Review

COMPLICATIONS OF DIABETES MELLITUS

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ABSTRACT

Observational and clinical trial data show a clear relationship between the degree of hyperglycemia and the risk to develop diabetic retinopathy, diabetic nephropathy and diabetic neuropathy. Intervention trials comparing two different levels of glycemic control demonstrate that for every 1% reduction in HbA_{1c}, there is approximately a 25-30% reduction in these complications of diabetes. Furthermore, data from the Diabetes Control and Complications Trial show that the effects of early intensive therapy are durable for periods of at least 7 years. Early detection of the complications permits early intervention. Furthermore, other specific intervention strategies may also reduce the risk for progression of complications. These strategies include laser photocoagulation for diabetic retinopathy (proliferative retinopathy and clinically significant macular edema), BP control and modulation of the renin-angiotensin-aldosterone system for diabetic nephropathy and unloading devices for diabetic neuropathy. Other potential strategies to reduce the risk for onset and progression of these complications include such approaches as lipid lowering, aldose reductase inhibition and protein kinase C inhibition.

KEY WORDS: Diabetes mellitus; Retinopathy; Nephropathy; Neuropathy.

INTRODUCTION

The complications of diabetes mellitus include retinopathy, nephropathy, and neuropathy (both peripheral and autonomic). The risk for atherosclerotic vascular disease is also increased in persons with diabetes mellitus. The risk for microvascular and neuropathic complications is related to both duration of diabetes and the severity of hyperglycemia; the increased risk for vascular disease actually antedates the onset of hyperglycemia to the degree associated with diabetes mellitus.

Diabetic retinopathy is a leading cause of blindness in the Western world and the leading cause of blindness in young people. Diabetic nephropathy is a leading cause of the need for renal replacement therapy (dialysis or transplantation). Diabetic neuropathy and lower extremity vascular disease combine to make diabetes the leading cause of non-traumatic lower extremity amputations. Finally, diabetes increases the risk for atherosclerotic vascular disease by 2-5 folds.

In light of these observations, strategies for detection, prevention and management of complications are all important in dealing with patients who have diabetes mellitus. This article will summarize key detection and treatment strategies for the complications of diabetes with special emphasis on eye, kidney and neuropathic (peripheral) complications.

DIABETIC RETINOPATHY

Detection

Diabetic retinopathy can be detected in the office with hand held opthalmoscopy. However, this method of detection is limited by both the area of the retina that can be observed, the fact that inexperienced opthalmoscopists may miss clinically important retinopathy and the fact that use of monocular vision seriously limits he ability to distinguish background retinopathy (changes within the plane of the retina) from proliferative retinopathy (vessel changes that extend out of the plane of the retina into the vitreous). Similarly, macular edema may be missed by hand held ophthalmoscopy unless it is associated with retinal hard exudates - cholesterol/lipid deposits that occur in conjunction with extravasation of crystalloid and protein.

To insure adequate screening for diabetic retinopathy, a dilated eye exam is required and should be performed by an experienced ophthalmoscopist - most commonly an ophthalmologist. More recently fundus photography has been used as a screening tool with properly obtained photographs then being read by an experienced reader. Stereo photography

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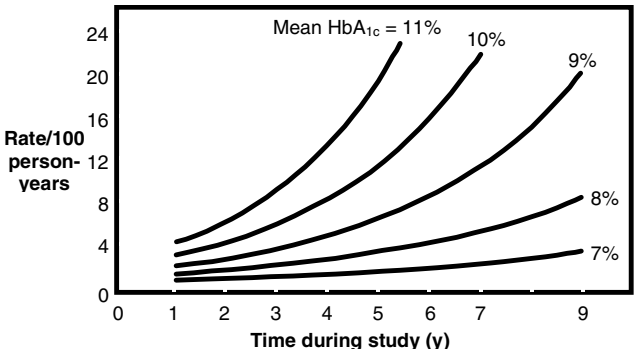
is required for best results. Technician training is required. Furthermore, this technique is often unsatisfactory in diabetic patients with cataracts.

Prevention and Treatment

Several observational studies have demonstrated a relationship between the risk for retinopathy and integrated measures of glycemic control (e.g. HbA_{1c}) (1). Two large clinical trials have demonstrated that diabetic subjects randomized to more intensive glucose control had a reduced risk for new onset retinopathy or progression of established retinopathy (2-6). In the Diabetes Control and Complications Trial (DCCT) type 1 diabetic patients without diabetic retinopathy at baseline in the intensive control group (mean in-trial HbA_{1c} ~ 7.0%) had a 76 % reduction in the risk for new onset retinopathy compared to the conventional control group (mean in trial HbA_{1c} ~ 9%). Similarly the progression of retinopathy was much less likely to occur in the intensive group (54% reduction) compared to the conventional group. Analyses of in-trial HbA_{1c} as a function of length of time in the study confirmed concept that higher HbA_{1c} concentrations and disease duration were associated with greater risk for retinopathy (Figure 1). The United Kingdom Prospective Diabetes Study (UKPDS) evaluated the effects of glycemic control in type 2 diabetic patients. The intensive policy group had a mean in trial HbA_{1c} of approximately 7% while the conventional policy group had a mean HbA_{1c} of just below 8%. The 0.9% delta HbA_{1c} in the UKPDS resulted in a 21% reduction in diabetic retinopathy.

Fig 1: Absolute Risk of Sustained Retinopathy Progression by HbA_{1c} and Years of Follow-up in DCCT Participants (adapted from DCCT Research Group. Diabetes.1995; 44: 968-83).



The observational extension to the DCCT is called the Epidemiology of Diabetes Intervention and Complications (EDIC) study (7). Results from EDIC for 7 years of follow-up have demonstrated that the favorable effects of intensive glucose lowering therapy are durable over time; this observation has been characterized as "metabolic memory" for intensive glycemic control. After the DCCT the mean HbA_{1c} difference in the 2 groups diminished to 0.4% by 1 year. Five years after DCCT closure, the mean HbA_{1c} was 8.1% in the original intensive group and 8.2% in the original conventional group. Nevertheless, there is a substantial reduction in the risk for progression of retinopathy in the group originally treated more intensively group.

The relationship of hypertension to retinopathy onset and progression has been less consistently established (8, 9). The best prospective data come from the UKPDS blood pressure arms (8). In the patients whose blood pressure was treated more aggressively, at 7.5 years there was a 34% reduction in the risk for retinopathy as determined by 2 step ETDRS progression and similar changes for retinopathy as determined by number of aneurysms or cotton wool exudates. There are two large observational studies that suggest a relationship between dyslipidemia and the risk for retinopathy-especially retinal hard exudates (10-12). However, no large intervention trial has yet evaluated or reported any effects of treating the dyslipidemia on diabetic retinopathy.

For patients who have established diabetic retinopathy, the use of laser photocoagulation therapy has documented efficacy. The Diabetic Retinopathy Study (DRS) evaluated the effect of scatter laser therapy in patients with proliferative diabetic retinopathy (13, 14). Eyes treated with argon or xenon laser has a reduced rate of progression of retinopathy and the associated visual loss. The Early Treatment Diabetic Retinopathy Study evaluated patients at an earlier stage of their disease (advanced pre-proliferative diabetic retinopathy or background retinopathy with macular edema). Laser therapy was associated with a reduced risk for visual loss in patients with clinically significant macular edema (15).

Mechanisms/and Studies in Progress

There is much interest in the mechanisms by which hyperglycemia may play a role in the development of diabetic retinopathy (16,17). Among the considerations are interests in whether the accumulation of the sugar alcohol, sorbitol, might play a role. Sorbitol concentrations may be reduced not only by reducing systemic glucose concentrations,

but also by interfering with the conversion of glucose to sorbitol, but blocking the enzyme aldose reductase. Studies using aldose reductase inhibitors have shown some suggestive favorable effects on diabetic retinopathy. More recently investigations related to protein kinase C (PKC) inhibition are underway. PKC is a family of enzymes found in many vascular tissues. Over activation of PKC may occur in the face of increased glucose concentrations as well as increased diacyl glycerol concentrations. Increased PKC as been associated with microvascular damage; the effect may be mediated through the production of VEGF—a compound that stimulates the proliferation of new vessels. Studies of PKC inhibitors in diabetic animals have shown a reduction in retinopathy. The studies in human subjects are not yet complete, but suggest improvement in vision even in the face of limited/modest effects on retinopathy.

DIABETIC NEPHROPATHY

Detection

Diabetic nephropathy is now most commonly detected by using sensitive measures or urinary albumin excretion-commonly called microalbuminuria. The natural history of diabetic nephropathy is generally associated with a progression from microalbuminuria to macroalbuminuria, which is then associated with progressive decline in renal function ultimately resulting in the need for renal replacement therapy. The American Diabetes Association recommends screening for microalbuminuria beginning 5 years after the onset of type 1 diabetes mellitus and at the time of diagnosis in type 2 diabetes mellitus. This latter recommendation derives from the observation that type 2 diabetes may go unrecognized for many years before it is diagnosed.

Prevention and Treatment

There are 3 major strategies to reduce the risk for onset and progression of diabetic nephropathy. These include glycemic control, management of elevated blood pressure and modification of the renin-angiotensin-aldosterone-system (RAAS) with angiotensin converting enzyme inhibitors or angiotensin receptor blockers. A summary of these interventions will be reviewed briefly.

The DCCT analyzed the effects of glycemic control on the risk for new onset of microalbuminuria and progression from microalbuminuria to albuminuria. The group whose glucose levels were more intensively treated had a reduction in the risk for new onset microalbuminuria of 39% and progression to albuminuria of 54% (2). In the UKPDS the 0.9% delta HbA_{1c} resulted in a 33% reduction in albumin excretion (3-6). The DCCT follow-up study called EDIC (see above) also demonstrated that the effects of intensive glycemic control on the risk for albuminuria were durable during the 7 years of follow-up. New onset microalbuminuria was reduced by 50% during the EDIC follow up in the DCCT intensive treatment group and new onset of clinical albuminuria was reduced by 87% (18).

The early studies of the relationships of increasing blood pressure, increasing albumin excretion and declining GFR published by Parving and others demonstrated the importance of blood pressure reduction in reducing the albumin excretion rates and attenuating the decline in GFR (19). Subsequently, modulating the RAAS with ACE-inhibitors and ARBs has demonstrated favorable effects on measures of diabetic nephropathy independent of blood pressure lowering. Specifically, the Lewis study in type 1 diabetes compared captopril to other blood pressure lowering therapies (excluding calcium channel blockers) in subjects who had moderately elevated albumin excretion and normal on mildly abnormal renal function (20). There was a marked reduction in doubling of serum creatinine (the primary end point) as well as progression to end stage renal disease or death. These observations were affirmed in other ACE-inhibitor studies. These include studies by Ravid showing a decline and loss of renal function and favorable effects on albuminuria using enalapril in type 2 diabetic subjects (21). Based on these and other studies, Kasiske analyzed the effects of both BP and angiotensin converting enzyme inhibition and reported that both effects contributed about equally to slowing the progression of loss of renal function (22). Specifically, for each 10mm Hg reduction in BP there was a 3.70 ml/min relative increase in GFR and additional favorable effect of ACE-inhibitors was 3.41 mg/min relative increase in GFR. One of the largest studies evaluating the effects of ACE inhibition on albuminuria was the Micro-HOPE study of more than 5,000 diabetic subjects who were randomized to ramipril (vs. placebo)(23, 24). By one year the subjects randomized to ramipril had diminished albumin excretion rate compared to those patients randomized to placebo. More recently 3 major trials using angiotensin receptor blocking agents (vs. placebo) in a wide variety of type 2 diabetic patients have shown 16% to 68% reductions in renal disease progression

as measured by albuminuria (25-27). One of these studies used 2 different doses of irbesartan (150 mg daily; 300 mg daily) and demonstrated a dose response effect (25). Compared to placebo the 150 mg dose showed a 44% reduction in albuminuria and the 300 mg dose a 68% reduction in albuminuria when compared to placebo.

There are tantalizing observational data that show relationships among dyslipidemia and the risk for diabetic nephropathy. In subjects from the Early Treatment Diabetic Retinopathy Study (ETDRS), elevated lipids at baseline were associated with a future risk for the need for renal replacement therapy (28).

A recent systemic review of ACE-I and ARB's summarized the effects of these agents on mortality and renal outcomes from 43 published trials (29). This review concluded that there were favorable effects from both classes of agents on measures of renal disease (Table 1), but that ACE-I trials were more likely to show a reduction in mortality. ACE-I therapy resulted in the following relative risks: doubling of creatinine of 0.60 (95% CI: 0.34-1.05), end stage renal disease of 0.64 (95% CI 0.40-1.03), progression microalbuminuria to macroalbuminuria of 0.45 (95% CI: 0.28-0.71) and all cause mortality of 0.78 (95% CI: 0.63-0.99). The point estimates for relative risk in renal disease end points were similar for the ARB's with the following risks: doubling of creatinine of 0.79 (95% CI: 0.67-0.91), end stage renal disease of 0.78 (95% CI 0.67-0.91), and progression microalbuminuria to macroalbuminuria of 0.49 (95% CI: 0.32-0.75). However, the point estimate for and all cause mortality did not favor ARB therapy 0.78 (95% CI: 0.63-0.99).

Table 1: Effects of Angiotensin Converting Inhibitor (ACE-I) and Angiotensin II Receptor Blockers (ARB) on Measures of Renal Disease and All Cause Mortality

	# of trials	# subjects	Relative Risk (treatment vs. placebo/no treatment)	95% CI
ACE-Inhibitor Trials				
Doubling of Serum Creatinine	8	1868	0.60	0.34-1.05
End Stage Renal Disease	9	1907	0.63	0.40-1.03
Micro → Macroalbuminuria	15	1888	0.87	0.69-1.10
Mortality	20	2838	0.79	0.63-0.99
ARB Trials				
Doubling of Serum Creatinine	3	3251	0.79	0.57-0.90
End Stage Renal Disease	3	3251	0.78	0.67-0.91
Micro → Macroalbuminuria	3	761	0.49	0.32-0,75
Mortality	5	3329	0.99	0.85-1.17

Adapted from Strippoli et al, BMJ 2004 (ref. 29)

NEUROPATHY

Peripheral

Detection

The onset of loss of sensation in the lower extremities is the commonest symptom associated with peripheral neuropathy (30-32). However, the onset is often insidious. Careful questioning of patients about loss of sensation or altered sensation to touch and temperature may provide clues to diabetic neuropathy. In addition regular screening with a number of simple techniques has become the standard of care (33-35). These techniques include testing for lower extremity reflexes, testing for vibration with a tuning fork (preferably 128 hertz), and some measure of touch usually with a pin or monofilament. Monofilament testing has become the gold standard. Patients need to be given instruction in the foot examination with special attention to development of callus formation and loss of skin integrity from either foot ulcers, pressure related blisters or infections such as tinea pedis. Good patient care dictates a foot exam at the time of every routine visit to the health care provider's office. Recognition of loss of sensation and early detection of foot lesions is necessary to help reduce the risk for neurotrophic foot ulcers or peripheral vascular disease-both of which contribute the risk for lower extremity amputations in diabetic patients

Prevention Strategies

As with the micro vascular complications of diabetes, there is a clear relationship between glycemic control and measures of neuropathy. The DCCT intensively controlled subjects had a 60% reduction in neuropathy (2). Similarly the subjects in the UKPDS with the intensive policy had a 40% reduction in peripheral neuropathy as measured by a bioesthesiometer (3).

Patients who have evidence of peripheral neuropathy need to be instructed in a careful foot examination to detect callus formation, ulcer formation or other threats to the integrity of the skin including blisters, cracks or infections such as tinea pedis. Patients who have significant loss of sensation, especially with foot deformities and callus formation, need to be placed in footwear that will reduce the risk for further callus formation and the development of neurotrophic foot ulcers. Orthotic devices that can be placed in foot wear help to reduce the risk for ulcer

formation. Patients need to be instructed that even short periods of time out of the footwear increase the risk for ulcer formation. In patients who have developed ulcers, footwear that "unloads" the pressure areas is absolutely necessary for ulcers to heal. Patients are not often as adherent to consistent use of unloading footwear as would be ideal for ulcer healing. Therefore, the use of total contact casts has become one of the most effective ways to insure ulcer healing. Total contact cast application must be done by experienced technicians to avoid pressure ulcers in other areas of the foot as a result of the cast.

Aldose Reductase Inhibitors

Postulated mechanisms for peripheral neuropathy have included micro vascular disease with vascular damage to the vasa nervorum, autoimmune damage to the nerves and metabolic damage as a result of the polyol pathway (36, 37). Each of these proposed mechanisms has evidence to support it as a contributing factor to neuropathy. Much of the investigation to reduce the risk for neuropathy has focused on clinical trials of inhibiting the enzyme aldose reductase to reduce sorbitol accumulation in the nerves (38). These trials have shown some favorable effects on nerve conduction studies, but limited actual clinical benefit. Most benefit seems to occur in patients who have very early neuropathic changes while more established neuropathy does not seem to have much change with the use of aldose reductase inhibitors.

Painful Neuropathy

One of the most distressing disorders associated with peripheral neuropathy is painful neuropathy. Often this is a self limiting disorder. However, the associated pain may be quite severe. In addition to treatment with analgesics, other agents have been used in an effort to reduce pain (39). These agents include systemic approaches (e.g. amitryptilline, mexilitene, gabapentin, topiramate, duloxetine) as well as topical preparations such as capsaicin. Each of these approaches is associated with approximately a 70% reduction in pain (compared to typical placebo responses of ~30%). Because these agents work by different mechanisms, the clinical approach to treating painful neuropathy often includes sequential treatment with each agent in an effort to find what works best for an individual patient.

Although the pain pattern of a burning type pain that is often worse at night is quite consistent with a diabetes related etiology, painful neuropathy may have other causes. Vitamin B12 deficiency (sometimes associated with metformin use) should be excluded in all patients with painful neuropathy. In addition, there are recent studies showing that there may be an association with monoclonal gammopathies or inflammation in some patients. If investigations for paraproteinemia or inflammatory markers such as GM1 are positive, then appropriate therapies may include the use of glucocorticoids.

SUMMARY

Glycemic control has a favorable effect on each of the microvascular complications of diabetes mellitus both in preventing new onset of the complication and slowing the progression of established complications. Furthermore data from the follow up of the DCCT suggest that the effects of intensive glycemic control are durable. Control of blood pressure and use of modulators of the renin-angiotensin-aldosterone system favorably affects the progression of nephropathy. Early detection of complications may also slow the progression of disease with such interventions as laser therapy for retinopathy (macular edema and proliferative retinopathy) and proper footwear for patients with insensate feet. Modulation of other mechanisms such as PKC inhibitors, aldose reductase inhibitors, and treatment of dyslipidemia are under investigation and will likely afford new ways to reduce the risk for onset/progression of microvascular complications of diabetes mellitus.

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