ORIGINAL ARTICLE

Longitudinal relation between limited joint mobility, height, insulin-like growth factor 1 levels, and risk of developing microalbuminuria: the Oxford Regional Prospective Study

R Amin, T K Bahu, B Widmer, R N Dalton, D B Dunger

Aims: To determine risk factors for development of microalbuminuria (MA) in relation to detection of limited joint mobility (LJM) of the interphalangeal joints in a longitudinal cohort of type 1 diabetic (T1DM) subjects.

Methods: A total of 479 T1DM subjects diagnosed <16 years were followed from diagnosis of diabetes with annual assessments consisting of assessment of LJM, measurement of HbA1c, and insulin-like growth factor 1 (IGF-1), and three urine samples for albumin:creatinine ratio (ACR).

Results: After a median follow up of 10.9 years, 162 subjects (35.1%) developed LJM at median age 13.0 years and duration 5.2 years. More subjects developed LJM after compared to before puberty (67.6 v 32.4%). In LJM+ compared to LJM− subjects, HbA1c (mean 10.1 (SD 1.6) v 9.6 (1.4) %) and ACR levels (median 1.1 (range 0.2–242.9) v 0.9 (0.4–70.7) mg/mmol) were higher, and in a Cox model probability of developing LJM was related to puberty and higher HbA1c levels. ACR levels were higher after detection of LJM compared to before (median 1.2 (range 0.4–102.6) v 0.8 (0.2–181.9) mg/mmol). Probability of developing MA was related to puberty, HbA1c, female sex, and presence of LJM (a 1.9-fold increased risk). Both LJM and MA were associated with lower height SDS (LJM: mean 0.0 (SD 1.0) v 0.2 (1.1); MA: 0.0 (1.0) v 0.2 (1.0)) and lower IGF-1 levels.

Conclusion: The development of LJM was associated with an increased risk of microalbuminuria, independent of glycaemic control. Risk for both microalbuminuria and LJM was associated with puberty, reduced growth, and reduced IGF-1 levels, and may indicate underlying shared pathogenic mechanisms.
for height, weight, and BP, and examined for presence of LJM. In each district examinations were undertaken by the same observer, who was blind to the results of previous years.

Definition of LJM and microalbuminuria
Joint limitation was classified as: normal (no joint limitation or limitation of two or more proximal inter- or metacarpophalangeal joints at one annual assessment only); mild (limitation of two proximal inter- or metacarpophalangeal joints on two or more annual assessments) (fig 1); moderate (limitation of three or more inter- or metacarpophalangeal joints on two or more annual assessments); and severe (obvious hand deformity at rest). Thus for the purposes of this study, LJM was diagnosed only if present for two or more years. This strict definition of LJM was used to reduce intra-observer variation in diagnosis that may occur in a longitudinal study. Subjects with mild, moderate, and severe LJM were designated as cases (LJM+) and the remainder were designated as LJM− controls. Although no non-diabetic controls were available for comparison in the current study, previous studies have confirmed the reliability of using this definition, yielding consistent and reproducible results by different observers, compared to non-diabetic subjects. LJM tends to be painless, asymptomatic, and not disabling unless severe, when it is often associated with large joint involvement.6 MA was defined as an ACR >3.5 mg/mmol in males and >4.0 mg/mmol in females, and <35 mg/mmol in two of three consecutive early morning urine collections.19 Consistent with previous ORPS studies,27 persistent MA was defined as an ACR within the microalbuminuric range for two or more consecutive years. Transient MA was defined as microalbuminuria for one year, then regression to normoalbuminuria the subsequent year.

Methods

Auxology
Height was measured on wall mounted stadiometers, weight measured on electronic scales.

Albumin assay
Until 1994 urine samples were stored at −20°C and after this time at −70°C. Albumin was measured centrally by a double antibody ELISA method.27 The within and in-between assay coefficient of variation (CV) was 6% and 12% respectively.

Creatinine
Creatinine was measured using a modified Jaffe method (Unimate 7, Roche Diagnostic Systems, Basel, Switzerland) on a Cobas Mira (Roche Diagnostic Systems, Basel, Switzerland) automated spectrophotometer. The CV was 2% at 2.2 mmol/l.

HbA1c
Glycated haemoglobin was measured initially by an electrophoretic method (Ciba Corning Diagnostics, Halstead, UK) and then by high performance liquid chromatography (HPLC-DIAMAT; Bio-Rad, Hemel Hempstead, UK).28 The relation between the two methods was carefully evaluated and has been described previously.27 The within batch CV for the HPLC method was 2.2% and 1.3% at a level of 9.8% and 10.1% respectively. The between batch CV was 3.5% and 2.2% at 5.6% and 10.1% respectively.

IGF-1
IGF-1 levels were determined by radioimmunoassay following acid-acetone extraction using rabbit anti-serum developed by L Underwood (North Carolina University, Chapel Hill). The assay was standardised against a pool of normal human serum, defined as containing 1.0 U IGF-1/ml (equivalent to 159 ng/ml of a purified preparation of IGF-19). The intra-assay and inter-assay CV were 3.5% and 6.2% respectively.

Statistical methods
ACR was calculated from the geometric mean of the three annual urine samples. Height, and BMI standard deviation scores (SDS) were calculated from the UK growth reference charts.29 Data were normally distributed, except ACR which were log transformed to allow parametric analyses. For each subject data were summarised as means and compared using the independent t test, χ² analyses, a Kaplan-Meier survival curve, and log rank test. A Cox method was used to measure the proportional contribution of covariates to risk of developing LJM or MA. To display longitudinal changes in data, multilevel modelling software was used (MLwiN version 1.0 beta, Institute of Education, London, UK). This is an extension of multiple regression, using repeated measures data and analyses within and between individual effects, allowing consideration of individual curves and their summation by predefined groups. SPSS version 10.0 was used for analysis. Data are presented as mean (SD) or median (range). A p value <0.05 was considered significant.

RESULTS

Demographic characteristics of cohort
From 479 subjects (262 males), after a median of six observations per subject (range 1–16), 178 subjects (37.2%) met our definition for LJM. Sixteen subjects had evidence of LJM within one year of diagnosis of diabetes and were excluded from further analyses as it was assumed that this could be unrelated to the effects of diabetes. However, no differences existed in these subjects compared to the remainder of the cohort, in terms of glycaemic control and
prevalence of MA (data not shown). Remaining analyses were restricted to 162 subjects (35.1%) with LJM (LJM+) and 301 subjects without LJM (LJM-). The median age when LJM was first detected was 13.0 years (range 5.4–26.6) reflecting a median duration of diabetes of 5.2 years (1.0–13.6). Fifty subjects (32.4%) developed LJM before puberty compared to 112 subjects (67.6%) after puberty (p = 0.001). The median age when LJM was first detected was 13.0 years (range 5.4–26.6) and the median duration of diabetes to first appearance of MA was 5.9 years (range 0.0–12.2). More subjects developed MA after puberty (n = 163 (42.2%)) compared to before puberty (n = 83 (87.2%)) (58.1%, p < 0.001). In MA+ subjects, 29 (30.5%) had persistent and 66 (69.5%) transient MA; however no difference was found in prevalence of MA (table 1). In subjects with LJM compared to those without LJM, height SDS at first assessment and mean lifetime height SDS were lower (table 1, fig 3A). Mean IGF-1 levels were also lower in the LJM+ group (182.6 (SD 63.6) mg/mmol) v 199.8 (SD 79.5) mg/ml, p = 0.04).

### Determinants of risk for development of LJM using Cox method

The probability of developing LJM (with duration of diabetes to onset of LJM as the time variable and puberty as the time dependent covariate) was related to puberty (a 1.4-fold increased risk with pubertal onset) and HbA1c (a 10% increased risk for a 1% HbA1c rise), but not other covariates (table 2).

### Relation between LJM, IGF-1 levels, height, and risk of microalbuminuria

From 479 subjects in the cohort, 95 (19.8%) developed microalbuminuria (MA+). For MA+ subjects, the median age of onset was 15.4 years (range 6.0–24.4), and median duration of diabetes to first appearance of MA was 5.9 years (range 0.0–12.2). More subjects developed MA after puberty (age>11 years) compared to before puberty (n = 83 (87.2%) v n = 12 (12.8%)). In MA+ compared to normoalbuminuric subjects; mean HbA1c levels were higher (10.7 (SD 1.7) v 9.6 (1.4) %, p < 0.001), proportion of females was greater (n = 54 (58.1%) v n = 163 (42.2%)), χ² = 7.66, p = 0.006), and mean height SDS was lower (0.0 (SD 1.0) v 0.2 (SD 1.0), p = 0.006). IGF-1 levels were lower in MA+ compared to normoalbuminuric subjects and these differences have been described in detail previously.²¹

In subjects with LJM compared to those without LJM, mean ACR levels were higher (table 1 and fig 3B), but there was no difference in prevalence of MA (table 1). In subjects with LJM only, mean ACR levels were higher after the appearance of LJM compared to before (median 1.2 (range 0.4–102.6) v 0.8 (0.2–181.9) mg/mmol, p = 0.003). From 95 MA+ subjects, 29 (30.5%) had persistent and 66 (69.5%) transient MA; however no difference was found in prevalence of LJM. Other differences between persistent and transient subjects have been detailed previously.²⁵ ²⁷

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#### Table 1

Characteristics of cohort comparing all subjects with (LJM+) and without (LJM-) limited joint mobility

<table>
<thead>
<tr>
<th></th>
<th>LJM+</th>
<th>LJM-</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>162 (87 male)</td>
<td>301 (167 male)</td>
<td></td>
</tr>
<tr>
<td>Age diagnosis of diabetes (years)</td>
<td>8.5 (0.4–15.9)</td>
<td>9.6 (0.4–15.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>8.6 (4.2–15.0)</td>
<td>8.0 (4.1–15.7)</td>
<td>0.1</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.3 (0.6)</td>
<td>3.3 (0.6)</td>
<td>0.8</td>
</tr>
<tr>
<td>Smokers</td>
<td>47 (29.0%)</td>
<td>80 (26.6%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Insulin dose (U/kg/day)</td>
<td>0.8 (0.2)</td>
<td>1.0 (0.3)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Clinical and biochemical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>10.1 (1.4)</td>
<td>9.6 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subjects with microalbuminuria</td>
<td>39 (24.1%)</td>
<td>56 (18.6%)</td>
<td>0.3</td>
</tr>
<tr>
<td>ACR (mg/mmol)</td>
<td>1.1 (0.2–242.9)</td>
<td>0.9 (0.4–70.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>ACR in microalbuminuric subjects only (mg/mmol)</td>
<td>2.0 (0.1–533.9)</td>
<td>1.8 (0.1–184.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Height SDS at 1st assessment</td>
<td>0.1 (1.1)</td>
<td>0.3 (1.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Height SDS</td>
<td>0.0 (1.0)</td>
<td>0.2 (1.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>IGF-1 (mg/ml)</td>
<td>104.1 (8.5)</td>
<td>103.8 (10.1)</td>
<td>0.7</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>–1.1 (0.7)</td>
<td>–1.1 (0.7)</td>
<td>0.7</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>66.9 (6.6)</td>
<td>67.5 (6.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>Diastolic BP SDS</td>
<td>1.1 (0.6)</td>
<td>1.1 (0.6)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Data are expressed as means (SD) or median (range) for the total duration of follow up, unless stated otherwise. ACR, urine albumin:creatinine ratio; SDS, standard deviation score.

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#### Figure 2

Kaplan-Meier survival curve for probability of developing limited joint mobility.
Severity of LJM
A total of 139 (85.8%) had mild LJM and 23 (14.2%) had moderate or severe LJM. Mean HbA1c and ACR levels were higher in those with severe/moderate LJM compared to those with mild LJM and no LJM (HbA1c: mean 10.6 (SD 1.7) v 9.3 (0.9) v 9.1 (1.1) %, p < 0.001; ACR: median 1.1 (range 0.4–242.9) v 0.9 (0.1–81.2) mg/mmol, p = 0.02).

Comparison of data after the onset of LJM
In LJM+ subjects, using data only after the onset of LJM, compared to LJM− subjects: mean HbA1c (10.2 (SD 1.6) v 9.6 (1.4) %, p = 0.002) and median ACR levels (1.2 (range 0.4–102.6) v 0.9 (0.4–70.7) mg/mmol, p = 0.004) remained higher, and prevalence of MA was greater (n = 37 (23.7%) v n = 56 (18.6%), χ² = 3.2, p = 0.06). Furthermore height SDS (mean −0.1 (SD 1.0) v 0.2 (1.1), p < 0.001) and IGF-1 SDS (−1.0 (1.5) v −0.5 (1.4), p = 0.005) were lower.

Relation between LJM, MA, and blood pressure
Overall no difference existed in mean BP or BP SDS between subjects with and without LJM. In subjects with LJM after the development of LJM compared to before, mean systolic BP SDS was similar (−1.2 (SD 1.1) v −1.1 (1.1), p = 0.1); however mean diastolic BP SDS was greater (1.2 (1.3) v 0.9 (1.3), p = 0.001).

Comparing those with (MA+) and without MA (MA−), mean systolic BP SDS was higher (−1.1 (SD 0.6) v −0.9 (0.7), p = 0.04), however diastolic BP SDS was no different. When considering those with persistent MA compared to the MA− group, both systolic BP SDS (−1.1 (0.6) v −0.9 (0.7), p = 0.05) and diastolic BP SDS (1.3 (0.6) v 1.1 (0.6), p = 0.05) were higher. In subjects with MA, BP SDS was higher after compared to before the onset of MA (systolic: −0.8 (0.6) v −1.2 (0.7), p = 0.01; diastolic: 1.4 (1.0) v 1.0 (0.9), p = 0.005).

Determinants of risk for development of MA using Cox method
Following the development of LJM, probability of developing MA was related to pubertal onset (that is, a 6.6-fold increased risk with pubertal onset), HbA1c (that is, a 20% increased risk for a 1% HbA1c rise), female sex (that is, a 2-fold increased risk), and presence of LJM (a 1.9-fold increased risk if LJM was present) (table 2). Subjects with persistent MA were considered too few to analyse separately to transient subjects.

| Table 2 | Proportional contribution of covariates to probability of developing LJM and MA using a Cox method, with puberty as a time dependent covariate and duration of diabetes as the time variable |
|------------------------|------------------------|------------------------|
| **Probability of developing LJM** | **Baseline** | **p value** | **ExpB (95% CI)** |
| Puberty | Pre-puberty | 0.03 | 1.4 (1.0 to 2.0) |
| HbA1c (%) | 0.03 | 1.1 (1.01 to 1.2) |
| Covariates not contributing to model: sex, parental LJM, and height SDS | |
| **Probability of developing MA once LJM has occurred** | **Baseline** | **p value** | **ExpB (95% CI)** |
| Puberty | Pre-puberty | <0.001 | 6.6 (2.5 to 17.2) |
| HbA1c (%) | 0.02 | 1.2 (1.1 to 1.3) |
| Sex | Male | 0.006 | 2.0 (1.2 to 3.4) |
| LJM | No LJM | 0.04 | 1.9 (1.0 to 3.4) |
| Covariates not contributing to model: height SDS | |

Probability is expressed as a ratio of change, for each unit rise in covariate. For puberty, sex and LJM probability is relative to baseline.
DISCUSSION

The ORPS is a prospective study of 479 T1DM children followed from diagnosis of diabetes through puberty. We describe the development of LJM in this cohort in relation to the development of MA. To reduce intra-observer variation in diagnosis of LJM, we restricted the definition to the finding of LJM during two or more annual assessments, as measured repeatedly by the same observer. Overall incidence was 35.1%, which is comparable to previous reports, further validating this method of assessment.

We confirm longitudinal data from Rosenbloom et al indicating that risk of LJM is related to poor glycaemic control and duration of diabetes. This is further confirmed by reduced incidence of LJM with improved glycaemic control and in more contemporary cohorts. Chronic hyperglycaemia results in accumulation of advanced glycation end products which increase cross-linking in the subcutaneous tissues and formation of inflexible collagen. Other largely cross-sectional data are conflicting and show no such relation, which may reflect the use of only a single HbA1c value.

Two cross-sectional studies show LJM to be more prevalent in males, while others show no gender difference. These conflicting results may reflect differences in duration of diabetes and glycaemic control between the sexes. The current study detected no difference between genders despite differences in HbA1c levels, and further follow up is required to detect any sexual dimorphism for risk of LJM.

The longitudinal nature of our study allows us to explore the temporal relation between development of LJM and microvascular disease. Subjects with LJM had higher urine albumin excretion, and presence of LJM was associated with a twofold increased risk of developing microalbuminuria, which also related to severity of LJM, confirming findings of the original study of Rosenbloom and colleagues. Thus our data confirm that the presence of LJM is a sign of impending microvascular disease. BP was increased in subjects who developed both MA and LJM, but was not predictive of either, suggesting that hypertension may influence progression of microvascular disease but is not involved in its initiation. This is in keeping with previous, more carefully controlled data from our group. Other risk factors for developing both microalbuminuria and LJM were found to be independent of HbA1c, and suggest factors other than poor glycaemic control may be important.

Consistent with a cross-sectional study and longitudinal data, the appearance of LJM was more influenced by age than diabetes duration, we found that risk for developing LJM and microalbuminuria was associated with pubertal onset. Puberty is also a risk factor for retinopathy, and this suggests that the development of microvascular complications may be related to pubertal hormonal variables. Risk for diabetic complications may be associated with abnormalities of the GH–IGF-1 axis, particularly in females. We confirm previous findings that risk for microalbuminuria is increased in adolescent females. In the current study subjects with LJM had lower IGF-1 levels and GH hypersecretion, particularly in females. In rodent models raised GH induces diabetic nephropathy-like changes, including increased cross-linking of collagen in the glomerulus.

Previous data describe an association between LJM and attenuated growth and between nephropathy risk and short stature. The latter may relate to factors operating in utero to reduce birth weight and nephron number. However we found no differences in birth weight, suggesting that other mechanisms may be involved. Poor glycaemic control may lead to impaired growth in diabetic children; however the relation to puberty was independent of HbA1c levels, providing further evidence of the possible influence of the GH–IGF-1 axis on complications risk. The relation between short stature and nephropathy risk has been found in subjects diagnosed with T1DM after age 19 years, suggesting a genetic predisposition; however we found no evidence of familial clustering and further research is required to support this hypothesis.

In summary, this is the largest longitudinal study to describe the development of LJM and its association with microvascular disease. LJM is associated with puberty independent of glycemic control and is predictive of microalbuminuria. LJM is easily assessed in a clinic setting; however specificity is poor and therefore is certainly not a substitute for screening by ophthalmology and urine albumin excretion. Thus pubertal subjects with poor glycaemic control, especially if female or with LJM, should all have formal assessment for microalbuminuria, hypertension, and retinopathy on an annual basis. Lower IGF-1 levels and attenuated growth in subjects with LJM were also found in relation to the development of microalbuminuria and may reflect shared underlying pathogenic mechanisms.

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Consent was obtained for publication of figure 1

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