Limited Joint Mobility, Dupuytren's Contracture and Retinopathy in Type 1 Diabetes: Association with Cigarette Smoking

D. W. Eadington, A. W. Patrick, A. Collier, B. M. Frier

Diabetic Department, Royal Infirmary, Edinburgh, UK

To examine the associations between cigarette smoking, connective tissue changes, and diabetic retinopathy, a detailed smoking history was elicited from 150 normotensive non-diabetic subjects, and from 266 randomly selected adult patients with Type 1 diabetes, after examination for limited joint mobility, Dupuytren's contracture, and diabetic retinopathy. Mean insulin dose and current glycosylated haemoglobin concentrations were comparable in diabetic smokers and non-smokers. The historical duration of smoking correlated with the duration of diabetes ($r=0.72$, $p<0.001$). In diabetic patients limited joint mobility was positively associated with retinopathy, being found in 73/147 (50 %) patients with retinopathy compared with 20/114 (18 %) without retinopathy ($\chi^2=28.9$, $p<0.001$), and also with Dupuytren's contracture, 19/34 (56 %) of patients with limited joint mobility having Dupuytren's contracture, compared with 76/232 (33 %) of patients without Dupuytren's contracture ($\chi^2=7.05$, $p<0.01$). Limited joint mobility was observed in 50 % of diabetic smokers compared with 25 % of non-smokers (odds ratio = 2.87 (corrected for diabetes duration), 95 % confidence interval 1.64–5.01). Diabetic retinopathy was weakly associated with smoking (odds ratio 1.09; 95 % confidence interval 0.60–1.96). There was however an increased prevalence of background retinopathy among male smokers (50 % vs 29 %; $\chi^2=6.88$, $p<0.01$). In non-diabetic males limited joint mobility was observed in 37 % of smokers but only in 11 % of non-smokers (NS), while 33 % of smokers and 8 % of non-smokers had Dupuytren's contracture ($p=0.012$). These results suggest that cigarette smoking contributes to the development of extra-articular connective tissue changes in both diabetic patients and non-diabetic subjects, and possibly to the development of diabetic retinopathy.

KEY WORDS **Type 1 diabetes Smoking Limited joint mobility Dupuytren's contracture Diabetic retinopathy**

Introduction

The deleterious effects of smoking on the development and progression of macrovascular disease are recognized both in diabetic and in non-diabetic populations[1] but the contribution of smoking to the development of diabetic microvascular disease has seldom been examined directly, and the few available studies have provided conflicting results.[2–7] Limited joint mobility (diabetic cheiroarthropathy), and Dupuytren's contracture are common in diabetic patients[8–10] and limited joint mobility is associated with the presence of other microvascular complications.[11] In non-diabetic subjects limited joint mobility and Dupuytren's contracture have been observed more frequently in hypertensive individuals, suggesting an underlying vascular aetiology.[12] We have examined the relationship between cigarette smoking and the occurrence of limited joint mobility, Dupuytren's contracture and diabetic retinopathy in a random sample of patients with Type 1 diabetes, and in a group of normotensive, non-diabetic subjects, to assess whether smoking is a potential risk factor for the development of complications caused by microvascular disease.

Patients and Methods

Patients

A total of 266 adult patients (166 male, 100 female) with a mean age of 45 (range 18–81) years, and who have Type 1 diabetes, were selected at random from the diabetic clinic at Edinburgh Royal Infirmary over a 3-month period. All were considered to have Type 1 diabetes as judged by their presenting history and/or predisposition to ketosis. Patients with diabetes diagnosed for less than 5 years were excluded. Duration of diabetes was 18 (range 5–62) years. A group of 150 normotensive, non-diabetic subjects who were not receiving anti-hypertensive medication were selected from hospital inpatients, outpatients, and staff. The diabetic and non-diabetic groups were well matched for sex ratio and smoking

Correspondence to: Dr D. W. Eadington, Medical Renal Unit, Royal Infirmary, Edinburgh, EH3 9YW, UK.

152 0742–3071/89/020152–06 $05.00

Accepted 2 November 1988
DIABETIC MEDICINE, 1989; **6:** 152–157

Table 1. Characteristics of diabetic patients and non-diabetic subjects

	Diabetic		Non-diabetic	
	Male	Female	Male	Female
n (%)	162 (63)	94 (37)	88 (59)	62 (41)
Age (years)	42 ± 16	46 ± 17	52 ± 17[a]	50 ± 18
Duration of diabetes (years)	18 ± 8	18 ± 8	–	–
Smokers (%)	93 (57)	36 (38)	60 (68)	24 (39)
Body mass index (kg m^{-2})	24.6 ± 3.1	25.1 ± 4.1	–	–
Insulin dose (U kg^{-1} 24-h^{-1})	0.8 ± 0.3	0.8 ± 0.2	–	–
HbA_1 (%)	10.8 ± 1.9	11.2 ± 2.2	–	–

Mean ± SD.
[a] $p < 0.01$ compared with male diabetic patients.

habit, but the non-diabetic males were moderately older (Table 1). Among the diabetic patients who claimed to be 'non-smokers' at the time of examination two had a carboxyhaemoglobin (COHb) value greater than 2.5 %, indicating definite concealment of cigarette smoking,[13] and these individuals were excluded from further analysis. Of the 129 diabetic patients (93 M (57 %), 36 F (38 %)) defined as smokers, 76 (59 %) had started smoking before the clinical onset of diabetes and 53 (41 %) had smoked only after the diagnosis of diabetes. Among the non-diabetic group, 60 (68 %) men and 24 (39 %) women were smokers.

Body mass index, daily insulin dose, and glycosylated haemoglobin were similar in the subgroups of diabetic 'smokers' and 'non-smokers' (Table 1), and there were no demographic differences between the groups of diabetic patients when subdivided into those with and without retinopathy, limited joint mobility or Dupuytren's contracture. The duration of diabetes was longer in each of the diabetic groups affected by limited joint mobility, Dupuytren's contracture or retinopathy, but the duration of Type 1 diabetes in the smoking and non-smoking subsets of each of these groups was comparable. Among the diabetic smokers the total duration of exposure to cigarettes was comparable between the groups affected and unaffected by limited joint mobility, Dupuytren's contracture or retinopathy (data not shown). Fifty-two (20 %) diabetic patients had hypertension (30 M, 22 F).

Methods

Fundal examination was performed by direct ophthalmoscopy through dilated pupils and if diabetic retinopathy was present the severity was classified using the more affected eye. Limited joint mobility was diagnosed and graded using the 'prayer' manoeuvre as previously described.[8] Mild cheiroarthropathy was defined as bilateral involvement of one or two interphalangeal joints, one large joint or only the metacarpophalangeal joint; moderate cheiroarthropathy involved three or more interphalangeal joints, or one finger and one large joint bilaterally; and severe limited joint mobility comprised moderate limitation combined with cervical spine involvement. Dupuytren's contracture was defined as visible and/or palpable thickening of the palmar fascia overlying the flexor tendons. In patients with Dupuytren's contracture the assessment of joint mobility by the 'prayer' manoeuvre is liable to overestimate both the prevalence and the severity of limited joint mobility due to the loss of palmar apposition caused by the Dupuytren's deformity; to minimize this source of bias the finger affected by the Dupuytren's contracture was interlocked with the corresponding finger of the other hand when assessing the presence or severity of limited joint mobility.

The clinical examination was performed routinely by only one examiner, but when the first observer was in doubt over the interpretation of the hand abnormalities a second independent assessment was made. Whenever the choice between two grades of limited joint mobility was not clear-cut the less severe grade was recorded. The reliability and reproducibility of clinical examination was tested carefully in the two observers (DWE and AWP) before commencing the study. The diabetic patient samples examined by each observer during the study period were well matched for age and sex, duration of diabetes and smoking habit, and the closely matched detection rates for limited joint mobility (DWE 58/175 patients (33 %), AWP 38/93 (41 %)), background retinopathy (DWE 66/175 (38%), AWP 40/93 (43%)) and proliferative retinopathy (DWE 30/175 (17 %), AWP 17/93 (18 %)) suggest that the results obtained by both observers were comparable and reliable.

A detailed history of past and present smoking habits was not elicited until after the physical examination. A diabetic patient was designated a 'smoker' if cigarettes had been smoked for more than 1 year after the onset of diabetes and for more than 5 years in total. A 'non-smoker' had never smoked cigarettes. Non-diabetic 'smokers' had smoked cigarettes for more than 5 years during their adult life; pipe or cigar smokers were

Table 2. Prevalence of limited joint mobility, Dupuytren's contracture, and diabetic retinopathy found in Type 1 diabetic patients

		Male ($n=162$)		Female ($n=94$)	
		Smoker	Non-smoker	Smoker	Non-smoker
Limited joint mobility	Present	47 (51)	14 (20)	17 (47)	18 (31)
	Absent	46 (49)	55 (80)	19 (53)	40 (69)
Dupuytren's contracture	Present	15 (16)	6 (7)	3 (8)	5 (9)
	Absent	78 (84)	63 (93)	33 (92)	53 (91)
Diabetic retinopathy	Absent	32 (34)	34 (49)	19 (53)	26 (45)
	Background	46 (50)	20 (29)	10 (28)	24 (41)
	Proliferative	15 (16)	15 (22)	7 (19)	8 (14)

Number (%).

excluded. Ten diabetic patients had smoked only before the development of diabetes and were excluded from further analysis. No attempt was made to quantify total cigarette consumption because of the wide variations in daily consumption during the lifetime of an individual patient.

Venous blood was withdrawn with patients' informed consent for estimation of glycosylated haemoglobin (HbA_1) by an electrophoretic method [14] (normal range 6.0–8.0 %) and of carboxyhaemoglobin (COHb) content by spectrophotometry.

Statistical Analysis

Statistical analyses used Student's (unpaired) *t*-tests, the Chi-squared test (with Yates' correction where appropriate), and Fisher's exact probability test (two-tailed) for comparison between groups. Logistic regression analysis was used (see Appendix) to examine the effect of independent variables (age, duration of diabetes, etc.) on the dependent variables studied. Odds ratios quoted in the text are thus corrected for confounding factors and represent the true effects of smoking on the complications in question. Statistical significance was taken at the 5 % level ($p<0.05$).

Results

Diabetic Patients

The prevalence of the various complications studied is shown in Table 2. Limited joint mobility was present in 96 (37 %) patients; multivariate analysis showed no association with age or sex, but the prevalence, although not the severity, of limited joint mobility increased with the duration of diabetes. Limited joint mobility was found in (a) 73/147 (50 %) of the patients with diabetic retinopathy compared with 20/114 (18 %) of the patients without retinopathy ($\chi^2=28.9$, $p<0.001$) and (b) 19/34 (56 %) of the patients with Dupuytren's contracture compared with 76/232 (33 %) of patients without Dupuytren's contracture ($\chi^2=7.05$, $p<0.01$). Further details of the associations between the complications studied are shown in Table 3. Limited joint mobility was found in 64 (47 M, 17 F) (50 %) smokers and in 32 (14 M, 18 F) (25 %) non-smokers (odds ratio 2.87; 95 % confidence interval 1.64–5.01). The actual duration of smoking exposure was not a significant independent variable.

The presence of retinopathy was associated with duration of diabetes and (weakly) with smoking habit. Diabetic retinopathy was found in 78 (60 %) smokers (56 background, 22 proliferative) and in 67 (53 %) non-smokers (44 background, 23 proliferative), an overall odds ratio of 1.09 (95 % CI 0.60–1.96). However this result conceals an increased prevalence of background retinopathy among male smokers (50 % vs 29 %; $\chi^2=6.88$, $p<0.01$) which was independent of the mean duration of diabetes (smokers 20 ± 8 ($\pm$SD) years, non-smokers 21 ± 8 years).

Dupuytren's contracture was present in 21 (13 %) male and 8 (9 %) female diabetic patients. Logistic regression analysis showed association with both age and duration of diabetes (Appendix) but Dupuytren's contracture was not associated with smoking habit.

Non-diabetic Subjects

In the male subjects limited joint mobility was found in 22/60 (37 %) smokers and 3/28 (11 %) non-smokers (difference between proportions 26 %, 95 % CI of difference 20–54 %; $p=0.018$ (Fisher's exact test)). Dupuytren's contracture was found in 20/60 (33 %) smokers and 2/28 (7 %) non-smokers ($p=0.012$). In the non-diabetic female subjects limited joint mobility was found in 4/24 (17 %) smokers and 6/38 (16 %) non-smokers (NS) and Dupuytren's contracture was seen in 2/24 (9 %) and 3/38 (8 %) smokers and non-smokers, respectively (NS).

Table 3. Associations between diabetic retinopathy, limited joint mobility, and Dupuytren's contracture in Type 1 diabetic patients

Complications		Male						Female					
		Limited joint mobility		p	Dupuytren's contracture		p	Limited joint mobility		p	Dupuytren's contracture		p
		Present	Absent		Present	Absent		Present	Absent		Present	Absent	
Dupuytren's contracture	Present	12	12					7	3				
	Absent	48	96	NS				28	60	0.045			
Background retinopathy	Present	27	38		11	52		19	16		4	31	
	Absent	15	55	<0.01	6	63	NS	5	39	<0.0001	0	37	0.05
Proliferative retinopathy	Present	18	12		6	24		9	8		5	12	
	Absent	15	55	<0.001	6	63	NS	5	39	<0.001	0	37	0.002

Discussion

In the present study the increased prevalence of limited joint mobility in patients with Type 1 diabetes and the association of limited joint mobility with diabetic retinopathy confirm previous reports.[8–11] In addition the results show that limited joint mobility is significantly more common in patients with Type 1 diabetes who smoke cigarettes, and that limited joint mobility and Dupuytren's contracture are also more common in non-diabetic male smokers than in non-smokers, although the diabetic and non-diabetic groups must be compared with caution because of the deliberate exclusion of hypertensive subjects from the latter group. Smoking appears to be a weak factor promoting the occurrence of diabetic retinopathy, although its influence may be increased in certain subgroups of patients (such as males with background retinopathy). The use of logistic regression analysis to examine separately the influence of various independent variables indicates that the effect of smoking is direct and not simply the indirect linkage of two time-dependent variables.

The effects of smoking were independent of the prevailing degree of blood glucose control, but a single measurement of glycosylated haemoglobin cannot assess the long-term quality of blood glucose control over several years. Moreover the observed association of smoking with limited joint mobility and Dupuytren's contracture in non-diabetic individuals suggests that hyperglycaemia is only one of several factors involved in the development of these connective tissue changes in diabetic patients.

In females cigarette smoking appeared to be a less important factor for the occurrence of background diabetic retinopathy and limited joint mobility in both diabetic and non-diabetic individuals. This differential effect, which has been noted previously,[3] may either be related to the smaller number of female subjects (and the lower incidence of smokers among them) or may reflect a true difference in the effects which smoking exerts on men and women. If this apparent difference is a real phenomenon it suggests that smoking affects the microvasculature by a mechanism which is distinct from changes produced by hyperglycaemia, particularly in view of the excess of limited joint mobility and Dupuytren's contracture observed in the male non-diabetic subjects.

Previous studies have surmised that smoking acts as a catalyst to promote the progression rather than the initiation of microvascular complications.[2,4,5] In the present study a smoking habit appeared to have a greater effect on the occurrence of background rather than proliferative retinopathy, suggesting that cigarette smoking may have a pathogenic role from the onset of diabetes by imposing some adverse effect on the retinal microcirculation. The failure to establish an association in the diabetic patients between Dupuytren's contracture and smoking habit is not surprising in view of the smaller number of affected individuals and the superimposed confounding effects of age and hypertension as noted previously.[12]

The mechanisms by which hyperglycaemia causes tissue damage in diabetic patients are uncertain. Non-enzymatic glycosylation of collagen may contribute to the development of limited joint mobility by the formation of a ketoamine linkage[15] and by subsequent development of irreversible cross-linkages or 'browning' of collagen.[16] In previous studies the concentration of Amadori products in biopsies from diabetic skin has been related to blood glucose control[17] but not to the severity of tissue complications,[18] whereas the degree of browning of collagen was associated with objective measurements of microvascular disease.[19] No specific reproducible assay exists at present for browning products derived solely from glucose, and similar fluorescent compounds can be produced by the interaction between oxidized lipids and proteins.[20] The increased prevalence of Dupuytren's contracture in hypertensive non-diabetic patients[12] and the association in the present study between cigarette smoking and limited joint mobility in both diabetic patients and non-diabetic subjects suggest that microcirculatory changes may be of pathogenic importance. The distal parts of limbs and subcutaneous tissues may be particularly susceptible to the postulated effect of cigarette smoking in view of the pronounced reduction in skin blood flow which is induced by exposure to nicotine.[21] Tissue hypoxia in diabetes may promote lipid membrane peroxidation and collagen cross-linking, which are independent of a direct effect of hyperglycaemia, thus providing a hypothetical mechanism for the development of limited joint mobility and microvascular complications. The increased microvascular permeability induced by free radical species[22] and the suggested role of free radical oxidizing agents in the pathogenesis of non-diabetic Dupuytren's contracture[23] provide further possible mechanisms which may underlie these extra-articular changes.

The present study provides further evidence for the potential importance of 'vascular' as opposed to 'metabolic' factors in the pathogenesis of diabetic complications, and illustrates the importance of the inclusion of cigarette smoking as a potential variable in future studies of diabetic microvascular disease. Further studies are required to examine the effect of smoking habit on other microvascular complications in diabetes, but the desirability that diabetic patients should avoid cigarette smoking is once again clearly demonstrated.

Acknowledgements

We thank J. Slattery for statistical advice, N. Waugh for his helpful comments and C. Mackay for typing the manuscript.

References

1. Fielding JE. Smoking; health effects and control. *N Engl J Med* 1985; **313:** 491–498.
2. Paetkau ME, Boyd TAS, Winship B, Grace M. Cigarette smoking and diabetic retinopathy. *Diabetes* 1977; **26:** 46–49.
3. Muff Nielsen M, Hjollund E. Smoking and diabetic microangiopathy. *Lancet* 1978; **ii:** 533–534.
4. Mühlhauser I, Sawicki P, Berger M. Cigarette smoking as a risk factor for macroproteinuria and proliferative retinopathy in type 1 (insulin-dependent) diabetes. *Diabetologia* 1986; **29:** 500–502.
5. Stegmayr B, Lithner F. Tobacco and end stage diabetic nephropathy. *Br Med J* 1987; **295:** 581–582.
6. West KM, Endreich LS, Slotser JS. Absence of a relationship between smoking and microangiopathy. *Diabetes Care* 1980; **3:** 250–252.
7. Rand LI, Krolewski AS, Aiello LM, Warram JH, Baker RS. Multiple factors in the prediction of risk of proliferative diabetic retinopathy. *N Engl J Med* 1985; **313:** 1433–1438.
8. Rosenbloom AL, Silverstein JH, Lezotte DC, Richardson K, McCallum M. Limited joint mobility in childhood diabetes mellitus indicates increased risk of microvascular disease. *N Engl J Med* 1981; **305:** 191–194.
9. Buckingham BA, Vitto J, Sandburg C, *et al.* Scleroderma-like changes in insulin-dependent diabetes mellitus; clinical and biochemical studies. *Diabetes Care* 1981; **2:** 1027–1028.
10. Noble J, Heathcote JG, Cohen H. Diabetes mellitus in the aetiology of Dupuytren's disease. *J Bone Jt Surg* 1984; **66**(B): 322–325.
11. Lawson PM, Maneschi F, Kohner EM. The relationship of hand abnormalities to diabetes and diabetic retinopathy. *Diabetes Care* 1983; **6:** 140–143.
12. Larkin JG, Frier BM. Limited joint mobility and Dupuytren's contracture in diabetic, hypertensive and normal populations. *Br Med J* 1986; **292:** 1494.
13. Richmond R, Webster I. Blood cotinine, carboxyhaemoglobin and thiocyanate concentrations and cigarette consumption. *Br Med J* 1986; **293:** 1280.
14. Read A, Tibi L, Smith AF. Assessment of a simple electrophoretic method for measuring HbA_1. *Clin Chim Acta* 1980; **108:** 487–491.
15. Hodge JE. The Amadori rearrangement. *Adv Carbohydr Chem* 1955; **10:** 169–205.
16. Maillard LC. Action des acide amines sur les sucres; formation des melanoidines par voie methodique. *CR Acad Sci (Paris)* 1912; **154:** 55–58.
17. Paisey R, Hopton M, Hartog M. Correlation between skin glycosylation and glycaemic control in human diabetes. *Clin Endocrinol* 1984; **20:** 521–525.
18. Lyons TJ, Kennedy L. Non-enzymatic glycosylation of skin collagen in patients with Type 1 (insulin-dependent) diabetes mellitus and limited joint mobility. *Diabetologia* 1985; **28:** 2–5.
19. Monnier VM, Vishuranath V, Frank KE, Elmets CA, Dauchot P, Kohn RR. Relation between complications of type 1 diabetes mellitus and collagen-linked fluorescence. *N Engl J Med* 1986; **314:** 403–408.
20. Porter WL, Black ED, Drolet AM, Kapsalis JG. Analytical use of fluorescence-producing reactions of lipid and carbohydrate-derived carbonyl groups with amine end groups of polyamide powder. In: Waller GR, Feather MS, eds. *The Maillard Reaction in Foods and Nutrition.* Washington DC: American Chemical Society Symposium Series 215, 1983: 47–70.
21. Reus WF, Robson MC, Zachary L, Heggers JP. Acute effects of tobacco smoking on blood flow in the cutaneous micro-circulation. *Br J Plast Surg* 1984; **37:** 213–215.
22. Del Maestro RF, Bjork J, Arfors KE. Increase in microvascular permeability induced by enzymatically generated free radicals. *Microvasc Res* 1981; **22:** 239–270.
23. Murrell GAC, Francis MJO, Bromley L. Free radicals and Dupuytren's contracture. *Br Med J* 1987; **295:** 1373–1375.

Appendix

Logistic regression analysis using limited joint mobility, diabetic retinopathy, and Dupuytren's contracture in turn as the dependent variable produced the following regression equations (standard errors shown below each parameter).

1. Limited joint mobility:

$$\underset{}{\text{Log}_e}\ \frac{p}{1-p} = \underset{}{-2.61} + \underset{0.39}{0.082}\,D + \underset{0.017}{1.053}\,S \qquad \underset{0.285}{}$$

2. Retinopathy:

$$\underset{}{\text{Log}_e}\ \frac{p}{1-p} = \underset{}{-2.97} + \underset{0.46}{0.192}\,D + \underset{0.027}{0.084}\,S \qquad \underset{0.030}{}$$

3. Dupuytren's contracture:

$$\underset{}{\text{Log}_e}\ \frac{p}{1-p} = \underset{}{-6.01} + \underset{0.89}{0.060}\,D + \underset{0.022}{0.057}\,A \qquad \underset{0.015}{}$$

Where p = probability of dependent variable being found,
D = duration of diabetes (years),
A = patient age (years),
S = smoking habit (smoker = 1, non-smoker = 0).