

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

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BMJ 2008;336:697-701

doi:10.1136/bmj.39478.378241.BE

This article is an abridged version of a paper that was published on bmj.com on 18 March 2008.

Cite this article as: *BMJ* 18 March 2008, doi: 10.1136/bmj.39478.378241.BE

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 (HbA_{1c}) 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 HbA_{1c} concentrations (hazard ratio per 1% rise in HbA_{1c} 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 to 21.2) years. Although the sample size was small, modifiable predictors of macroalbuminuria were higher HbA_{1c} 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.¹ 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.¹ 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 (HbA_{1c}). 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 HbA_{1c} 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%)

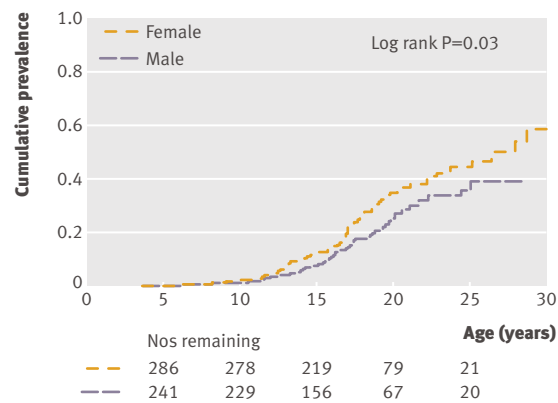
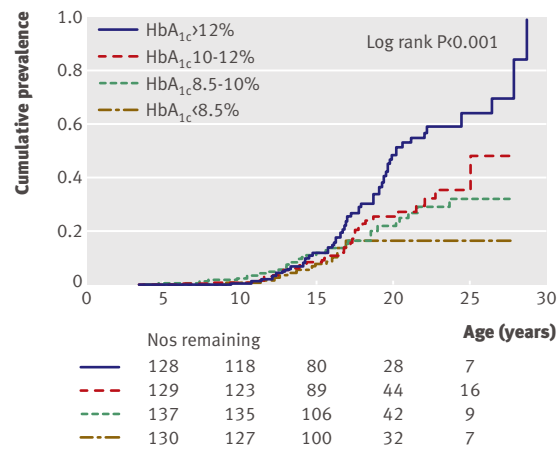


Fig 1 | Kaplan-Meier survival curves showing cumulative prevalence of developing microalbuminuria (135 events) across age in 527 children with type 1 diabetes, 1986-2005, in relation to quarters of mean lifetime HbA_{1c} concentrations (top) and sex (bottom)

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) v 18.4 (4.7), P=0.01), had had diabetes for longer (10.5 (3.4) years v 9.6 (3.8) years, P=0.009), and had higher mean lifetime HbA_{1c} concentrations (10.8% (1.7%) v 9.5% (1.4%), P<0.001) and higher HbA_{1c} concentrations at diagnosis of diabetes (10.9% (1.8%) v 9.7% (1.8%), P<0.001). The probability of microalbuminuria increased progressively with increasing quarters of HbA_{1c} (fig 1, log rank test P<0.001).

More females than males developed microalbuminuria (n=72 (53%) v n=63 (47%), fig 1, log rank test P=0.03). This sex difference was not explained by differences in age, HbA_{1c} 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 HbA_{1c} 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 HbA_{1c}), 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c}, 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 HbA_{1c} concentrations compared with the rest of the cohort and higher blood pressure after the development of microalbuminuria (systolic 126.5 mm Hg (15.6 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 HbA_{1c}), 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)

Cox model* with additional sensitivity analysis with adjusted* definition of macroalbuminuria 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

	Standard definition (M >35, F >47 mg/mmol)	Lower limit of definition reduced by 5 mg/mmol (M >30, F >42 mg/mmol)	Lower limit of definition reduced by 10 mg/mmol (M >25, F >37 mg/mmol)
HbA _{1c} (per % increase)†	1.42 (1.22 to 1.78), <0.001	1.42 (1.16 to 1.74), 0.001	1.42 (1.17 to 1.72), <0.001
Persistent microalbuminuria†	27.72 (7.99 to 96.12), <0.001	22.63 (7.54 to 67.94), <0.001	25.51 (8.60 to 75.64), <0.001
Intermittent microalbuminuria†	8.76 (2.44 to 31.44), 0.002	7.40 (2.10 to 26.18), 0.002	6.39 (1.83 to 22.32), 0.004

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 HbA_{1c} without microalbuminuria-type and microalbuminuria-type without HbA_{1c} were essentially unchanged.

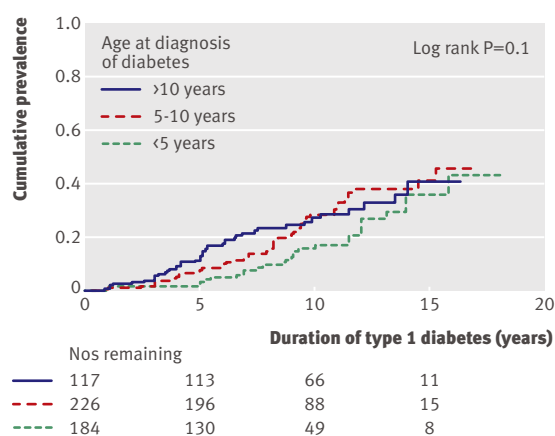


Fig 2 | Kaplan-Meier survival curve showing cumulative prevalence of development of microalbuminuria (135 events) across duration of diabetes in 527 children with type 1 diabetes, 1986-2005, in relation to age at diagnosis of diabetes

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 ($\chi^2=9.5$, *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.² This prevalence is greater than previously reported in longitudinal childhood studies,³⁻⁵ 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%.⁶⁻⁸

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 HbA_{1c} concentrations less than 9%,⁹ and the Hvidovre study also recently reported that HbA_{1c} concentrations during adolescence were disappointing.¹⁰ The poor levels of glycaemic control in our study reflect the high

ascertainment and are an accurate reflection of HbA_{1c} 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.

We acknowledge the study field workers, the laboratory assistance of Angie Watts and Dot Harris, the Barts-Oxford study field workers, paediatricians, physicians, and diabetes nurse specialists in the Oxford region. Full details of the steering committee and study members are on bmj.com.

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Funding: Diabetes UK, the Juvenile Diabetes Research Foundation, the Wellcome Trust, NIHR Cambridge Biomedical Research Centre.

Competing interests: None declared.

Ethical approval: District ethics committees.

Provenance and peer review: Not commissioned; externally peer reviewed.

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 HbA_{1c} concentrations

Modifiable predictors of macroalbuminuria were high HbA_{1c} 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

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Accepted: 25 January 2008

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

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BMJ 2008;336:701-4

doi:10.1136/bmj.39497.500903.25

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-rifampicin 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-aminoglycoside (triple drug regimen) (2.50, 1.26 to 5.00; two trials). Gentamicin was not inferior to streptomycin (1.45, 0.52 to 4.00 for failure; two trials). Quinolones combined with rifampicin were significantly less effective than doxycycline combined with rifampicin or streptomycin (1.83, 1.11 to 3.02, for failure; five trials). Monotherapy was associated with a higher risk of failure than combined treatment when administered for a similar duration (2.56, 1.55 to 4.23; five trials). Treatment for six

weeks or more offered an advantage over shorter treatment durations.

Conclusions There are significant differences in effectiveness between currently recommended treatment regimens for brucellosis. The preferred treatment should be with dual or triple regimens including an aminoglycoside.

INTRODUCTION

Brucellosis is the commonest zoonotic infection worldwide. Treatment is given to shorten the duration of symptoms, prevent relapse, and avert complications. Recommendations for specific regimens are inconsistent. Guidelines of the World Health Organization, last published in 1986, recommend doxycycline with 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.¹ The relative merits of these two regimens are still being discussed.²⁻⁵ Recent consensus recommendations of an expert panel proposed doxycycline-streptomycin and doxycycline-rifampicin as first line regimens, without quantifying the differences between them.⁶

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

This article is an abridged version of a paper that was published on bmj.com on 5 March 2008.

Cite this article as: *BMJ* 5 March 2008, doi: 10.1136/bmj.39497.500903.25