Archives of Disease in Childhood 1992; **67**: 96–99

Limited joint mobility in subjects with insulin dependent diabetes mellitus: relationship with eye and kidney complications

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Abstract

Three hundred and fifty seven subjects (178 males and 179 females) with insulin dependent diabetes mellitus were evaluated for the presence of limited joint mobility of the interphalangeal joints. Sixty six subjects (19%) had stage 1 and 26 subjects (7%) had stage 2 involvement of their interphalangeal joints. The presence of contractures was significantly related to mean longitudinal glycated haemoglobin (HbA_1) concentrations, duration of diabetes, age of onset, mean longitudinal cholesterol concentrations and blood pressure. Limited joint mobility was also significantly associated with early diabetic retinopathy and raised albumin excretion rates. Limited joint mobility remained a significant factor in the logistic regression model for albuminuria and grade of retinopathy when controlled for smoking, cholesterol concentrations, duration of diabetes, age, gender, and blood pressure. However, limited joint mobility was only significantly associated with diabetic retinopathy when the effect of HbA_1 concentrations was included in the multivariate model.

Diabetes mellitus is the leading cause of new cases of blindness from the ages of 20–74 years[1 2] and the number one cause of new cases of dialysis is adults[3] in the US. Poor metabolic control,[4] duration of diabetes, high normal blood pressure,[5 6] and smoking[7] have been shown to be associated with early diabetic retinopathy and/or early renal damage.

Limited joint mobility has been observed with variable prevalence (8·4%–46%) in subjects with insulin dependent diabetes.[8 9] These contractures may involve the hands, feet, and larger joints. Thickening of the skin (waxy appearance) had also been associated with limited joint mobility.[10] An increased risk for diabetic microvascular complications in subjects with limited joint mobility has also been described.[10] The increased prevalence of microvascular complications in subjects with limited joint mobility may be partly due to other associated factors. Previous reports have not used multivariate statistical models such as logistic regression to control for the effects of longitudinal glycated haemoglobin (HbA_1) concentrations, duration of diabetes, smoking, blood pressure levels, and other confounding variables when analysing the data for an association of limited joint mobility with early diabetic retinopathy and/or renal damage.

The purpose of this study was to evaluate the relationship of limited joint mobility with early diabetic renal and retinal damage. The influences of other factors were controlled using logistic regression models.

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Accepted 16 September 1991

Subjects and methods

Three hundred and fifty seven subjects (178 males and 179 females) with insulin dependent diabetes who were at least 14 years old and who had had diabetes for at least five years were evaluated for renal and retinal changes in our eye-kidney clinic. The eye-kidney clinic began in 1986 and after their initial evaluation, subjects were asked to return at least once a year. Subjects were included in this report only if they had brought in a minimum of two overnight timed urine samples for microalbumin determinations. There were no other exclusion criteria for the study. Approximately 95% of eligible subjects from our diabetic clinic have been evaluated in the eye-kidney clinic.

During routine physical examination, each subject was asked to approximate the palmar surfaces of the interphalangeal joints of both hands with fingers extended. Normal approximation at the interphalangeal joints is usually a minimum of 180°. Subjects are designated by numbers of fingers with interphalangeal joint contractures as stage 0 (no limitation), stage 1 (one interphalangeal joint involved in both hands), or stage 2 (two or more interphalangeal joints involved with or without one large joint involvement).

All subjects had direct ophthalmoscopy (with pupils dilated) by at least two examiners (one ophthalmologic, and one paediatric) followed by colour retinal photographs, intravenous fluorescein angiograms and a slit lamp examination during their initial visit to the eye-kidney clinic. Subsequent visits included repeating all measurements except fluorescein angiography. Retinal findings were graded using a modified Airlie House classification of diabetic retinopathy.[11 12] Subjects were classified into three groups based on the eye findings of the worst eye (grade 1: no retinal change, grade 2: microaneurysms only, and grades 3 to 6: more advanced retinopathy). The retinal specialist made the final grading with no knowledge of previous eye grades, joint contractures, glycaemic control, smoking status, blood pressure, or albumin excretion rate values, so that the grading was done in a masked fashion.

Timed overnight urine samples were collected for albumin excretion rate (AER) determinations as previously described.[4 13] Albumin concentrations were determined by radioimmunoassay

(albumin double-antibody kit, Diagnostic Products Corporation). The subjects with or without limited joint mobility were then classified into three groups based on their overnight AER: (i) normal, less than 7·6 μg/min, (ii) borderline, 7·6–30·0 μg/min or, (iii) abnormal, over 30 μg/min. The accuracy of microalbumin concentrations at the lower limit was improved by routinely including a 2·5 mg/l standard in the samples for the standard curve. The AER detection limit by this method in our laboratory is 0·5 μg/min, our interassay and intra-assay coefficients of variation are 1·7–4·4% and 3·6–7·4%, respectively.[13]

Serial HbA_1 values for all subjects were determined using ion exchange resin,[4] (Isolab fast haemoglobin test system, Isolab Inc) with normal concentrations of 6·3 to 8·2%. The normal values for HbA_1 have remained in this range since 1979. A mean of 7·6 years of HbA_1 concentrations were available for each subject and for the purposes of this study a mean of all values ever recorded was used for data analyses. Serum cholesterol was measured by enzymatic assay using the Cobas autoanalyser and Beckman reagents.

Blood pressure was measured at each visit as previously described.[7] Subjects were considered to have a 'high normal' systolic and/or diastolic blood pressure if levels above the 90th centile for age were detected on at least two separate clinic visits and were lower than 141/90 mm Hg, the level defining hypertension. All subjects signed a consent form approved by the University of Colorado Health Sciences Center human subjects commitee. Smoking was defined as previously described.[9]

STATISTICAL METHODS

Statistical analyses included use of χ^2 test, Pearson correlation coefficients, and analysis of variance. When significant differences were found using analysis of variance, Dunnett's multiple *t* test was used to compare individual groups.

Multinomial logistic regression for ordinal response variables (also called proportional odds model) was used to assess the influence of limited joint mobility on diabetic retinopathy (grade 1, 2 and 3–6) and raised AER (normal, borderline, and abnormal) with and without the presence of other factors such as age, sex, duration of diabetes, HbA_1 concentrations, smoking, cholesterol concentrations, and blood pressure. A multinomial logistic regression was also used to assess the influence of the above factors on limited joint mobility.

Results

Limited joint mobility was present in 26% of the subjects (table 1). The subjects were classified into the three groups depending on the presence and stage of limited joint mobility. The mean (SEM) ages for subjects in the three groups were similar (table 1). The age ranges for the three groups, stages 0, 1, and 2, were 14 to 30, 14 to 34, and 14 to 34 years, respectively. The mean (SEM) duration of diabetes was 10·5 (0·2), 14·0 (0·6), and 14·0 (0·8) years for subjects with stages 0, 1, and 2, respectively ($p<0·001$, analysis of variance). Sex distribution was not significantly different for subjects with or without limited joint mobility ($p=0·08$, χ^2 test), although a tendency for more males having limited joint mobility was observed (table 1). Tobacco consumption and mean systolic blood pressure were not different between the three groups. Cholesterol concentrations were significantly different ($p=0·024$, analysis of variance) for the three groups (table 1). Limited joint mobility was significantly associated with mean HbA_1 concentrations (table 1). Mean HbA_1 concentrations were significantly higher in subjects with grade 2 limited joint mobility than subjects without limited joint mobility (Dunnett's multiple *t* test).

Mean diastolic blood pressures were also significantly different between the three groups ($p=0·005$, analysis of variance, table 1). When individual comparisons were made, only subjects with stage 2 limited joint mobility had significantly different levels from subjects without limited joint mobility. Hypertension was detected in seven subjects and was similarly distributed in the three groups. High normal blood pressure was observed in 14% (37/265) with stage 0, in 14% (9/66) with stage 1, and in 47% (12/26) with stage 2 limited joint mobility. A significant difference was observed in the frequency of high normal blood presssure among the three groups, especially in subjects with stage 2 limited joint mobility ($p=0·01$, χ^2 test).

Using actual values the joint classification correlated significantly with the AER ($r=0·31$, $p<0·001$; Pearson correlation coefficient). The distribution of subjects by AER categories among the three groups of limited joint mobility was statistically different ($p<0·002$, χ^2 test, table 2). Forty six percent of subjects with stage 2 limited joint mobility had AER values above 30 μg/min compared with 23% of subjects with stage 1 and 15% of subjects without limited joint mobility.

Using actual values, the joint classification also correlated significantly with the grade of

Table 1 Demographic data of subjects with various stages of limited joint mobility

Stage of limited joint mobility	*No (%)*	*Mean (SEM) age at last visit (years)*	*Mean (SEM) duration of diabetes (years)*	*Sex (M/F)*	*Smoking (Yes/No)*	*Mean (SEM) blood pressure (mm Hg)*		*Mean (SEM) HbA_1 (%)*	*Mean (SEM) cholesterol (mmol/l)*
						Systolic	*Diastolic*		
0	265 (74)	19·5 (0·2)	10·5 (0·2)	123/142	201/64	114·4 (0·7)	71·5 (0·5)	11·40 (0·09)	4·6 (0·05)
1	66 (19)	21·0 (0·5)	14·0 (0·6)*	40/26	47/19	116·3 (1·3)	70·2 (1·3)	11·73 (0·19)	4·7 (0·09)
2	26 (7)	19·5 (0·8)	14·0 (0·8)*	15/11	19/7	118·9 (2·5)	76·7 (1·6)*	12·47 (0·82)*	5·1 (0·23)*
p Value		>0·05†	0·001†	>0·05‡	>0·05‡	>0·05†	0·005†	0·0014†	0·024†

*Significantly different when compared with value for no limited joint mobility (stage 0), using Dunnett's multiple *t* test.
†Analysis of variance.
‡χ^2 test.

*Table 2 Number (%) of subjects as classified by limited joint mobility and AER**

AER (μg/min)	Limited joint mobility		
	Stage 0	Stage 1	Stage 2
<7·6	158 (60)	35 (53)	8 (31)
7·6–30	67 (25)	16 (24)	6 (23)
>30	40 (15)	15 (23)	12 (46)
Total	265 (100)	66 (100)	26 (100)

*χ^2 test=0·002.

Table 3 Number (%) of subjects as classified by limited joint mobility and grade of retinopathy

Eye grades	Limited joint mobility		
	Stage 0	Stage 1	Stage 2
1	106 (40)	14 (21)	2 (8)
2	98 (37)	17 (26)	9 (34)
3–6	61 (23)	35 (53)	15 (58)
Total	265 (100)	66 (100)	26 (100)

*χ^2 test=0·001.

retinopathy ($r=0·36$, $p<0·001$; Pearson correlation coefficient). The distribution of subjects by grade of retinopathy and limited joint mobility was also significantly different ($p<0·001$, χ^2 test, table 3). Subjects with limited joint mobility had more advanced diabetic retinopathy as compared with subjects without limited joint mobility.

Multivariate logistic regression was used to assess the relative importance of gender, duration of diabetes, blood pressure, mean HbA_1 concentrations, smoking status, and cholesterol concentrations on AER and retinal grades. When age, sex, duration of diabetes, smoking, cholesterol, and blood pressure were controlled using the logistic regression model, limited joint mobility remained significantly associated with diabetic retinopathy and AER values (as described in methods). However, when HbA_1 was included in this model, limited joint mobility remained significantly associated only with diabetic retinopathy.

Using logistic regression with limited joint mobility as a response variable, the only factors having a significant effect were duration of diabetes and mean HbA_1 values.

Discussion

Twenty six percent of the 357 young subjects with insulin dependent diabetes in this study demonstrated limited joint mobility. The presence of limited joint mobility was significantly associated with the duration of diabetes, with longitudinal HbA_1 and cholesterol concentrations, and with diastolic blood pressure. The latter three factors were primarily associated with stage 2 joint contractures (table 1). Joint contractures of the fingers were also significantly associated with a greater likelihood of having increased AER and retinal changes. However, when longitudinal HbA_1 concentrations were considered in the logistic regression model, only diabetic retinal changes remained significantly associated with limited joint mobility.

The relationship between limited joint mobility, diabetic renal and retinal complications, and glucose control has previously been confusing. The initial study noting the association of limited joint mobility with microvascular disease did not attempt to differentiate between renal and retinal damage.[8] It is now known that there is a relationship between longitudinal glucose control, as monitored by longitudinal HbA_1 concentrations, and both the renal and the retinal complications of diabetes.[4] Increased glycosylation of connective tissue has been shown in biopsy specimens of skin taken from diabetic subjects with limited joint mobility. However, several studies have not shown a relationship between HbA_1 and limited joint mobility. The most likely reason for this relates to previous studies using a single HbA_1 value, reflecting glucose control for only a short period. This single value may not be representative of the accumulative effect of glucose control over the many years of having diabetes. In the present study, when longitudinal HbA_1 concentrations from a mean period of 7·6 years were studied, the limited joint mobility clearly related to the HbA_1.

Another reason for the variability in reports of the relationship of limited joint mobility and diabetic renal and retinal complications and glucose control relates to inadequate statistical methods used in most previous papers. Most previous studies have not evaluated the effect of limited joint mobility on the renal and retinal complications when controlled by longitudinal HbA_1 concentrations using a multivariate statistical model. When logistic regression analysis was used in the present study, limited joint mobility had no statistically significant influence on diabetic renal disease, although a significant effect on retinal disease remained. In the only other study of limited joint mobility in which logistic regression models were used (in adults with non-insulin dependent diabetes), limited joint mobility was also found to be significantly associated with retinopathy, but not with the AER.[10]

The main association of limited joint mobility and HbA_1 concentrations was for subjects who had two or more joints involved (table 1). Studies in which different grades of involvement were not considered in the statistical analysis might have missed this association. It is our current hypothesis that when only the interphalangeal joints of the little finger are involved, a genetic aetiology may be predominant. However, when other joints are also involved, longitudinal poor glucose control is likely to be a major factor. In support of this hypothesis is the frequent finding of limited joint mobility of the interphalangeal joints of the little finger in first degree relatives of children with insulin dependent diabetes.[9] However, we have never seen involvement of other joints in non-diabetic first degree relatives.

The mechanism by which limited joint mobility continues to influence retinal changes, even when the effect of longitudinal HbA_1 concentrations are taken into account is unknown. It has been suggested that the initial lesion in the retina relates to loss of endothelial

connective tissue support cells. Possibly, similar changes in connective tissue might also occur in the skin and joint capsules. The pathophysiology of diabetic retinopathy is also related to factors other than just longitudinal glucose control, such as the duration of diabetes.[4] Duration of diabetes was also found to be related to the presence of limited joint mobility in the present study. Further studies are clearly needed to identify other factors influencing the development of diabetic retinal disease.

Our data suggest an association of joint contractures with the eye complications of diabetes. HbA_1 was an important factor influencing joint contractures. The association of joint contractures with eye (but not kidney) changes remained when HbA_1 concentrations (and other variables) were included in the multivariate model.

This study was supported in part by the Children's Diabetes Foundation at Denver and by a grant (RR-69) from the General Clinical Research Centers Program, the National Center for Research Resources, National Institutes of Health, Bethesda, Maryland.

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