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Risk of microalbuminuria and progression to macroalbuminuria in a cohort with childhood onset type 1 diabetes: prospective observational study

Rakesh Amin,1 Barry Widmer,1 A Toby Prevost,2 Phillip Schwarze,1 Jason Edge,4 Julie Edge,4 Loredana Marcovecchio,1 Andrew Neil,5 R Neil Dalton,6 David B Dunger1

ABSTRACT

Objectives To describe independent predictors for the development of microalbuminuria and progression to macroalbuminuria in those with childhood onset type 1 diabetes.

Design Prospective observational study with follow-up for 9.8 (SD 3.8) years.

Setting Oxford regional prospective study.

Participants 527 participants with a diagnosis of type 1 diabetes at mean age 8.8 (SD 4.0) years.

Main outcome measures Annual measurement of glycated haemoglobin (HbA1c) and assessment of urinary albumin: creatinine ratio.

Results Cumulative prevalence of microalbuminuria was 25.7% (95% confidence interval 21.3% to 30.1%) after 10 years of diabetes and 50.7% (40.5% to 60.9%) after 19 years of diabetes and 5182 patient years of follow-up. The only modifiable adjusted predictor for microalbuminuria was high HbA1c concentrations (hazard ratio per 1% rise in HbA1c 1.39, 1.27 to 1.52). Blood pressure and history of smoking were not predictors. Microalbuminuria was persistent in 48% of patients. Cumulative prevalence of progression from microalbuminuria to macroalbuminuria was 13.9% (12.9% to 14.9%); progression occurred at a mean age of 18.5 (5.8) years. Although the sample size was small, modifiable predictors of macroalbuminuria were higher HbA1c levels and both persistent and intermittent microalbuminuria (hazard ratios 1.42 (1.22 to 1.78), 27.72 (7.99 to 96.12), and 8.76 (2.44 to 31.44), respectively).

Conclusion in childhood onset type 1 diabetes, the only modifiable predictors were poor glycaemic control for the development of microalbuminuria and poor control and microalbuminuria (both persistent and intermittent) for progression to macroalbuminuria. Risk for macroalbuminuria is similar to that observed in cohorts with adult onset disease but as it occurs in young adult life early intervention in normotensive adolescents might be needed to improve prognosis.

INTRODUCTION

The Oxford regional prospective study is a population based inception cohort of children with type 1 diabetes designed to determine prospectively the natural course of microalbuminuria during childhood and adolescence. Initial data indicated a cumulative prevalence of microalbuminuria of 40% after 11 years of diabetes, and this was predicted by poor glycaemic control but not blood pressure. The prognostic value of microalbuminuria for progression to macroalbuminuria has not been adequately determined in a childhood cohort. We report on data from this study after up to 19 years of follow-up and focus on predictors for the development of microalbuminuria and macroalbuminuria.

METHODS

Oxford regional prospective study

The Oxford regional prospective study was established in 1986.1 It identified children with type 1 diabetes aged under 16 over a 10 year period from the diabetes register and recruited children within three months of diagnosis. Case ascertainment for the register was over 95%. From 1986 to 1997, 91% (n=527) of eligible children were recruited at a mean age 8.8 (SD 4.0) years. To date the dropout rate is 9.6%. Mean duration of follow-up to date is 9.8 (3.8) years. Only 4% of the participants have been followed up for under three years, and 9% have over 15 years’ follow-up. Microalbuminuria was treated with angiotensin converting enzyme inhibitors or β blockers in those aged over 18 with persistent microalbuminuria or hypertension, or both.

Annual assessments

Research nurses assessed participants annually from the first year of diagnosis and recorded height, weight, blood pressure, and collected three consecutive early morning urine specimens for the measurement of albumin:creatinine ratio. Blood samples were collected for centralised measurement of glycated haemoglobin (HbA1c). See bmj.com for definitions of microalbuminuria, persistent microalbuminuria, intermittent microalbuminuria, transient microalbuminuria, and macroalbuminuria.

Statistical methods

We averaged results of annual urine collections from each participant using the geometric mean, which were...
log transformed. All data were summarised as means for each patient. We analysed time, blood pressure, and HbA1c as continuous variables; these were normally distributed. Smoking status, antihypertensive treatment, microalbuminuria and macroalbuminuria were analysed as dichotomised variables. We used a life table method to calculate the cumulative prevalence of microalbuminuria and macroalbuminuria and a log rank test to compare cumulative prevalence between groups, based on follow-up ending September 2005.

A Cox’s proportional hazard regression model was used to evaluate the relative contribution of covariates to the risk of developing microalbuminuria and macroalbuminuria, with duration of diabetes as the time covariate. We used the same method for sensitivity analyses, using alternative cut off values. Data are shown as means (SD) unless otherwise stated. See bmj.com.

RESULTS
Cumulative prevalence of microalbuminuria
Of 527 participants, 135 (26%) met the study definition of microalbuminuria after 5182 patient years of follow-up. The cumulative prevalence of microalbuminuria was 25.7% (95% confidence interval 21.3% to 30.1%) after 10 years of diabetes and 50.7% (40.5% to 60.9%) after 19 years. The mean age at onset of microalbuminuria was 16.1 (4.3) years. Compared with those without, those with microalbuminuria were older (19.5 (4.0) vs 18.4 (4.7), P=0.01), had had diabetes for longer (10.5 (3.4) years vs 9.6 (3.8) years, P=0.009), and had higher mean lifetime HbA1c concentrations (10.8% (1.7%) vs 9.5% (1.4%), P<0.001) and higher HbA1c concentrations at diagnosis of diabetes (10.9% (1.8%) vs 9.7% (1.8%), P<0.001). The probability of microalbuminuria increased progressively with increasing quarters of HbA1c (fig 1, log rank test P<0.001).

More females than males developed microalbuminuria (n=72 (53%) vs n=63 (47%), fig 1, log rank test P=0.03). This sex difference was not explained by differences in age, HbA1c concentrations, or duration of diabetes.

In those with a diagnosis of diabetes before the age of 5 (n=27), compared with those with a diagnosis at ages 5-11 (n=64) and after 11 (n=44), there was a longer interval between age at diagnosis to first appearance of microalbuminuria (8.8 (3.8) years v 7.7 (3.8) v 5.5 (3.3) years, P=0.01, with or without adjustment for HbA1c concentrations) (fig 2). After 10 years of diabetes, in the group with a diagnosis before the age of 5 compared with the two other groups, cumulative prevalence of microalbuminuria was lower (age at diagnosis <5 years: 17.4% (9.8% to 25.0%); 5-10 years: 28.7% (21.7% to 35.7%); >11 years: 28.9% (20.5% to 37.3%); log rank test P=0.035). After 15 years of diabetes, however, cumulative prevalence was similar in the three groups (<5 years: 43.0% (25.0% to 61.0%); 5-11 years: 45.7% (33.3% to 58.1%); and >11 years: 40.8% (27.2% to 54.4%); log rank test P=0.1, fig 2).

Predictors for development of microalbuminuria
 Significant unadjusted correlates of microalbuminuria were poor glycaemic control (1.35, 1.24 to 1.47, P<0.001)—that is, a 35% increased risk for a 1% rise in HbA1c, female sex (1.43, 1.02 to 2.01, P=0.04), diastolic blood pressure (1.02, 1.00 to 1.04, P=0.04), and younger age at diagnosis of diabetes (1.06, 1.01 to 1.10, P=0.01). Non-contributory variables included systolic blood pressure (1.01, 0.99 to 1.02, P=0.17) and history of smoking (1.32, 0.89 to 1.94, P=0.23). In a Cox model, the only modifiable adjusted predictor for the development of microalbuminuria was poor glycaemic control. Female sex was also associated with microalbuminuria.

Course of microalbuminuria
Of the 135 participants with microalbuminuria, 65 (48%) developed persistent microalbuminuria, 17 (13%) had intermittent microalbuminuria, and 53 (39%) had transient microalbuminuria, giving a cumulative prevalence of regression to the normoalbuminuric range of 51.9% (42.3% to 61.5%) after 4.9 years after the onset of microalbuminuria. Duration of diabetes was greater in participants with persistent
rather than with intermittent and transient microalbuminuria. Overall mean HbA1c concentrations were highest in those with persistent microalbuminuria and lowest in those with transient microalbuminuria and this was most apparent after the onset of microalbuminuria—that is, lower concentrations of HbA1c after the onset of microalbuminuria were associated with regression of microalbuminuria (hazard ratio 1.21, 1.07 to 1.54—that is, a 21% increased occurrence of regression for a 1% lowering of HbA1c, after adjustment for duration of diabetes).

Development of macroalbuminuria
Eighteen participants developed macroalbuminuria (13% of those with microalbuminuria, 3% of total cohort) giving a cumulative prevalence of 13.9% (12.9% to 14.9%) after 3.2 (2.9) years after onset of microalbuminuria. Median age at development of macroalbuminuria was 18.5 (5.8) years and duration of diabetes was 10.0 (4.0) years. Those who developed macroalbuminuria had higher mean HbA1c concentrations compared with the rest of the cohort and higher blood pressure after the development of microalbuminuria (systolic 126.5 mm Hg v 118 mm Hg (13.8 mm Hg), P=0.009; diastolic 85.6 mm Hg (9.9 mm Hg) v 79.4 mm Hg (8.4 mm Hg), P=0.03).

Significant unadjusted correlates of macroalbuminuria were poor glycaemic control (1.47, 1.18 to 1.82, P<0.001—that is, a 47% increased risk for a 1% rise in HbA1c), persistent microalbuminuria (39.10, 11.33 to 135.21, P<0.001), intermittent microalbuminuria (15.78, 4.24 to 60.62, P<0.001), and systolic blood pressure (1.02, 0.99 to 1.06, P=0.04). The modifiable adjusted predictors for progression from microalbuminuria to macroalbuminuria were poor glycaemic control and persistent and intermittent microalbuminuria (table).

Intervention with antihypertensive medication
Twenty (15%) participants with microalbuminuria (13 with persistent microalbuminuria and seven with intermittent microalbuminuria and hypertension) were treated with an angiotensin converting enzyme inhibitor or a β blocker. Seven (35%) participants receiving treatment progressed to macroalbuminuria (and these were all previously categorised as having persistent microalbuminuria) compared with 11 (10%) with microalbuminuria not receiving treatment (χ²=9.5, P=0.002). See bmj.com.

DISCUSSION
In this inception cohort of people with childhood onset type 1 diabetes, the cumulative prevalence of microalbuminuria was 25.7% and 50.7% after 10 and 19 years of diabetes, respectively, and the cumulative prevalence of macroalbuminuria was 13.9% after 19 years.

Comparisons with other studies
For microalbuminuria, the cumulative prevalence was significantly higher than that from an adult only inception cohort in which prevalence was nearly 34% after 18 years of follow-up and similar glycaemic exposure. This prevalence is greater than previously reported in longitudinal childhood studies, but those previous studies were clinic based, with variable duration of diabetes at inclusion compared with our cohort. The prevalence of macroalbuminuria of 13.9% was similar to that in the adult inception data but occurred at a much earlier age. No comparable data exist for children, although previous small clinic based studies indicate a prevalence of macroalbuminuria of 7–32%.

Implications of poor glycaemic control
In children the goal should be improvement of glycaemic control from the onset of diabetes. The 2002 Diabetes UK audit, however, indicated that 48% of adolescents were not achieving HbA1c concentrations less than 9%, and the Hvidore study also recently reported that HbA1c concentrations during adolescence were disappointing. The poor levels of glycaemic control in our study reflect the high

Cox model* with additional sensitivity analysis with adjusted* definition of microalbuminuria showing adjusted modifiable predictors for development of macroalbuminuria in 527 children with type 1 diabetes followed for up to 19 years, after correction for duration of diabetes. Figures are hazard ratios (95% confidence intervals) with P values

<table>
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<td>HbA1c (per % increase)†</td>
<td>1.42 (1.22 to 1.78), P=0.001</td>
<td>1.42 (1.16 to 1.74), P=0.001</td>
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<td>Persistent microalbuminuria†</td>
<td>27.72 (7.99 to 96.12), P=0.001</td>
<td>22.63 (7.54 to 67.94), P=0.001</td>
<td>25.51 (8.60 to 75.64), P=0.001</td>
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<td>Intermittent microalbuminuria‡</td>
<td>8.76 (2.44 to 31.44), P=0.002</td>
<td>7.40 (2.10 to 26.18), P=0.002</td>
<td>6.39 (1.83 to 22.32), P=0.004</td>
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M=Male; F=Female.

* Non-significant variables also included in model were female sex (1.3, 0.5 to 3.3), diastolic blood pressure (1.1, 0.9 to 1.1), systolic blood pressure (1.1, 0.9 to 1.1), history of smoking (1.3, 0.4 to 4.1), and younger age at diagnosis of diabetes (1.0, 1.0 to 1.1).

†Hazard ratios for HbA1c without microalbuminuria-type and microalbuminuria-type without HbA1c were essentially unchanged.
ascertainment and are an accurate reflection of HbA1c concentrations during adolescence, particularly during transition to adult clinics in the UK.11

Other predictors of microalbuminuria
Microalbuminuria occurred more frequently in females. This might be explained by data indicating a role for sex steroids in renal damage associated with diabetes12 and associations between hyperandrogenism and abnormalities in the growth hormone insulin-like growth factor I axis in adolescent girls with microalbuminuria.13

Cumulative prevalence of microalbuminuria at the end of follow-up was unaffected by age at diagnosis, though in those with a diagnosis before the age of 5 there was a longer interval to first appearance of microalbuminuria. Other data indicate that before the onset of microalbuminuria, the annual rate of rise of urinary albumin excretion increases after the age of 11, coinciding with the onset of puberty and adolescence.14

Transient microalbuminuria
Definition of regression of microalbuminuria is complicated by regression to the mean and duration of follow-up. Our data indicate that people who have microalbuminuria in one year but become normoalbuminuric in the next year might be at risk of recurrence in one to seven years.

Risk for macroalbuminuria
Only 18 patients developed macroalbuminuria, so predictors and comparison with the remainder of the cohort should be interpreted with caution. The only modifiable predictor for the development of macroalbuminuria was poor glycaemic control. Both persistent and intermittent microalbuminuria are important predictors in the transition to macroalbuminuria in children, and these factors are robust after sensitivity analyses. In contrast with findings from studies in adults, those taking angiotensin converting enzyme inhibitors had higher rates of progression to macroalbuminuria. Only 20 patients had started this treatment, however, and our study was not designed to determine the effects of treatment. See bmj.com.

Limitations of study
We collected annual urine samples on three consecutive days rather than spaced through the year. Annual assessment of urinary albumin:creatinine ratio, however, is based on the average of three measurements, which reduces measurement error and regression to the mean. The use of Cox models is associated with inherent problems, as it requires a strict cut off point for the definition of microalbuminuria and macroalbuminuria. We validated the outcomes with sensitivity analyses. Finally, we did not have sufficient data on variables such as insulin regimens, which may have had a confounding effect on the outcome.

Conclusion
There is higher cumulative prevalence of microalbuminuria with predominance of risk in females in people with childhood onset type 1 diabetes compared with data from those with adult onset disease. Our data indicate that microalbuminuria is not persistent in over half of cases. As this depends on duration of follow-up, however, further cases of intermittent microalbuminuria might occur with longer follow-up of those with “transient” microalbuminuria. The probability of progression to macroalbuminuria is remarkably similar to that in adult onset disease, but it occurs at an earlier age and in people with both intermittent and persistent microalbuminuria. There is a need to consider earlier different intervention strategies in those diagnosed with diabetes during childhood.

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Contributors: See bmj.com.
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WHAT IS ALREADY KNOWN ON THIS TOPIC
Microalbuminuria and macroalbuminuria are associated with the development of end stage renal disease in adult onset type 1 diabetes and might be predicted by poor glycaemic control and higher blood pressure.

WHAT THIS STUDY ADDS
In those with childhood onset type 1 diabetes, microalbuminuria occurred more frequently and was more common in females but the only modifiable predictor was high HbA1c concentrations.

Modifiable predictors of microalbuminuria were high HbA1c concentrations and both persistent and intermittent microalbuminuria.

Risk for macroalbuminuria is similar to adult onset type 1 diabetes but as it occurs in young adult life, early intervention during adolescence might be needed to improve prognosis.

Treatment of human brucellosis: systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Objectives To determine and quantify differences in efficacy between treatment regimens for brucellosis. Design Systematic review and meta-analysis of randomised controlled trials assessing different antibiotic regimens and durations of treatment for human brucellosis. Data sources PubMed, CENTRAL, Lilacs, conference proceedings, and bibliographies with no restrictions on language, study year, or publication status. Review methods Search, application of inclusion and exclusion criteria, data extraction, and assessment of methodological quality independently performed in duplicate. Primary outcomes were relapse and overall failure resulting from primary failure or relapse. Relative risks with 95% confidence intervals were calculated and pooled with a fixed effect model. Results 30 trials and 77 treatment arms were included. Overall failure was significantly higher with doxycycline-streptomycin compared to doxycycline-streptomycin, mainly due to a higher rate of relapse (relative risk 2.80, 95% confidence interval 1.81 to 4.36; 13 trials, without heterogeneity). Results were consistent among patients with bacteraemia and complicated brucellosis. Doxycycline-streptomycin resulted in a significantly higher rate of failure than doxycycline-rifampicin for six weeks in place of their previously recommended regimen of tetracycline for six weeks in combination with streptomycin for the first two to three weeks. The relative merits of these two regimens are still being discussed. Recent consensus recommendations of an expert panel proposed doxycycline-streptomycin and doxycycline-rifampicin as first line regimens, without quantifying the differences between them. We performed a systematic review and meta-analysis of all randomised controlled trials that assessed different antibiotic regimens for the treatment of brucellosis to identify the optimal treatment regimen and duration of treatment and to obtain quantitative estimates of effect for the difference between existing regimens.

Methods We included randomised or quasi-randomised controlled trials that tested any single or combination