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Diabetic microvascular complications: can patients at risk be identified? A review

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SUMMARY

People with diabetes have an increased risk of developing microvascular complications, diabetic retinopathy, diabetic nephropathy and diabetic neuropathy, which, if undetected or left untreated, can have a devastating impact on quality of life and place a significant burden on health care costs. In addition, diabetic microvascular complications can reduce life expectancy. The strongest risk factors are glycaemic control and diabetes duration; however, other modifiable risk factors such as hypertension, hyperlipidaemia and smoking, and unmodifiable risk factors including age at onset of diabetes and genetic factors may all play a part. Along with the presence of external risk factors, some associations have also been noted between diabetic microvascular complications themselves. There is evidence that diabetic retinopathy in association with increased blood pressure is an important risk factor for diabetic nephropathy progression. Significant correlations have also been shown between the presence of diabetic peripheral neuropathy and the presence of background or proliferative diabetic retinopathy. Clinical trials are currently in progress looking at a number of approaches to designing treatments to prevent the adverse effects of hyperglycaemia. It is essential however, that risk factors associated with the progression and development of diabetic microvascular complications are detected and treated at an early stage in order to further reduce morbidity and mortality. Considering all three complications as interrelated may well facilitate early detection of microvascular disease. Despite good long-term glycaemic and blood pressure control, diabetes remains a major cause of blindness, renal failure and amputations. As the incidence of diabetes continues to rise, the burden of diabetic microvascular complications will increase in future, hence the need for early detection. Considering the microvascular complications of diabetes as related, and enquiring proactively about complications, may well facilitate early detection of microvascular disease.

Keywords: Diabetes; microvascular complications; nephropathy; retinopathy; neuropathy

INTRODUCTION

Diabetes mellitus is a global health problem, affecting all age groups (1). Currently, around 177 million people have diabetes worldwide; however, it has been projected that this number will increase to at least 300 million by 2025 (2). This epidemic relates in particular to type 2 diabetes, which accounts for around 90% of all diabetes cases. The increased prevalence of type 2 diabetes can be attributed to the ageing population and rising incidence of obesity in developed countries, among other factors (3).

Prevention of complications specific to diabetes is a key issue because of the morbidity and mortality associated with the disease (4). Clinically significant morbidity may often develop before diagnosis (5). Between one-third and one-half of all people with diabetes have evidence of organ or tissue damage (6,7). Although not everyone with diabetes will develop a complication, a recent epidemiological study (8) reported that two or more complications are apparent in almost one-fifth of people with diabetes.

If diabetes is undetected or not treated, or if its complications are poorly managed, it can have a devastating impact on quality of life (1). Diabetes also places a significant burden on health care costs, with the major single item of expenditure being hospital admissions for the treatment of complications (2).

Landmark studies, including the Diabetes Control and Complications Trial (DCCT) (9) and the United Kingdom Prospective Diabetes Study (UKPDS) (10), have shown that intensive control of blood glucose levels and tight blood pressure control reduce the risk of complications related to diabetes. In addition, early identification of risk factors can help reduce the development and progression of diabetic

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microvascular complications, and improve patients' quality of life.

Although it is clear that diabetes complications result from the abnormal metabolic environment engendered by chronic hyperglycaemia (specifically affected by factors such as age, age of onset and disease duration) (11), the actual development of these complications in any individual is a function of the genetic susceptibility to damage in that particular individual. One study demonstrated the familial factors influencing development of microvascular complications, suggesting a trend towards gender susceptibility (12). Furthermore, the presence or absence of environmental factors or other conditions also affects the risk of developing complications; for example, hypertension, hyperlipidaemia, alcohol consumption, glaucoma and smoking can all influence the susceptibility of an individual to diabetes. This implies that specific gene definition may help to determine which patients require a more (or less) aggressive approach to glycaemic control and that risk of complications can be substantially reduced by attention to co-existing conditions and environmental factors.

The key to preventing complications from diabetes is to prevent the development of diabetes itself. The Diabetes Prevention Program has shown that type 2 diabetes can be prevented or delayed in a significant number of people at high risk for the disease, by means of appropriate treatment or lifestyle modification (13). Current research is also looking at possible interventions for the prevention of type 1 diabetes.

METHODS

A comprehensive review of the literature was undertaken to establish the interrelationship and relative risks for the development and progression of diabetic peripheral neuropathy, diabetic retinopathy and diabetic nephropathy, together with current approaches to scoring or grading risk. Published trials were found by searching Medline from 1966 to 2005 and Embase from 1974 to 2005 using a comprehensive search strategy, and by searching Biosis to identify abstracts. Information was collected by means of computerised literature searches, including MEDLINE and EMBASE. In addition, DEC Reports (Development and Evaluation Committee Reports), Evidence Based Medicine Reviews databases and the Cochrane Library were searched through direct Internet access to the appropriate site. Citations for review were checked to identify multiple publications of the same trial data.

DIABETIC RETINOPATHY

Diabetic retinopathy is a major vision-threatening diabetic microvascular complication and a leading cause of visual disability and blindness (2). Several studies have also shown that visual impairment caused by diabetic retinopathy is associated with poor survival (14), which is often attributed to cardiovascular disease (14–16). Diabetic retinopathy can involve the peripheral retina, the macula or both. The range of severity includes background (mild to moderate non-proliferative), preproliferative (or severe and very severe non-proliferative), proliferative and advanced diabetic retinopathy (17). The impact of diabetic retinopathy with its associated clinical features is fundamentally similar in type 1 and type 2 diabetes (18,19).

Prevalence of Diabetic Retinopathy

The prevalence of diabetic retinopathy varies widely depending on the population studied (8,20–30). Background diabetic retinopathy however, is almost universal after 20 years of diabetes, whilst proliferative diabetic retinopathy affects 70% of people with type 1 diabetes after 30 years' duration (31). Incidence data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) (32) showed that people taking insulin, and diagnosed to have diabetes before the age of 30 years, have the highest prevalence of diabetic retinopathy (71%), 4-year incidence (59%) and progression to proliferative diabetic retinopathy (11%), while older-onset people diagnosed to have diabetes at or after 30 years of age and not taking insulin have the lowest prevalence (39%), incidence (34%) and progression to proliferative diabetic retinopathy (3%).

Risk Factors for the Development and Progression of Diabetic Retinopathy

Although background diabetic retinopathy may be present in some cases of recently diagnosed patients with type 1 or type 2 diabetes, its prevalence is significantly higher in patients with long-standing disease (31,33–35). The Pittsburgh Epidemiology of Diabetes Complications Study (31), which evaluated 657 patients with childhood-onset (< 17 years) type 1 diabetes, found that almost all patients had background diabetic retinopathy after 14 years of diabetes. After 25–29 years of diabetes, three quarters of patients aged 18–29 years and more than half of patients aged 30 years or over had proliferative diabetic retinopathy (Table 1). Similar findings were reported in the WESDR (33), in which the prevalence of proliferative diabetic retinopathy was greater among patients with prolonged duration of disease (0% in patients with diabetes for <5 years, 25% in patients with diabetes for 15 years and 67% in patients who had had diabetes for 35 years).

The age at onset of diabetes has also been found to be a relevant factor in the development of diabetic complications (36,37). Studies have shown that there is a significantly increased risk of diabetic microvascular complications, including diabetic retinopathy in patients with diabetes onset in puberty (up to diabetes duration of 20 years), compared to

Table 1 Prevalence of diabetic retinopathy in the Pittsburgh Epidemiology of Diabetes Complications Study (31)

Duration (years)	*Aged 18–29 years*			*Aged ≥30 years*		
	n	*≥Background %*	*Proliferative %*	*n*	*≥Background %*	*Proliferative %*
5–9	44	57	2	–	–	–
10–14	103	89	7	1	100	0
15–19	119	91	22	28	93	33
20–24	50	98	38	63	98	44
25–29	13	100	77	89	98	54
30+	–	–	–	68	100	68

diabetes onset before puberty with one possible hypothesis being changes of hormonal status during puberty (36,37). Kostraba et al. (38) demonstrated that the effect of prepubertal duration on the risk of diabetic microvascular complications is minimal. Vogt et al. (37) theorised that patients developing diabetes before the onset of puberty are protected for some time against the microvascular complications, but the overall risk of developing diabetic retinopathy remains the same. Despite the high prevalence of diabetes in the elderly population, the prevalence of vision-threatening diabetic retinopathy, particularly proliferative diabetic retinopathy, in patients diagnosed after the age of 70 years is low (39,40). Cahill et al. (39) reported a much lower overall prevalence of diabetic retinopathy than was seen in the WESDR (41) (14% vs. 40%), which included a subgroup of patients diagnosed after the age of 70 years.

Microaneurysms have also been found to be important lesions of diabetic retinopathy (42). The UKPDS (42) reported that, in patients with type 2 diabetes who had either no diabetic retinopathy or microaneurysms only at entry, the presence of microaneurysms alone, and also the number of microaneurysms, had a highly predictive value for worsening of disease at 3, 6, 9 and 12 years after entry in the study. The UKPDS also looked at the relationship between the severity of diabetic retinopathy and progression to photocoagulation in 3709 patients with type 2 diabetes (43). Results showed that few patients without diabetic retinopathy progress to photocoagulation in the following 3–6 years. However, 15.3% of patients with more severe diabetic retinopathy lesions required photocoagulation by 3 years and 31.9% by 9 years (Table 2).

Table 2 Progression to photocoagulation (43)

At baseline	*Progression to photocoagulation*		
	3 years	*6 years*	*9 years*
No diabetic retinopathy ($n = 2316$)	0.2	1.1	2.6
Microanuerysms in one eye only ($n = 708$)	0	1.9	4.7
More severe diabetic retinopathy features ($n = 509$)	15.3	25.2	31.9

Values are given in %.

There is clear evidence that elevated plasma glucose levels correlate with diabetic microvascular complications in patients with type 1 diabetes (9,44–47). The DCCT (9), which was designed to study the effect of enforcing optimised metabolic control on the complications of diabetes in a large cohort of 1441 patients aged 13–39 years with type 1 diabetes for 1–15 years, found that intensive therapy (insulin administered at least thrice daily by injection or external pump; doses adjusted according to monitored blood glucose levels and anticipated dietary intake and exercise) effectively delayed the onset and slowed the progression of diabetic retinopathy. In patients with no diabetic retinopathy at baseline, intensive therapy reduced the risk of developing this disease by 76% when compared with conventional therapy (one to two daily insulin injections, self-monitored urine or blood glucose levels and diet and exercise education). In patients with mild diabetic retinopathy, intensive therapy reduced the development of proliferative or severe nonproliferative diabetic retinopathy by 47%.

Further data from the DCCT confirm that once progression of diabetic retinopathy occurred, subsequent recovery was at least twice more likely with intensive treatment than with conventional treatment (45). Extrapolations of these results to a lifetime span suggest that intensive treatment can leave patients 14.7 more years free of proliferative diabetic retinopathy, 8.2 years free of clinically significant macular oedema and 7.7 more years without blindness (48). Although no glycaemic threshold could be demonstrated in the DCCT when the progression of diabetic retinopathy was plotted against HbA_{1c} (46), Reichard (47) found that patients with type 1 diabetes and mild diabetic retinopathy at onset randomised to intensified treatment did not develop serious retinopathy if their mean HbA_{1c} during 7.5 years was below 7%.

The Epidemiology of Diabetes Interventions and Complications (EDIC) study (49) is presently following 1400 (96%) subjects who were enrolled in the DCCT to determine the interactions between established and putative risk factors for long-term microvascular, neurological and cardiovascular outcomes, including prior diabetes treatment and the level of glycaemic control during the DCCT. The prolonged effect of 6.5 years of intensive glycaemic control has shown to be effective in reducing subsequent complications

in the follow-up EDIC/DCCT studies looking at the 4, 7 and 10 year time frames (50,51).

Poor glycaemic control has also been shown to be significantly associated with diabetic retinopathy progression in patients with Type 2 diabetes (36). Data from the UKPDS (52) demonstrated that intensive blood glucose control after diagnosis of Type 2 diabetes prevents the development of microvascular complications of diabetes and reduces associated morbidity and mortality. In the EDIC trial there was no effect on a reduction in cardiovascular outcomes 6 years after the end of the DCCT (53), although there was decreased progression of carotid intimal thickness (a presumed marker of atherosclerotic vascular disease) in the previous intensively treated cohort of the DCCT compared to the conventionally treated group (53). However, 5 years later in the EDIC trial, a total of 17 year follow-up of the combined duration of the DCCT and EDIC trials, there was indeed a lower risk of a cardiovascular disease event in the previous intensively treated cohort compared to the conventionally treated group of 42% and a reduction of severe clinical events, such as non-fatal myocardial infarction, stroke or death by 57% (54). Most of the risk reduction in the diabetes-related aggregate end point was due to a 25% risk reduction in microvascular end points, including the need for retinal photocoagulation. Conversely, studies, including the DCCT, have also shown that intensive treatment with insulin may adversely affect the development of diabetic retinopathy in patients with Type 1 and Type 2 diabetes (36,55,56). It has been suggested, however, that the progression of diabetic retinopathy in patients switched from oral drugs to insulin may be a result of poor glycaemic control and rapid lowering of blood glucose levels, rather than insulin as an independent risk factor (36).

In recent years, there have been several important studies examining the effect of blood pressure control and different antihypertensive agents on diabetic microvascular complications. Hypertension is especially common in newly diagnosed type 2 diabetes and is often associated with obesity (57). People with diabetes who also have hypertension are more likely to see deterioration in their level of diabetic retinopathy (10). In addition, there is a direct relationship between the risk of all complications of diabetes and systolic blood pressure over time (58). In the UKPDS (10), 758 hypertensive patients with type 2 diabetes were allocated to tight control of blood pressure ($< 150/85$ mmHg), and 390 hypertensive patients with type 2 diabetes to less tight control ($< 180/105$ mmHg). After a medial follow-up of 8.4 years, the tight control group had a 34% reduction in risk in the proportion of patients with deterioration of diabetic retinopathy by two steps, and a 47% reduced risk of deterioration in visual acuity by three lines of the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart.

Cigarette smoking may be related to the development of diabetic retinopathy, but the evidence is less conclusive than for diabetic nephropathy and diabetic peripheral neuropathy. Although the EURODIAB IDDM Complications Study (59) demonstrated that smoking was a risk factor for the development and progression of diabetic retinopathy, other studies have argued that smoking is not an important associated risk factor (60–63).

Several other significant risk factors for the development and progression of diabetic retinopathy have been documented, including unfavourable lipid profiles (64). Fong et al. (65) noted that patients with persistent visual loss had higher levels of cholesterol at baseline than those without persistent visual loss (244.1 vs. 228.5 mg/dl; $p = 0.0081$). Other factors, secondary to hyperglycaemia or dyslipidaemia must also be considered, such as serum advanced glycation end-products (AGE) levels (66,67). Data from the DCCT (68) provide the first available evidence that the severity of diabetic retinopathy is also influenced by familial factors, which are possibly genetic. More data from the DCCT support the importance of individual variability, as about 10% of patients who were in the lowest HbA_{1c} quintile during the study developed diabetic retinopathy nevertheless, whereas 43% of those in the worst quintile remained lesion-free (69).

DIABETIC NEPHROPATHY

Diabetic nephropathy is one of the most serious complications of diabetes and the leading cause of end-stage renal disease (ESRD) (70). The prevalence of diabetic nephropathy is projected to rise in future as the incidence of diabetes increases and the age of onset declines (71). Once in the advanced stages of diabetic nephropathy, patients are at high risk of cardiovascular death as well as renal failure (72). In the UKPDS (71), the reported annual death rates were 1.4% in patients at the 'no diabetic nephropathy stage', 3.0% at the 'microalbuminuria' stage, 4.6% at the 'macroalbuminuria' stage and 19.2% in patients with an 'elevated plasma creatinine or renal replacement therapy'. Patients with elevated plasma creatinine but without renal replacement therapy had an annual death rate of 18.9%. Death was usually due to cardiovascular disease. A correlation was noted between stage of diabetic nephropathy and percentage of patients still alive at 10 years; the more advanced the disease, the smaller this percentage of patients (Table 3).

Diabetic nephropathy is usually first manifested as an increase in urinary albumin excretion (microalbuminuria), which progresses to overt albuminuria and then to renal failure (73). However, the EDIC/DCCT study showed that a significant number of patients develop renal insufficiency without the presence of microalbuminuria (74). Although the risk of developing diabetic nephropathy appears to be similar in type 1 and type 2 diabetes (75), the occurrence of this complication in type 2 diabetes is a much larger burden in society (72). A number of factors may interplay in the

Table 3 Proportion of patients alive 10 years following onset of different stages of diabetic nephropathy (71)

	Proportion, % (95% CI)
No nephropathy	87.1 (86.8–87.3)
Microalbuminuria	70.8 (67.4–74.2)
Macroalbuminuria	65.1 (57.5–72.6)
Elevated plasma creatinine or renal replacement therapy	8.5 (0–100)

pathogenesis of diabetic nephropathy, including metabolic, hemodynamic and, as yet poorly defined, genetic and/or environmental determinants (76). Microalbuminuria develops early in the course of diabetic nephropathy and is currently considered as an indicator of renal endothelial dysfunction, as well as an independent predictor of cardiovascular risk in individuals with or without diabetes (77,78).

Prevalence of Diabetic Nephropathy

The prevalence of diabetic nephropathy varies dependent on the study population. The incidence of ESRD in patients with type 2 diabetes in particular, however, is rising sharply in many regions of the world (70). Data from the UKPDS (71) demonstrated that approximately 25% of patients with type 2 diabetes develop microalbuminuria or worse diabetic nephropathy by 10 years. It is estimated that almost 50% of patients who develop microalbuminuria do so within 19 years from diagnosis of diabetes. From any stage of diabetic nephropathy, the rate of deterioration to the next stage is 2–3% per year. Data from a prospective cohort study by Brancati et al. (79) confirm that diabetes mellitus is a strong independent risk factor for ESRD, even for ESRD ascribed to causes other than diabetes, including hypertension. In the WESDR (80) 14% of the study population with type 1 diabetes developed renal insufficiency or ESDR over a 10-year period.

Risk Factors for the Development and Progression of Diabetic Nephropathy

The main risk factors for the frequency, severity and progression of diabetic nephropathy include hyperglycaemia, hypertension, diabetes duration, age at onset, protein overload and smoking. There is also evidence to suggest that some individuals with diabetes have a genetic predisposition to diabetic nephropathy (81,82) with strong familial clustering recognised. The level of glycaemic control appears to be the dominant risk factor for the occurrence of microalbuminuria (72,83), whereas progression through the more advanced stages of diabetic nephropathy is affected by hypertension, hypercholesterolaemia and genetic factors (72). In a study by Krolewski et al. (84) the prevalence of microalbuminuria in patients with type 1 diabetes increased with increasing postpubertal duration of diabetes and, within each 6-year interval of disease duration, it showed an overall trend towards increasing with the HbA_1 value (Table 4).

Randomised intervention trials have shown that intensive treatment delays the onset and slows the progression not only of diabetic retinopathy, but also of diabetic nephropathy in patients with type 1 diabetes (9). In the DCCT (9) intensive therapy reduced the mean adjusted risk of the cumulative incidence of microalbuminuria in the primary prevention cohort by 34%, and the albumin excretion rate by 15% after the first year of therapy. In the secondary prevention cohort, intensive therapy reduced the mean adjusted risk of microalbuminuria by 43%, the risk of a more advanced level of microalbuminuria by 56% and the risk of clinical albuminuria by 56% (76). This beneficial effect of intensive glycaemic control on reducing the progression of diabetic nephropathy was maintained in the subsequent 4 year follow-up study (50) and 7- to 8-year study (85). Similarly, data from the UKPDS (51) demonstrated that improved blood glucose control reduces the risk of diabetic nephropathy in patients with type 2 diabetes.

There is evidence that hypertension is also an important risk factor for microalbuminuria (86). The Hypertension in Diabetes Study (57) reported that hypertensive patients suffered a higher prevalence of microalbuminuria compared with normotensive ones (24% vs. 14%). Intensive blood pressure control in normotensive patients with type 2 diabetes has been shown to slow progression to incipient and overt diabetic nephropathy and decrease the progression of diabetic retinopathy in normotensive (BP $<$ 140/90 mmHg) Type 2

Table 4 Odds ratios for the effect of variations in HbA_1 values on the development of microalbuminuria (84)

	Haemoglobin A_1 values in 1990–1991				
Duration of diabetes (years)	*5.9–8.8%*	*8.9–9.8%*	*9.9–10.7%*	*10.8–11.9%*	*12.0–21.3%*
1–6	1.0 (104)*	1.6 (65)	2.6 (64)	2.2 (49)	5.8 (74)
7–12	2.4 (58)	2.3 (82)	2.4 (81)	6.8 (94)	13.2 (107)
13–18	2.3 (47)	4.7 (69)	3.9 (52)	7.5 (52)	28.8 (43)
19–24	11.3 (45)	15.0 (40)	14.3 (44)	12.1 (52)	23.6 (35)
25–32	7.1 (27)	7.9 (25)	13.0 (35)	19.0 (37)	12.5 (21)

Values are presented as odds ratio (total number of patients).
*The prevalence of microalbuminuria was 3.8% in the reference group (patients with the lowest HbA_1 values [range, 5.9–7.9%; mean, 7.3%]).

diabetic patients (86). The UKPDS (10) reported that, at 6 years of follow-up, a smaller proportion of patients assigned to tight control of blood pressure, aiming for a blood pressure $< 150/85$ mmHg, had a urinary albumin concentration of ≥ 50 mg/l, a 29% reduction in risk.

Evidence of a link between development and progression of diabetic nephropathy and duration of diabetes in type 2 diabetes was clearly demonstrated in the UKPDS (Table 5) (71). Following diagnosis, progression to microalbuminuria occurred at 2.0% per year, from microalbuminuria to macroalbuminuria at 2.8% per year, and from macroalbuminuria to elevated plasma creatinine or renal replacement therapy at 2.3% per year. Ten years following diagnosis, microalbuminuria or worse diabetic nephropathy was present in 24.9% of patients; macroalbuminuria or worse diabetic nephropathy in 5.3% of patients and elevated plasma creatinine or renal replacement therapy in 0.8% of patients (71). In the Pittsburgh Epidemiology of Diabetes Complications Study (29) of 657 patients with type 1 diabetes with a mean duration of 20 years, no significant differences for microalbuminuria were found.

Several studies have shown the relationship between smoking and the development of diabetic nephropathy in diabetes. Chase et al. (62) conducted a study of 359 patients with type 1 diabetes. When compared with non-smokers, smokers were at 2.8 greater risk for albuminuria. Sawicki et al. (87) also found that cigarette smoking represents an important factor associated with the progression of diabetic nephropathy in treated hypertensive patients with type 1 diabetes. Progression of diabetic nephropathy was less common in non-smokers (11%) than in smokers (53%), and ex-smokers (33%). In a more recent study, Rossing et al. (88) reported smoking to be associated with progression in albuminuria, which is similar to the findings of the EURODIAB IDDM Complications Study (59). Other studies support the notion that smoking is a risk factor for diabetic nephropathy and its progression in type 2 diabetes (89,90).

Similar to diabetic retinopathy, the prevalence of overt diabetic nephropathy has been found to be significantly greater in patients diagnosed during puberty compared with those diagnosed before puberty (38). The authors noted that the risk of nephropathy correlated with the duration of post-pubertal diabetes, with diabetes during the pre-pubertal years having minimal contribution to this risk (38). Serum AGE levels resulting from hyperglycaemia and dyslipidaemia also seem to play a role in the progression of diabetic nephropathy and have been found localised in nodular lesions on nephropathic kidneys, impairing the assembly of proteins *in vivo* (91). The accumulation of AGEs at these lesions is in itself determined by many factors including renal function, glycaemic control, the patient's age and renal tissue damage in patients with diabetic nephropathy (92). Genetic factors may also play a role in the development of diabetic nephropathy (93).

DIABETIC PERIPHERAL NEUROPATHY

Diabetic peripheral neuropathy is very common and often the most difficult complication to diagnose and manage because it is frequently asymptomatic and mostly untreatable except by palliative measures (94,95). It has long been known that this is caused by alterations in nerve blood flow, although more recently aspects of neuronal signalling and Schwann cell functions are believed to play a role and are currently being investigated (96). People with diabetes are up to 15 times more likely to have a lower limb amputation than non-diabetic individuals, and foot problems are the most common reason for diabetes-related hospitalisation (97). Consistent with the mortality from diabetic retinopathy and nephropathy, deaths in patients with diabetic neuropathy are frequently due to cardiovascular disease (98).

In the pathogenesis of diabetic polyneuropathy metabolic mechanisms appear to cause neuronal degeneration with progressive impairment of regeneration, particularly of thinly myelinated fibres, whereas, differently from retinopathy and glomerulopathy, the contribution of microvascular changes is disputed and may be marginal. Much information on the pathology and mechanisms of nerve degeneration has been obtained from animals with experimental diabetes. The consequences of hyperglycaemia leading to nerve damage, however, are similar to those invoked for vascular complications and include activation of the polyol pathway, synthesis of AGE products and excess activation of protein kinase C (PKC)-driven pathways under the possible

Table 5 Prevalence of diabetic nephropathy over 15 years (71)

Time (years)	*Number alive and examined*	*Microalbuminuria or worse nephropathy*	*Macroalbuminuria or worse nephropathy*	*Elevated plasma creatinine or renal replacement therapy*
0	5097	7.3 (6.6–8.0) (370)	0.7 (0.5–1.0) (37)	0 (0.0–0.0) (0)
5	4791	17.3 (16.3–18.4) (830)	3.1 (2.6–3.6) (149)	0.4 (0.2–0.6) (19)
10	2799	24.9 (23.3–26.5) (696)	5.3 (4.5–6.1) (148)	0.8 (0.5–1.1) (22)
15	435	28.0 23.8–32.3) (122)	7.1 (4.7–9.5) (31)	2.3 (0.9–3.7) (10)

Values are expressed as observed % (95% CI) (*n*).

common denominator of reactive oxygen species generation (99,100). The possibility that microangiopathy of the vasa nervorum contributes to diabetic polyneuropathy has been elegantly suggested by the demonstration of abnormal microvessels feeding large nerves (101).

Diabetic neuropathy has diverse manifestations affecting both the somatic and autonomic nervous systems (102). Different forms of neuropathy can co-exist and diabetic peripheral neuropathy does not always co-exist with autonomic neuropathy (103). Distal symmetric sensorimotor polyneuropathy, or diabetic peripheral neuropathy, is one of the most common forms and the leading cause of lower limb amputation (104). Most people with distal symmetric sensorimotor polyneuropathy are asymptomatic or mildly symptomatic, and the syndrome is detected by careful physical examination (104). In addition to the symmetric polyneuropathies, people with diabetes are also susceptible to a variety of asymmetric or focal peripheral neuropathies (104).

Most clinical signs and symptoms of autonomic neuropathy are also subclinical, so that autonomic function tests must be used to identify patients at risk of the morbidity associated with neuropathy (105). Several scoring systems have been developed to assess severity of neuropathic pain and identify diabetic patients at risk of developing diabetic peripheral neuropathy, including the Neurological Symptom Score; based on patient-reported symptoms including subcategories of sensory, motor and autonomic symptoms, Neuropathy Disability Score; determined by the presence or absence of ankle reflexes, temperature, vibration and pain sensation, and vibration perception thresholds; a test using electromechanical instrumentation on the patients foot to provide a quantitative measure of vibration perception and therefore, an estimation of foot ulcer risk (106–110). Age, disease duration, skin changes in feet and myocardial infarction/ischaemia are all associated factors and can help identify patients at risk (111).

Prevalence of Diabetic Peripheral Neuropathy

The prevalence of diabetic peripheral neuropathy varies considerably, due to the variation in criteria for diagnosis, patient selection and employment of different diagnostic tests (102,112). In the EURODIAB IDDM Complications Study (112), 28% of patients with type 1 diabetes had diabetic neuropathy. Fedele et al. (113) reported a similar prevalence rate of diabetic neuropathy (32.3%) in patients with type 1 or type 2 diabetes. High prevalence rates of diabetic neuropathy were reported in the Pittsburgh Epidemiology of Diabetes Complications Study (114) and the DCCT (115), which used similar criteria to Fedele et al. (113) In the Seattle Prospective Diabetic Foot Study (116), 50% of the study participants for whom neuropathy testing was available were found to have peripheral sensory neuropathy at baseline.

Risk Factors for the Development and Progression of Diabetic Peripheral Neuropathy

Compared to the wealth of information on the risk factors affecting diabetic retinopathy and nephropathy, data regarding diabetic peripheral neuropathy are far less exhaustive, possibly due to greater difficulties in diagnosing and classifying the disease. Available evidence implicates metabolic control, age, duration of diabetes, the presence of diabetic retinopathy and nephropathy, cigarette smoking and height. Important information derives from the Rochester cohort longitudinal assessment (117), in which Dyck et al. reported that glycated haemoglobin, duration of diabetes and type of diabetes were all independent risk factors for severity of polyneuropathy, severity of retinopathy and proteinuria being important covariates. In the EURODIAB IDDM Complications Study (112) significant correlations were observed between the presence of diabetic peripheral neuropathy and increasing age, duration of diabetes, HbA_{1c}, height, the presence of background or proliferative diabetic retinopathy, smoking, high-density lipoprotein cholesterol and the presence of cardiovascular disease. In addition, new associations were identified, including elevated diastolic blood pressure, the presence of severe ketoacidosis, an increase in the levels of fasting triglyceride, and the presence of microalbuminuria. The Seattle Prospective Diabetic Foot Study (116) also identified numerous clinical and historical variables associated with an increased risk of diabetic peripheral sensory neuropathy, including age at entry into the study, glycohaemoglobin levels, history of lower-extremity ulceration, and body height, as patients who developed neuropathy during the 10-year follow-up period were more likely to be taller compared to those who remained free of neuropathy. Excessive alcohol consumption had also been suggested as a risk factor for neuropathy (118).

The DCCT (95) demonstrated that intensive therapy with three or more daily insulin injections or continuous subcutaneous insulin infusion reduced the development of confirmed clinical neuropathy by 64% in the combined cohorts after 5 years of follow-up compared with conventional therapy. The prevalence of abnormal nerve conduction and abnormal autonomic nervous system function were also reduced by 44% and 53% respectively. Further data from the DCCT (119) confirm that the electrophysiological abnormalities associated with diabetic neuropathy are delayed or prevented by intensive diabetes treatment. The benefits of intensive therapy administered over a period of 6.5 years on the status of neuropathy were apparent at 4 years' (50) follow-up and extended for at least 8 years beyond the end of the DCCT (120).

As with diabetic retinopathy and nephropathy, duration of diabetes is a documented risk factor for the development of diabetic neuropathy. Toyry et al. (121) reported that the

Table 6 Prevalence of sympathetic and parasympathetic neuropathy over 10 years (117)

	Parasympathetic neuropathy	*Sympathetic neuropathy*	*Combined autonomic neuropathy (both)*
After 5 years	19.6	6.8	2.1
After 10 years	65.0	24.4	15.2

Values are given in %.

frequency of different subtypes of neuropathy increases over time in patients with type 2 diabetes when evaluated at 5 and 10 years (Table 6). Partanen et al. (122) also reported an increased prevalence of polyneuropathy among patients with type 2 diabetes with time. Baseline prevalence of definite or probable diabetic neuropathy was 8.3% compared with 2.1% among control subjects. After 10 years, these values increased to 41.9% and 5.8% respectively.

Significant correlation between the presence of diabetic peripheral neuropathy and cigarette smoking has also been reported in the EURODIAB IDDM Prospective Complications Study (112). Evidence that cigarette smoking is also associated with the development of various types of diabetic neuropathy in patients with type 1 or type 2 diabetes has also been documented (94,123).

DISCUSSION

Diabetic microvascular complications develop in most people with type 1 or type 2 diabetes and are associated with clinically significant morbidity and mortality. Individuals may be susceptible to microvascular complications due to factors such as age, age of disease onset, abnormal metabolic environment and disease duration. However, it has also been suggested that subsets of patients with type 1 diabetes may have a genetically determined susceptibility, as not all people with type 1 diabetes and very high blood glucose levels develop complications. Conversely, some develop complications even if blood glucose levels are only slightly elevated (47). Type 2 diabetes is increasing across all ethnic groups, particularly among black and minority groups (1). Because type 2 diabetes is often not diagnosed until the patient has had the disease for many years (1), long-term complications may be present at the time diabetes is discovered.

The economic burden resulting from diabetes is of major importance. Type 2 diabetes and its related complications, incur significant costs, both direct and indirect, due to its increasing prevalence across all age groups. Although estimates of the precise cost of diabetes vary from study to study, Clarke et al. (124) determined the substantial impact of many diabetes-related complications on hospital costs in the year that they occur, and long-term, using data on 5102 UKPDS patients. Non in-patient costs for microvascular complications (e.g. home, clinic and telephone contacts with general practitioners, nurses etc.) were estimated at £273 in the year of event, and £204 in each subsequent year. Diabetes can also have a major impact not only on the physical and material well-being of an individual, but also on the psychological aspect of their life. Studies have shown that diabetes-related complications can induce morbidity and consequently, affect quality of life (125,126).

Although there are several known risk factors, chronic hyperglycaemia is a major initiator of diabetic retinopathy, nephropathy and peripheral neuropathy. The DCCT has shown that the more time individuals are exposed to chronically elevated plasma glucose levels, the greater their risk of developing diabetic microvascular complications. In addition, the deleterious effects of hyperglycaemia on the microcirculation have been shown to persist for a considerable time after glucose levels have decreased (50). The concept that 'metabolic memories' are stored early in the course of diabetes could explain why both the beneficial effects of intensive therapy and the deleterious effects of conventional therapy persist (127, 128). It is thought that long before the advent of hyperglycaemia, events occur that scar cells and thus lay the groundwork for the development of both the microvascular and macrovascular complications of diabetes (128). Both the DCCT and UKPDS have shown that intensive glycaemic management slows the progression of diabetic microvascular complications in type 1 and type 2 diabetes, and thereby improves quality of life. Although intensive therapy may adversely affect the development of diabetic retinopathy, the DCCT concluded that the long-term benefits of intensive insulin therapy greatly outweigh the early risks of diabetic retinopathy (55).

Tight control of blood pressure in both hypertensive and normotensive patients with type 2 diabetes has also been shown to reduce the risk of the development and progression of diabetic microvascular complications (10,129). Data from a recent cost-analysis study (130) show that the policies to improve control of blood glucose and blood pressure of people with type 2 diabetes are not only effective in reducing complications associated with the disease, but are also cost-effective.

A wide range of other risk factors have also been investigated including age at onset, smoking, height, age, genetic factors, unfavourable lipid profiles and AGE levels. The duration of diabetes is also a factor that is clearly involved in the prevalence of microvascular complications. However, it is not known if the prevalence of the microvascular complications increases because of cumulative microvascular damage related to the duration, or whether it is a reflection of the escalating involvement of other risk factors such as poor glycaemic control and hypertension.

Along with the presence of external risk factors, some associations have been noted between complications themselves. The DCCT (131) reported that even very early in

the development of the microvascular complications there is a relationship between diabetic retinopathy and diabetic nephropathy. Within the study group that had evidence of minimal diabetic retinopathy at baseline, 10% had elevated urinary albumin excretion rate levels. There was also a strong relationship between elevated urinary albumin excretion rate levels and more advanced degrees of diabetic retinopathy. Rossing et al. (88) also reported the presence of diabetic retinopathy in patients with type 1 diabetes to be predictive of onset of microalbuminuria, although no difference was found between background or proliferative diabetic retinopathy. The EURODIAB study (132) showed that the correlation between increasing blood pressure and albumin excretion rate was only confirmed in patients who also had diabetic retinopathy, independently of glycaemic control or diabetes duration, suggesting that diabetic retinopathy, in association with increased blood pressure, is an important independent risk factor for diabetic nephropathy progression. On the other hand, the fact that diabetic retinopathy and nephropathy can occur in isolation suggests there are important differences in some aspects of the pathogenesis of these two diabetic microvascular complications.

Ongoing research has led to a better understanding about diabetes and its related complications. Although currently available data on the evolution of long-term complications are limited, the EDIC study (49) should provide important evidence of micro- and macrovascular end points and definitive data on type 1 diabetes as distinct from type 2 diabetes. Clinical trials are also currently in progress looking at a number of approaches to designing treatments to prevent the adverse effects of hyperglycaemia including aldose reductase inhibitors, AGE inhibitors and inhibitors of PKC.

CONCLUSION

Despite good long-term glycaemic and blood pressure control, diabetes remains a major cause of blindness, renal failure and amputations, all of which result in significant health care expenditure. As the incidence of diabetes continues to rise, the burden of diabetic microvascular complications will increase in future. To further reduce the associated morbidity and mortality it is essential that factors associated with the onset and progression of diabetes-related complications are identified as early as possible. In addition, risk factors, such as smoking and hypercholesterolaemia, need to be addressed and new interventions developed to tackle unmodifiable risk factors, such as disease duration and genetics. In this respect, considering all three diabetic microvascular complications as sharing similar pathogenetic mechanisms in different cells and tissues (e.g. microvessels, mesangial cells and peripheral neurones) and the need to enquire proactively about complications that may not be present or apparent yet, but could develop or become more apparent in future, may well facilitate early detection of microvascular disease. Work is currently being undertaken to identify a unifying method of assessing the overall level of microvascular activity. This would be a significant step towards the early identification of those patients at risk of diabetic microvascular complications.

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CONFLICTS OF INTEREST

AG and DM are employees of Eli Lilly and Co. MP has served as a consultant on Advisory Boards for Eli Lilly and Co.

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