

Microalbuminuria is associated with limited joint mobility in type I diabetes mellitus

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Abstract

Objective—To determine whether limited joint mobility (LJM) is associated with microalbuminuria in type I diabetes mellitus.

Methods—Joint mobility was measured in a control group of 63 healthy subjects and in 63 type I diabetic patients, older than 18 years (mean 31.7 years, range 18–57), recruited from the outpatient clinic of the Endocrine Unit. Patients with established diabetic nephropathy (proteinuria or increased creatinine) were excluded. Joint mobility was assessed qualitatively with the prayer manoeuvre and quantitatively by measuring the angles of maximal flexion and extension of the fifth and third metacarpophalangeal (MCP) joints and wrist. Diabetic retinopathy was assessed by direct ophthalmoscopy. Urinary albumin excretion (UAE) was determined in at least two 24 hour urine samples.

Results—Joint mobility was limited in diabetic patients compared with control subjects. Diabetic patients with LJM had longer duration of diabetes (12.1 (SD 6.4) years compared with 6.9 (5.7) years; $p < 0.001$). Joint mobility was limited in patients with retinopathy: prayer manoeuvre was positive in 96.4% of patients with retinopathy, but in only 40.0% of patients with no retinopathy ($p < 0.001$); mobility of MCP joints and wrist was limited in diabetic patients with retinopathy even when the longer duration of their diabetes was taken into consideration. Microalbuminuria, present in 11 patients (17.5%), was associated with LJM: prayer manoeuvre was positive in 90.9% of patients with microalbuminuria, but in only 57.4% of patients with normal UAE ($p < 0.05$). Maximal flexion of MCP joints was reduced in patients with microalbuminuria. Microalbuminuria, but not LJM, was associated with risk factors of cardiovascular disease.

Conclusion—LJM is associated with microalbuminuria and retinopathy in type I diabetes. The association is independent of age and duration of diabetes.

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Hard abnormalities, such as stiff painful hands, Dupuytren's contracture, skin tightness, pseudoscleroderma, reflex sympathetic dystrophy, carpal tunnel syndrome, or limited

joint mobility, are frequently found in diabetic patients. The most common hand abnormality in diabetes is non-painful contracture of finger joints¹, referred to as limited joint mobility (LJM).² LJM was initially described in type I patients with long standing diabetes,³ but it is found in both type I and type II diabetes mellitus,^{4–9} and can be detected very early in the evolution of the disease.²

The association between LJM and microangiopathic complications of diabetes, particularly diabetic retinopathy, has been reported repeatedly.^{1, 2, 9–12} Although age and diabetes duration have been found to influence the development of LJM, their role in the association between LJM and retinopathy has been controversial.^{13, 14} In contrast, the association of LJM with diabetic nephropathy, a leading cause of death in type I diabetes mellitus¹⁵ has been reported infrequently. A relationship was found between already established diabetic nephropathy and LJM in a paediatric population,¹⁶ and recently a decreased mobility of MCP joints was reported in a group of elderly diabetic patients with renal functional impairment.¹⁷ The early stages of diabetic nephropathy can be identified by the presence of microalbuminuria,^{18, 19} but it cannot be predicted which individuals will develop microalbuminuria. In this study, we have investigated whether LJM is associated with microalbuminuria in type I diabetes. As detection of LJM may precede that of microangiopathy,^{2, 6} the possible help of LJM in identifying the subjects at risk for diabetic nephropathy is discussed.

Subjects and methods

SUBJECTS

Sixty three diabetic patients conforming to the National Diabetes Data Group criteria for type I diabetes mellitus²⁰ were included in the study. Table 1 summarises their clinical characteristics. Patients were recruited from the outpatient clinic which they visited every two to four months. Patients with overt diabetic nephropathy (proteinuria greater than 500 mg/day or increased serum creatinine), severe neuropathy, or vasculopathy were excluded. Subjects with a past history of joint disease were also excluded. We have previously reported a negative correlation between age and joint mobility in diabetic patients²¹: joint mobility was significantly greater in diabetic subjects younger than 18. To minimise the influence of age in the current study, therefore, subjects younger than 18 years were excluded.

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Table 1 Clinical characteristics of diabetic patients

Age (yr)	31.7 (10.5) [18-57]
Sex (men/women)	33/30
Age at diabetes diagnosis (yr)	21.7 (9.7) [5-52]
Duration of diabetes (yr)	10.2 (6.6)
BMI (kg/m ²)	23.2 (2.5)
Blood pressure (mm Hg)	
Systolic	119 (21)
Diastolic	74 (7)
Glucose (mmol/l)	11.4 (4.2)
HbA _{1c} (%)	11.1 (1.6)
Insulin dose (U/kg)	0.70 (0.20)
Cholesterol (mmol/l)	5.02 (1.5)
Triglycerides (mmol/l)	0.99 (0.7)
Retinopathy (+)	28 [44.4%]
Microalbuminuria (+)	11 [17.5%]

Values are mean (SD) [range for quantitative variables or percentage for qualitative variables]. BMI = Body mass index; HbA_{1c} = glycated haemoglobin.

Joint mobility was also studied in a control group of 63 healthy subjects with ages (30.5 (9.7) years) and sex distribution (32 men, 31 women) similar to those of the diabetic patients; these subjects were not genetically related to the diabetic patients.

STUDY DESIGN

To assess the degree of chronic metabolic control we calculated the mean values of fasting blood glucose, glycated haemoglobin (HbA_{1c}), and insulin requirement of the preceding two years (six to eight determinations). Body mass index, systolic and diastolic blood pressures, fasting blood glucose, HbA_{1c}, plasma cholesterol, triglycerides, and creatinine were also determined when joint mobility was measured. Stable HbA_{1c} was determined by ion exchange chromatography; reference values were 6.2-9.0%. Diabetic retinopathy was assessed by direct ophthalmoscopy through dilated pupils and was classified as absent, background retinopathy, or proliferative retinopathy. Retinopathy was defined as proliferative when retinal vessel neovascularisation was present. Urinary albumin excretion (UAE) was determined by radioimmunoassay in at least two 24 hour sterile urine samples. Microalbuminuria was defined as UAE greater than 20 µg/min in two consecutive samples, or in two of three consecutive samples.²²

Joint mobility was determined qualitatively with the prayer manoeuvre² and quantitatively by measuring the maximal flexion and extension of the fifth and third metacarpophalangeal (MCP) joints and wrist. The prayer manoeuvre was defined as positive when subjects were unable to oppose palmar surfaces at any interphalangeal or MCP joint. To measure the angles of active maximal flexion and extension of the fifth MCP joint, the fourth finger was fixed on a flat surface and the subject was asked to actively perform the flexion or extension of the fifth finger at the level of the MCP joint. The angles of maximal flexion and extension were measured with a goniometer and expressed in degrees using the zero method. To measure the mobility of the third MCP joint, the second finger was fixed. Arm and forearm were fixed in complete extension to measure the angles of active maximal flexion and extension of the wrist. In all patients both

hands were evaluated; the mean value between left and right measurements was used for statistical calculations. In all joints, the correlation coefficient between mean joint mobility and right or left joint mobility was greater than 0.88 ($p < 0.001$). All measurements were performed by the same observer (AR) who was unaware of the metabolic control or diabetic complications of the patients. The mean coefficient of variation of joint mobility measurements repeated on six different days in six normal subjects was less than 4% on all joints.

The presence of shoulder capsulitis, defined as pain in the shoulder for more than one month with limited active and passive shoulder joint movements in at least three planes, was assessed. Patients were asked about past history of painful shoulder. Dupuytren's contracture, defined as palpable or visible thickening of the palmar fascia overlying the flexor tendons, was also determined.

STATISTICAL ANALYSIS

Results are expressed as mean (SD). Statistical analysis was performed with the SPSS package. The chi square test and Student's unpaired *t* test (two tailed) were used for comparisons between groups. A covariate analysis was used to correct for the influence of variables found to be associated with joint mobility. $p < 0.05\%$ was considered significant.

Results

Table 2 summarises joint mobility in the diabetic and control groups. Diabetic patients showed decreased joint mobility: prayer manoeuvre was positive in 65.1% of diabetic patients compared with 17.5% of control subjects, and mobility of fifth and third MCP joints was significantly reduced in diabetic patients. Wrist mobility was similar in diabetic and control subjects. Maximal flexion and extension angles were significantly reduced in all joints examined in diabetic patients with a positive prayer manoeuvre (data not shown). Dupuytren's contracture was present in one subject in each group, and capsulitis was found in two diabetic patients. A past history of painful non-traumatic shoulder was reported by two diabetic patients.

Age did not correlate with joint mobility in diabetic or control subjects and patients with positive and negative prayer manoeuvre had

Table 2 Joint mobility in control and diabetic groups

	Diabetic patients	Control group
Prayer sign (+)	41 (65.1%)	11 (17.5%)*
5th Metacarpophalangeal (deg)		
Flexion	81.8 (7.2)	85.6 (4.4)*
Extension	8.73 (8.4)	16.2 (7.3)*
3rd Metacarpophalangeal (deg)		
Flexion	86.1 (4.2)	88.0 (3.9)*
Extension	5.56 (6.0)	14.3 (6.8)*
Wrist (deg)		
Flexion	75.0 (7.2)	73.8 (6.7)
Extension	63.8 (9.2)	65.2 (5.3)

Values are mean (percent or SD). * $p < 0.05$, *** $p < 0.001$, compared with diabetic patients.

similar ages (32.8 (11.0) *v* 29.6 (9.3) years). Diabetic patients with a positive prayer sign had a longer duration of diabetes than patients with negative prayer sign (12.1 (6.4) *v* 6.9 (5.7) years; $p < 0.01$). Chronic metabolic control, insulin requirement, systolic and diastolic blood pressures, cholesterol, and triglycerides did not correlate with joint mobility.

Diabetic retinopathy was present in 44.4% of patients; it was proliferative in four subjects. Patients with retinopathy were older and had a longer duration of diabetes than patients with no retinopathy (table 3). Joint mobility was impaired in patients with retinopathy: prayer manoeuvre was positive in 96.4% of diabetic patients with retinopathy, compared with 40.0% of patients with no retinopathy, and joint mobility in MCP and wrist joints was significantly decreased. Since patients with diabetic retinopathy were older and had a longer duration of diabetes, the relationship between retinopathy and joint mobility was analysed again using age and duration of diabetes as covariates. The new analysis showed that the limitation in joint mobility in diabetic patients with retinopathy was independent of their older age or longer duration of diabetes.

Eleven patients (17.5%) had microalbuminuria. The mean UAE in these patients was 67 $\mu\text{g}/\text{min}$ (range 24–285 $\mu\text{g}/\text{min}$). Table 4 summarises the clinical characteristics and joint mobility of diabetic patients with normal and increased UAE. Age and diabetes duration were similar in both groups. Patients with microalbuminuria had greater insulin requirements, despite a tendency towards worse metabolic control. Blood pressure was in the normal range and differences in blood pressure between patients with normal and increased UAE did not reach statistical significance. Total cholesterol was greater in patients with microalbuminuria. Microalbuminuria was associated with retinopathy: diabetic retinopathy was found in 72.7% of patients with increased UAE, but in only 38.5% of patients

Table 3 Diabetic retinopathy and joint mobility

	No retinopathy (n = 35)	Retinopathy (n = 28)
Age (yr)	27.8 (8.4)	35.9 (11.0)**
Sex (men/women)	18/17	15/13
Age at diabetes diagnosis (yr)	21.0 (9.6)	21.9 (9.4)
Duration of diabetes (yr)	7.3 (4.8)	14.2 (6.5)***
BMI (kg/m^2)	22.9 (2.5)	23.4 (2.5)
Blood pressure (mm Hg)		
Systolic	113 (24)	126 (6)*
Diastolic	70 (15)	75 (8)
Glucose (mmol/l)	11.3 (4.2)	11.7 (4.2)
HbA _{1c} (%)	11.3 (1.8)	11.4 (1.3)
Insulin dose (U/kg)	0.68 (0.20)	0.73 (0.20)
Cholesterol (mmol/l)	4.51 (1.3)	5.23 (1.8)
Triglycerides (mmol/l)	0.86 (0.54)	1.01 (0.71)
Microalbuminuria (+)	3 (8.6%)	8 (28.6%)*
Prayer sign (+)	14 (40.0%)	27 (96.4%)*
5th Metacarpophalangeal (deg)		
Flexion	82.8 (8.3)	80.7 (5.7)
Extension	11.0 (8.9)	6.19 (7.2)*
3rd Metacarpophalangeal (deg)		
Flexion	87.4 (4.4)	84.7 (3.5)*
Extension	7.29 (6.6)	3.58 (4.8)*
Wrist (deg)		
Flexion	77.2 (6.7)	72.4 (7.1)*
Extension	67.2 (8.7)	59.5 (8.0)*

Values are mean (percent or SD). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared with diabetic patients with no retinopathy.

Table 4 Urinary albumin excretion and joint mobility

	No microalbuminuria (n = 52)	Microalbuminuria (n = 11)
Age (yr)	31.6 (10.3)	32.0 (11.7)
Sex (men/women)	25/27	8/3
Age at diabetes (yr)	21.7 (9.7)	20.8 (10.4)
Duration of diabetes (yr)	9.7 (6.9)	12.6 (4.8)
BMI (kg/m^2)	23.0 (2.4)	24.0 (2.7)
Blood pressure (mm Hg)		
Systolic	117 (22)	129 (13)
Diastolic	72 (13)	76 (9)
Glucose (mmol/l)	11.0 (4.1)	13.4 (4.0)
HbA _{1c} (%)	11.1 (1.7)	12.1 (1.1)
Insulin dose (U/kg)	0.67 (0.2)	0.83 (0.2)*
Cholesterol (mmol/l)	4.62 (1.3)	5.85 (2.3)*
Triglycerides (mmol/l)	0.91 (0.6)	1.15 (0.9)
Retinopathy (+)	20 (38.5%)	8 (72.2%)*
Prayer sign (+)	31 (59.6%)	10 (90.9%)*
5th Metacarpophalangeal (deg)		
Flexion	82.7 (6.2)	77.6 (9.9)*
Extension	9.40 (8.8)	5.54 (6.1)
3rd Metacarpophalangeal (deg)		
Flexion	86.6 (3.6)	83.7 (5.8)*
Extension	5.84 (6.4)	4.22(4.1)
Wrist (deg)		
Flexion	75.7 (7.0)	71.9 (7.6)
Extension	65.3 (8.8)	56.7 (7.6)**

Values are mean (percent or SD). * $p < 0.05$, ** $p < 0.01$ compared with diabetic patients with normal UAE.

with normal UAE ($p < 0.05$). LJM was more prevalent in patients with microalbuminuria: a positive prayer manoeuvre was found in 90.9% of microalbuminuric patients, but in only 57.4% of diabetic patients with normal UAE ($p < 0.05$). The association between microalbuminuria and positive prayer sign was highly significant when the duration of diabetes was used as covariate ($p < 0.01$). However, only 21 patients (40.4%) with normal UAE had normal joint mobility, therefore LJM was sensitive in identifying patients with microalbuminuria, but had a low specificity. MCP joint and wrist mobility was significantly decreased in patients with microalbuminuria compared with diabetic patients with normal albumin excretion (table 4).

Discussion

The increased prevalence of LJM in diabetes has been clearly established in the past^{1–11} and our results confirm this association. LJM has usually been measured with the prayer manoeuvre and passive extension of the patient's fingers, which are useful in assessing the presence or absence of LJM, but allow a limited evaluation of the severity of impaired mobility. In contrast, we have determined joint mobility both qualitatively with the prayer manoeuvre and quantitatively by measuring the angles of maximal extension and flexion of MCP joints and wrist. Our results show that LJM is associated with microalbuminuria in type I diabetes. Patients with microalbuminuria had a greater prevalence of LJM and a more severe limitation of joint mobility than diabetic patients with normal UAE. Furthermore, LJM was associated with diabetic retinopathy, an association that was independent of age or diabetes duration.

A relationship between LJM and microvascular disease in the form of retinopathy has been described in type I and type II diabetes.^{1 2 9–12} The prevalence of diabetic retinopathy²³ and LJM^{1 2 4 9 11} increases with duration of diabetes. However, diabetes

duration has not usually been considered when the association between LJM and retinopathy has been reported. In our diabetic population we found, as expected, that joint mobility was more severely impaired in patients with retinopathy and that these patients were older and had a longer duration of diabetes than patients with no retinopathy. When we included age and duration of diabetes in the study of LJM in patients with retinopathy, we found that LJM and retinopathy are associated in type I diabetes, irrespective of age or diabetes duration.

The association between LJM and microalbuminuria had not been reported previously. Recently Aoki *et al.*,¹⁷ using a quantitative method to measure joint mobility, reported the association between mobility of MCP joints and diabetic nephropathy in diabetic and non-diabetic populations. They studied a group of elderly diabetic patients, most of them non-insulin dependent, with a wide range of functional renal impairment including end stage renal disease. In contrast, we analysed a more homogeneous group: all patients had type I diabetes mellitus and only subjects with normal UAE or microalbuminuria were included. Our study group was representative of an adult population of type I diabetic patients with medium term duration of diabetes and moderate diabetic complications and the prevalence of microalbuminuria in our diabetic patients was 17.5%, well within the range described in other diabetic populations.²⁴ We found that LJM was more prevalent and that the impairment of joint mobility was more severe in patients with microalbuminuria than in patients with normal UAE. Microalbuminuria is the earliest manifestation of diabetic nephropathy and patients with microalbuminuria are at very high risk of progressing to established diabetic nephropathy,²⁵ which is a leading cause of death and cardiovascular disease.^{15 24} However, although poor metabolic control is a risk factor for developing diabetic nephropathy,^{26 27} we cannot predict which individuals will develop the disease.²⁸ Since detection of LJM may precede that of microangiopathy,^{2 6} LJM might be a potential marker of the risk of developing microalbuminuria, but our cross sectional study was not designed to address this question. A follow up study of the patients with LJM but normal UAE is in progress. However, the low specificity of LJM in our patients suggests that its role as a marker of individuals at risk of developing diabetic nephropathy may be limited.

Type I diabetic patients with microalbuminuria show cardiovascular risk factors such as increased blood pressure,^{29 30} lipid abnormalities,³¹ and insulin resistance.³² Accordingly, our patients with microalbuminuria had a high requirement for insulin despite relatively worse metabolic control, suggesting insulin resistance and greater cholesterol concentrations. In contrast, we did not find any association between LJM and blood pressure, plasma lipids, insulin requirement, or metabolic control; therefore, LJM is not

associated with risk factors for cardiovascular events.

It has been suggested that the association of LJM with long term complications of diabetes might simply reflect longer duration of diabetes.¹³ In agreement with previous reports, we found that patients with LJM had a longer duration of diabetes. However, after correcting for diabetes duration, the association between LJM and diabetic retinopathy persisted. In addition, patients with microalbuminuria had LJM despite a diabetes duration similar to that of non-microalbuminuric patients. Therefore, our results show that the association of microangiopathic complications of diabetes mellitus and LJM in type I diabetes is independent of the duration of diabetes.

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