotide (NADH) phosphate (NAD(P)H) oxidase. By inhibiting NAD(P)H, production of reactive oxygen species (superoxide anion, hydrogen

peroxide and peroxynitrite) is reduced. Angiotensin receptor blocker (ARB) on the other hand improves endothelial function by reducing inactivation of NO by superoxide anion.⁴⁵

Abnormal Sulphation of Heparan Sulphate (HS)²⁴

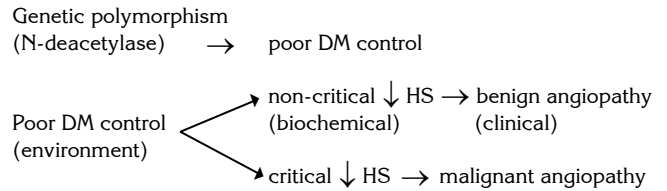


Fig. 2. Vascular Changes from Abnormal Sulphation of Heparan Sulphate

Peters and Shiger⁴⁶ advise screening for type 2 DM patients who are >45 years with family history of DM or younger if obese (>27 kg/m² BMI), hypertensive, low HDL (<35 mg/dl) or triglycerides >250 mg/dl, gestational DM or delivered baby >9 lb and impaired glucose tolerance or impaired fasting glucose in previous test.

CONCLUSION

The intimately incriminating connection between DM and CVD is compelling. The vascular manifestations of DM affect more vascular beds than any other disease. None of the presently known risk factors inflicts more morbidity and mortality in the cardiovascular system than DM. Indeed, DM is not only a major risk factor for CVD but in reality DM is CVD that destroys the vascular beds of several target organs.

The putative mechanisms for the generalized vascular lesions are through heparan sulfate loss, glucose scavenging and insulin resistance separately or jointly producing endothelial dysfunction. Without physical denudation of the endothelium these 3 mechanisms per se can effect widespread endothelial dysfunction. In addition these mechanisms are usually associated with other factors like hemostatic alterations, dyslipidemia and permeability abnormalities.

Today not many internists, diabetologists, nephrologists, neurologists and cardiologists think of DM as a classic model of cardiovascular pathology. DM begins to damage the cardiovascular system even before it is diagnosed, silently building atherosclerotic lesions and aneurysms (micro and macroaneurysms) in coronary arteries and other vessels. Importantly DM causes abnormal lipid levels and impairs vascular homostasis. Patients with impaired glucose tolerance

may already have heart and vascular disease before they become diabetic, hence should be treated to prevent deterioration of vascular complications before DM becomes clinically overt. Treating a patient with impaired glucose tolerance and overt DM must be a “shared responsibility” among specialties of vascular beds involved.

REFERENCES

1. Editorial. Diabetes Mellitus: A Risk Factor for Cardiovascular Disease. *Circulation*; 100:1132, 1999.
2. Pell S, D'Alonzo CA: Factors Associated with Long Term-Survival of Diabetics. *JAMA*; 214:1833, 1970.
3. Garcia MJ, McNamara PM, Gordon T, Kannel WB: Morbidity and Mortality in Diabetes in the Framingham Population. *Diabetes*; 23:105, 1974.
4. Marble A: Late Complications of Diabetes A Continuing Challenge. *Diabetologia*; 12:193, 1976.
5. Kannel WB, McGee DL: Diabetes and Cardiovascular Disease. The Framingham study. *JAMA*; 241:2035, 1978.
6. Beacg KW, Strandness DE: Atherosclerosis Obliterans and Associated Risk Factors in Insulin-Dependent and Non-Insulin Dependent Diabetes. *Diabetes*; 29:822, 1981.
7. Jarrett RJ, McCartney P, Keen H: The Bedford Survey. Ten Year Mortality Rates in Newly Diagnosed Diabetics, Borderline Diabetes and Normoglycemic Controls and Risk Indices for Coronary Artery Disease in Borderline Diabetics. *Diabetologia*; 22:79, 1982.
8. Eschwege P, Richard JL, Thibault N, *et al.*: Coronary Heart Disease Mortality in Relation with Diabetes, Blood Glucose and Plasma Insulin Levels. The Paris Prospective Study, Ten Years Later, *Hown Metab Res*; 15:41, 1985.
9. Steiner G: Diabetes and Atherosclerosis. Epidemiology and Intervention Trials in Woolford FP, Davignon J, Guidelines A (eds): *Atherosclerosis X*. Amsterdam, The Netherland, Elsevier, pp749, 1995.
10. Nathan D, Meigs J, Singer D: The Epidemiology of Cardiovascular Disease in Type 2 Diabetes Mellitus: How Sweet It Is or Is It? *Lancet*; 350 (suppl 1): 4, 1997.
11. Ruderman NB, Haudenschild C: Diabetes As An Atherogenic Factor. *Prog Cardiovasc Dis*; 26:374, 1984.
12. ACC News: Diabetes Outworks Smoking As Risk Factor for Cardiovascular Disease. *Cardiology*; 31:16, 2002.
13. Waife SO: *Diabetes Mellitus 7th ed.*, Eli Lilly and Co., Indianapolis, Indiana 1967 p. 1.
14. Grundy SM, Benjamin IJ, Burke GL, *et al.*: Diabetes and Cardiovascular Disease. *Circulations*; 100:1134, 1999.
15. Ditzel A, Rooth G: The Microangiopathy in Diabetes Mellitus. A Concept Regarding the Mechanism of Its Origin. *Diabetes*; 4:474, 1955.
16. Haffner SM, Stern MP, Hazuda HP, *et al.*: Cardiovascular Risk Factor in Pre-Diabetic Individuals: Does the Clock for Coronary Artery Disease Start Ticking Before the Onset of Diabetes? *JAMA*; 263:2293, 1990.
17. McMillan DE: Deterioration of the Microcirculation in Diabetes. *Diabetes*; 24:944, 1975.
18. Mogensen CE: Natural History of Renal Functional Abnormalities in Diabetes Mellitus: From Normoalbuminuria to Incipient and Overt Nephropathy. *Contemp Issues Nephrol*; 20:19, 1989.
19. Ledru F, Ducimetiere P, Battaglia S, *et al.*: New Diagnostics Criteria for Diabetes and Coronary Artery Disease: Insights from An Angiographic Study. *JACC*; 37:1543, 2001.
20. Waller BF, Palumbo PJ, Roberts WC: Status of Coronary Arteries at Necropsy in Diabetes Mellitus with Onset After Age 30 Years. *Am J Med*; 69:498, 1980.
21. Pickering G: Hypertension – Definition, Natural Histories and Consequences. *Am J Med*; 32:570, 1972.
22. Velasquez MI, Bhatena DJ, Striffler JS, *et al.*: Role of Angiotensin Converting Enzyme Inhibition in Glucose Metabolism and Renal Injury in Diabetes. *Metabolism*; 47 (suppl 1):7, 1998.
23. Rubler S, Diugash J, Yuceoglu YS, *et al.*: New Type of Cardiomyopathy Associated with Diabetic Glomerulosclerosis. *Am J Cardiol*; 30: 595, 1972.
24. Deckert T, Feldt-Rasmussen B, Borch-Johnson K, *et al.*: Albuminuria Reflects Widespread Vascular Damage: The Steno Hypothesis. *Diabetologia*; 12:219, 1989.
25. Hoogwerf B, Sprecher DL, Pearce GI: Blood Glucose Concentrations ≤ 125 mg/dl and Coronary Heart Disease Risk. *Am J Cardiol*; 89:596, 2002.
26. Goligorsky MS, Chen J, Brodsky S: Endothelial Cell Dysfunction Leading to Diabetic Nephropathy: Focus on Nitric Oxide. *Hypertension*; 37 (part 2): 744, 2001.
27. Cooper ME, Gilbert RE, Epstein M: Pathophysiology of Diabetic Nephropathy. *Metabolism*; 47 (suppl 1):3, 1998.
28. Giugliano D, Marfella R, Cappola L, *et al.*: Vascular Effects of Acute Hyperglycemia in Humans are Reversed by L-Arginine: Evidence for Reduced Availability of Nitric Oxide During Hyperglycemia. *Circulation*; 95:1783, 1997.
29. Mather K, Anderson TJ, Verma S: Insulin Action in the Vasculature: Physiology and Pathophysiology. *J Vasc Res*; 38:415, 2001.
30. Schener U, Sartori C: Insulin as A Vascular and Sympathoexcitatory Hormone: Implications for Blood Pressure, Regulation, Insulin Sensitivity and Cardiovascular Morbidity. *Circulation*; 96:4104, 1997.
31. Cleland SJ, Petrie JR, Schninichiro U, *et al.*: Insulin-Mediated Vasodilation and Glucose Uptake are Functionality Linked in Humans. *Hypertension*; 33 (part II): 554, 1999.
32. Cleland SJ, Petrie JR, Small M, *et al.*: Insulin Action is Associated with Endothelial Function in Hypertension and Type 2. *Diabetes*; 35 (I Pt 2): 507, 2000.
33. Hayoz D, Brunner HR, Ruiz J: Diabetes Mellitus and Vascular Lesions. *Metabolism*; 47 (supl 1):16, 1998.

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34. Grundy SM, Howard B, Smith S, *et al.*: Prevention Conference VI: Diabetes and Cardiovascular Disease. *Circulation*; 105:2231, 2002.
35. Berk BC: Vascular Dysfunction in Hypertension and Diabetes. Cardiovascular Summit, Orlando, Florida. March 17, pp34, 2001.
36. Jarrett RJ: Type 2 (Non-Insulin Dependent) Diabetes Mellitus and Coronary Artery Disease: Chicken, Egg or Either? *Diabetologia*; 26:99, 1984.
37. Jarrett RJ, Shipley MJ. Type 2 (Non-Insulin Dependent) Diabetes Mellitus and Cardiovascular Disease: Putative Association via Common Antecedents-Further Evidence from Whitehall Study. *Diabetologia*; 34:737 1988.
38. Stern MP: Diabetes and Cardiovascular Disease: The "Common Soil" Hypothesis. *Diabetes*; 44:369, 1995.
39. Taegtmyer H: Insulin Resistance and Atherosclerosis: Common Roots for Two Common Diseases. *Circulation*; 93:1977, 1996.
40. Reaven GM, Chen YDI: Insulin Resistance, Its Consequences and Coronary Artery Disease: Must We Choose One Culprit? *Circulation*; 93:1780, 1996.
41. Roffi M, Chew DP, Mukherjee D, *et al.*: Platelet Glycoprotein IIb/IIIa Inhibitors Reduce Mortality in Diabetic Patients with Non-ST-T Segment-Elevation Acute Coronary Syndrome. *Circulation*; 104:2767, 2001.
42. Haffner SM, Lelito S, Rounemaa T, *et al.*: Mortality from Coronary Artery Disease in Subjects with Type 2 Diabetes and in Nondiabetic Subjects With and Without Prior Myocardial Infarction. *N Engl J Med*; 339, 1998.
43. Pyorala K, Laakso M, Uusitupa M: Diabetes and Atherosclerosis: An Epidemiologic View. *Diabetes Metab Rev*; 3:463, 1987.
44. Munzel T, Keaney JF: All ACE Inhibitors A "Magic Bullet" against oxidative stress? *Circulation*; 104:1571, 2001.
45. Cheetham C, Collis J, O'Driscoll G, *et al.*: Losartan, An Angiotensin Type 1 Receptor Antagonist, Improves Endothelial Function in Non-Insulin Dependent Diabetics. *JACC*; 36:1461, 2000.
46. Peters AL, Shriger DL: The New Diagnostic Criteria for Diabetes: The Impact on Management of Diabetes and Macrovascular Risk Factors. *Am J Med*;105(1A):15S-19S, 1998.