Is screening and intervention for microalbuminuria worthwhile in patients with insulin dependent diabetes?

K Borch-Johnsen, H Wenzel, G C Viberti, C E Mogensen

Abstract

***Objective*—To analyse the cost-benefit of screening for and antihypertensive treatment of early renal disease indicated by microalbuminuria in patients with insulin dependent diabetes mellitus.**

***Design*—Previously published data were used to estimate transition probabilities for each step from normoalbuminuria until death. The effect of intervention on urinary albumin excretion rate by antihypertensive treatment was arbitrarily set at three different levels. All direct costs (screening, antihypertensive treatment, treatment of end stage renal failure) were included in the cost-benefit analysis by using real discount rates of 2·5% and 6%.**

***Setting*—Computer simulation.**

***Subjects*—Simulated cohort of 8000 patients.**

***Main outcome measures*—Mortality, incidence of diabetic nephropathy, incidence of end stage renal failure, and costs versus savings.**

***Results*—Assuming treatment effects of 33% and 67% median life expectancy increased by four to 14 years, respectively, and the need for dialysis or transplantation decreased by 21% to 63%. Costs and savings would balance if the annual rate of increase of albuminuria was decreased from 20% to 18% a year.**

***Conclusions*—Screening and intervention programmes are likely to have life saving effects and lead to considerable economic savings.**

Introduction

Without intervention diabetic nephropathy develops in one third of all patients with insulin dependent diabetes mellitus and is a major threat to their survival and quality of life.[1,2] These patients are characterised by increased mortality,[3,4] increased risk of proliferative retinopathy,[5,6] and increased morbidity and mortality due to vascular disease.[7,8] Diabetic nephropathy leads to progressive loss of renal function and will necessitate dialysis or transplantation in most cases. Microalbuminuria (defined as urinary albumin excretion rate of 20-200 μg/min) predicts development of clinical diabetic nephropathy,[9-12] thus enabling screening for patients at high risk.

Treatment with antihypertensive drugs decreases the rate of decline of the glomerular filtration rate in patients with nephropathy by 60-70%[13,14] and mortality seems also to decrease.[15] In patients with microalbuminuria the long term effect of treatment with antihypertensive drugs has not yet been studied, but short term studies (one to four years) consistently show that the degree of albuminuria is lowered.[16,17] The qualitative and quantitative effect with respect to postponement or prevention of diabetic nephropathy must, however, be studied in long term prospective controlled clinical trials.

We know that firstly, identification of patients at high risk of developing diabetic nephropathy is possible by screening for microalbuminuria; secondly, antihypertensive treatment of patients with diabetic nephropathy postpones end stage renal failure; and thirdly, antihypertensive treatment in patients with microalbuminuria considerably lowers the rate of albumin excretion and probably postpones or prevents clinical nephropathy. We therefore carried out a simulation study of the likely long term outcome of a programme of screening and antihypertensive intervention for microalbuminuria in patients with insulin dependent diabetes mellitus. We aimed firstly to estimate the effectiveness in terms of survival and need for kidney transplantation and the incidence of overt diabetic nephropathy, and secondly to estimate the efficiency of a screening programme by looking at all direct costs and savings.

We used the results from previous epidemiological studies of the incidence of diabetic nephropathy, the mortality of patients with and without diabetic nephropathy,[18] and observational data regarding the rate of progression of microalbuminuria. The long term effect of antihypertensive treatment was set at three different levels due to lack of long term experience in patients with microalbuminuria.

Methods

The flow chart in figure 1 shows the different stages from onset of diabetes until death. Each lambda (λ) represents the hazard function for progression or death at each stage adjusted for sex, age, and duration of diabetes. These hazard functions were estimated from

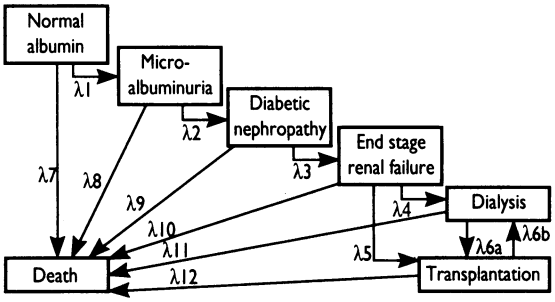

FIG 1—*Flow chart for development of diabetic renal disease used in model. Each lambda (λ1-12) represents transition probability specific for age, gender, and duration of diabetes from one step to next in model*

a Danish cohort of 2890 patients with insulin dependent diabetes diagnosed from 1933 to 1972 and followed up until death, emigration, or 1 January 1984.[18] As screening for microalbuminuria was not possible at the time of the study the hazard functions for development of microalbuminuria (λ1) and progression from microalbuminuria to nephropathy (λ2) were estimated assuming firstly, that all patients developing proteinuria emerge from a phase with microalbuminuria and, secondly, the median annual increase rate in the rate of urinary albumin excretion is 20%. This assumption is compatible with the data from the control group in clinical trials[19] and studies of the natural course of microalbuminuria.[9-12,20]

SCREENING AND TREATMENT PROGRAMME

The analysis was based on a programme over 30 years with annual screening for microalbuminuria beginning five years after onset of diabetes as the prevalence of microalbuminuria before five years is very low.[21] Microalbuminuria was defined as two out of

Institute of Preventive Medicine, Kommunehospitalet, DK-1399 Copenhagen K, Denmark
K Borch-Johnsen, *senior research fellow*

School of Public Health, University of Bielefeld, Germany
H Wenzel, *lecturer*

Unit for Metabolic Medicine, United Medical and Dental School Guy's Hospital, London
G C Viberti, *professor*

Medical Department M, Århus Kommunehospital, University Hospital of Århus, DK-8000 Århus, Denmark
C E Mogensen, *professor*

Correspondence to:
Dr Borch-Johnsen.

BMJ 1993;306:1722-3

three consecutive urine samples showing an excretion rate between 20 and 200 μg/min. Treatment was initiated at the onset of microalbuminuria and consisted of antihypertensive treatment with an angiotensin converting enzyme inhibitor. The impact of treatment was calculated by using three different levels of effect, decreasing the proposed progression rate of 20% in microalbuminuria by 33%, 67%, and 100% (see table I).

ANALYTICAL MODEL

The study was designed as a cost-benefit analysis, with benefits equivalent to saved costs by preventing or postponing development of nephropathy. The impact of the screening programme was estimated by comparing two scenarios: one describing the natural progression of a cohort of about 8000 patients and a second describing the clinical progression of the same cohort with screening and treatment. The simulation of the cohort and the estimation of hazard function for transition from one stage to the next in figure 1 was based on a Markov-Chain model in combination with a second order Monte Carlo technique[22] by using the estimates obtained from the Danish cohort.[18] The model was run by the Institute for Medical Informatics and Biostatistics, Basle, Switzerland.

MORTALITY

Mortality data from the German Department of Statistics were used as reference for calculation of lost years of life.[23] In the patients in whom diabetic nephropathy was prevented by the intervention programme the mortality throughout the years was set to be identical to that of diabetic patients who never developed diabetic nephropathy in the Danish study.

In patients who developed diabetic nephropathy the mortality was estimated by using the Danish data.[18] These data are from a period before the introduction of antihypertensive treatment. Thus the mortality of patients with nephropathy (as evidenced by persistent proteinuria) was overestimated, and the treatment effects in the present study (life expectancy and time to dialysis) were underestimated.

ECONOMIC IMPACT

The economic evaluation was based on all direct costs including screening costs, costs of antihypertensive treatment in the case of microalbuminuria and nephropathy, costs of dialysis, costs of kidney transplantation, and costs of immunosuppressive agents in cases of transplantation (table I). All costs were based on the 1991 prices in Germany as reimbursed by the sickness funds, and the economical analysis was carried out from the point of view of the German sickness fund.

A broader viewpoint would certainly show greater benefits, especially to society. Most of the savings, however, would not occur with the financier who pays most of the costs—the sickness funds—but with the government and employers. Furthermore, indirect costs (for example, loss of working capacity due to dialysis) and indirect savings (for example, increased number of active years of work) are influenced by variable factors such as educational level, rate of unemployment, etc. Costs due to potential side effects of the antihypertensive treatment were not included in the analysis but severe side effects are rare with the antihypertensive treatment suggested here. As the calculations were based only on direct costs and savings the present study underestimates the total savings associated with the screening programme. The number of visits to diabetes centres was assumed not to be affected by the programme as urinary albumin excretion was measured only once a year and thus could be done at a routine consultation.

As the costs (and saved costs) will occur at different points in time discounting of the cash flow was necessary to make the economic consequences of the alternative programmes comparable. The calculations were performed with two different real discount rates: 2·5% and 6% a year, respectively.

All costs and savings are given in deutschmarks (DM) according to the recommendations of the Organisation for Economic Cooperation and Development as the calculations of costs and savings were based on the German sickness fund subsidiaries.

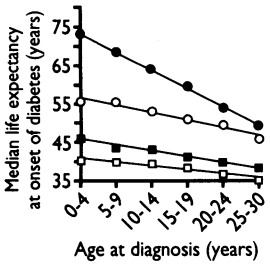

FIG 2—*Median life expectancy at onset of diabetes in patients developing microalbuminuria without intervention (●) and at treatment effect 33% (■) and 67% (○). Life expectancy of general population of Germany shown for comparison (□)*

TABLE I—*Annual costs associated with screening programme for microalbuminuria in patients with insulin dependent diabetes and with treatment of end stage renal failure*

Screening	Cost per patient per year (DM (US$) 1991 prices)	
	Range	Assumption
Cost for screening when result is negative	13 (9)	13 (9)*
Cost for screening when result is positive	13 (9)	13 (9)*
Treatment:		
Cost for additional treatment with angiotensive converting enzyme inhibitor in patients with microalbuminuria	500 (350)	500 (350)
Mean annual cost of dialysis	50-80 000 (35-55 000)	67 500 (47 000)†
Cost of transplantation, first year	20-50 000 (14-35 000)	45 000 (31 000)‡
Cost of immunosuppressive treatment after transplantation	10 000 (7 000)	10 000 (7 000)

*Independent of screening method used as this represents cost for sickness fund.
†Weighted average based on types of dialysis used in Germany 1991.
‡Including immunosuppression in first year of treatment.

TABLE II—*Estimated effects of antihypertensive treatment in patients with microalbuminuria*

Strategy	Efficacy of antihypertensive treatment	Annual rate of increase of urinary albumin excretion	Duration from microalbuminuria to nephropathy	Median age at onset	
				Nephropathy	End stage renal failure*
No screening	0	20%	13 Years	46 Years	52 Years
Screening	33%	13·4%	19 Years	52 Years	58 Years
Screening	67%	6·6%	37 Years	70 Years	76 Years
Screening	100%	0%	—	—	—

*Progression rate from clinical nephropathy to end stage renal failure was assumed to be independent of screening and intervention programmes and was set to be identical with progression in group not screened and thus with situation before introduction of antihypertensive treatment.

Results

Incidence of nephropathy and end stage renal failure—Table II shows the estimated effect of antihypertensive treatment on the rate of increase of urinary albumin excretion and on the duration from onset of microalbuminuria to nephropathy. Onset of nephropathy would be delayed by six years, assuming an effect of 33%, while a 67% effect would delay onset by 24 years. Because of the delayed onset of nephropathy the patients would be older when developing nephropathy. Thus some of the patients would die from other natural causes or diseases before entering end stage renal failure. The need for kidney transplantation or dialysis would therefore decrease by 21% and 63% assuming an effect of treatment of 33% and 67%, respectively.

Mortality—Figure 2 shows the median life expectancy for the subgroup of patients developing microalbuminuria. The median life expectancy increased by four to 14 years, and the effect was greatest in patients who developed diabetes during childhood. As only one out of three patients would develop diabetic nephropathy the increase in median life expectancy was lower when calculated on the entire cohort (two to five years). The increase in life expectancy was 50% higher in patients developing diabetes before the age of 5 years than in patients developing diabetes after the age of 25 years.

Costs and savings—Figure 3 shows the relation between real discount rate, treatment efficacy, and net savings. Each line in the figure represents a constant level of net savings per patient over the entire life time of the patient. The line denoted 0 represents the point of balance between costs and savings. With a real

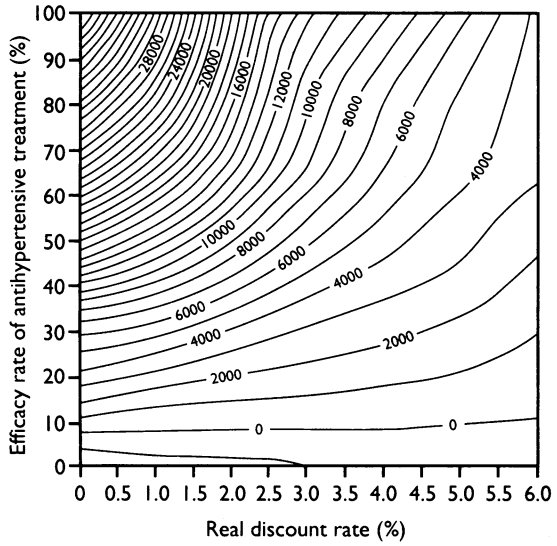

FIG 3—*Net savings (in DM) by real discount rate (%) and efficacy of antihypertensive treatment (% reduction in annual increase of urinary albumin excretion rate). Each solid line represents constant level of savings per patient. Line denoted 0 represents line with balance between costs and savings*

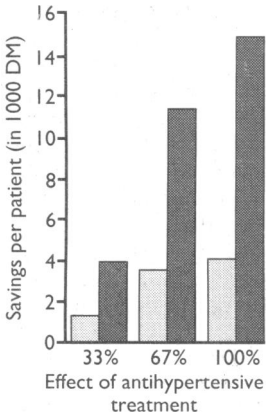

FIG 4—*Costs saved per patient (in DM 1000) assuming three different treatment effects (33%, 67%, and 100%) and two different real discount rates (2·5% closed bars, 6% open bars)*

discount rate of 6% an effect of 11% of the antihypertensive treatment would be needed to balance costs and savings. With a real discount rate of 2·5% an 8% effect would be needed. Thus, reducing the annual rate of increase of albuminuria from 20 to 18% would balance costs and savings. Figure 4 shows the net savings for two different levels of treatment effect and two different discount rates. The savings per patient would range from DM 1500 ($800) (real discount rate of 6%, effect of treatment of 33%) and DM 11 000 ($7700) (real discount rate of 2·5%, effect of treatment of 67%).

Discussion

Annual screening for microalbuminuria in all patients with insulin dependent diabetes over the age of 12 years who have had diabetes for more than five years has been recommended by the World Health Organisation and International Diabetes Foundation[24] and by the 1992 WHO study group on prevention of diabetes (WHO technical report in preparation). Both publications also recommend programmes of treatment that include strict metabolic control and early antihypertensive treatment (blood pressure $\geq$140 mm Hg systolic or $\geq$90 mm Hg diastolic) of patients with microalbuminuria. These recommendations were based on intervention studies that showed that the rate of progression of diabetic nephropathy can be decreased considerably (60-70%) by treatment with antihypertensive drugs[13,14] and that strict metabolic control[19] and antihypertensive treatment seems to reduce the progression of microalbuminuria,[16,17] although long term data are still lacking.

Initiating a screening programme is, however, both expensive and time consuming. Furthermore, screening programmes should be initiated only if they benefit patients (survival or quality of life) or society (health care costs). It is necessary to decide on priorities between programmes, and setting different programmes in order of priority raises the need for evaluation of efficiency for each programme.

In accordance with a recent American study[25] the present analysis showed that an intervention programme which includes screening for microalbuminuria and early treatment with antihypertensive drugs would be neutral with respect to costs and savings if antihypertensive treatment could reduce the annual increase in the rate of albumin excretion by 8 to 10% (from 20 to 18% a year). The programme would offer considerable life saving and a reduced incidence of end stage renal failure at treatment effects of 33% and 67%.

In the present design screening for albuminuria was performed on an annual basis. If one urine sample screened showed microalbuminuria, testing should be repeated twice to confirm the diagnosis.[26] Annual screening was chosen on the basis of a likely increase in the rate of urinary albumin excretion of 20% a year and a day to day variability between individual patients of 40%.[27] More frequent testing is unnecessary as the patients are likely to remain in the lowest range of microalbuminuria (20-60μg/min) for a period of six years.[28]

The intervention used in this programme was antihypertensive treatment, which has proved effective in patients with diabetic nephropathy. Two different studies have shown that the rate of decline in the rate of glomerular filtration is reduced by about 60/70% by antihypertensive drugs.[13,14] In concordance with this Mathiesen *et al* found that the eight year survival of patients with nephropathy increased from 49% to 87% after the introduction of antihypertensive drugs.[15] In patients with microalbuminuria it is still unknown whether antihypertensive drugs affect the long term prognosis (that is, risk of developing end stage renal failure and mortality). Microalbuminuria can be lowered (and in several cases normalised) by antihypertensive drugs, and several studies (table III) have consistently shown that antihypertensive drugs reduce microalbuminuria in patients with insulin dependent diabetes. Most of these studies were small and of short duration (one to two years). In the only

TABLE III—*Trials of antihypertensive treatment in young patients with insulin dependent diabetes mellitus and microalbuminuria but no hypertension*

Study	Randomised with parallel controls	Double blind	Treatment	No of patients and duration of treatment	Outcome measures		
					Microalbuminuria	Development of proteinuria	Glomerular filtration rate
Christensen *et al* 1987[33]	No*	No	β Blockers and diuretics	6, 5 years	Reduced	Not seen	Stable
Marre *et al* 1988[16]	Yes	Yes	Angiotensin converting enzyme inhibitor	20, 1 year	Reduced	Prevention†	Stable on angiotensin converting enzyme inhibitor‡
Melbourne Diabetic Nephropathy study Group 1991[34]	Yes	No	Angiotensin converting enzyme inhibitor *v* calcium blocker	43, 1 year	Reduced	Not seen	Stable
Mathiesen *et al* 1991[17]	Yes	No	Angiotensin converting enzyme inhibitor and thiazide	44, 4 years	Reduced	Prevented by angiotensin converting enzyme inhibitor	Stable (angiotensin converting enzyme inhibitor) Fall (placebo)
European Microalbinuria Captopril Study Group 1992[29]	Yes	Yes	Angiotensin converting enzyme inhibitor	92, 2 years	Reduced by angiotensin converting enzyme inhibitor	Prevented by angiotensin converting enzyme inhibitor	Stable
Hallab *et al* 1993[35]	Yes	Yes	Angiotensin converting enzyme inhibitor *v* thiazide	21, 1 year	Reduced by angiotensin converting enzyme inhibitor	Not seen	Stable

*Self controlled. †Non-significant tendency for prevention by angiotensin converting enzyme inhibitor. ‡Non-insignificant tendency to fall on placeo.

long term study (four years' duration) a considerable number of patients in the control group developed proteinuria and an associated decline in the glomerular filtration rate whereas this was not seen in the group treated with angiotensin converting enzyme inhibitors.[17] This protective effect of treatment with angiotensin converting enzyme inhibitors was recently confirmed in a multicentre controlled clinical trial.[29] In patients with an albumin excretion rate between 20 and 200 μg/min, four out of 44 actively treated patients progressed to clinical nephropathy whereas this was the case in 12 out of 44 controls. The annual rate of increase of the albumin excretion rate was reduced from 18·3% to 2·1% by captopril. As development of proteinuria is consistently associated with a fall in glomerular filtration rate the reduction or stabilisation in microalbuminuria will probably preserve renal function.[28 30] Antihypertensive treatment in microalbuminuria is therefore likely to postpone considerably the development of proteinuria and to postpone or prevent development of end stage renal failure.

In patients with diabetic nephropathy the clinical effect of antihypertensive drugs seems to be a 60-70% reduction in the rate of decline of the glomecular filtration rate. In patients with microalbuminuria the precise effect cannot be estimated on the basis of the present studies, but in the study by Mathiesen *et al* 30% of the control group developed overt nephropathy compared to none in the actively treated group,[17] and in the multicentre trial the control group was three times more likely to develop overt nephropathy than the actively treated group (30% versus 10%).[29]

The risks of developing nephropathy and mortality rates were calculated from the previously published Danish cohort study of 2890 patients with insulin dependent diabetes.[18] Information regarding microalbuminuria was not available as the study covered a period when tests for microalbuminuria had not yet been developed. Thus the observed mortality for patients without nephropathy in that study included patients with normal albuminuria as well as microalbuminuria. More recent studies of patients with non-insulin dependent diabetes[31] and subjects without diabetes[32] show a clear excess mortality in patients with microalbuminuria, predominantly due to cardiovascular disease. Whether this is also the case in patients with insulin dependent diabetes is unknown. If there is an excess mortality in patients with insulin dependent diabetes and microalbuminuria, irrespective of intervention, our analysis would overestimate the true effect on survival. The costs and the benefits are, however, not affected by this as we have not included the increased life expectancy in our economic analysis.

In conclusion we have shown that establishment of screening programmes for microalbuminuria for all patients with insulin dependent diabetes would be economically neutral at a treatment effect of 10%. With an estimated treatment effect of 33% to 67% the screening and intervention programme would lead to substantial increases in life expectancy and reduction in the incidence of end stage renal failure. We therefore recommend a screening programme for all patients with insulin dependent diabetes, including annual measurement of urinary albumin excretion rate. Based on the data from intervention studies we would also recommend that very early antihypertensive treatment be carefully considered. Screening programmes should be established with the purpose of monitoring the effects and the efficiency of the programme.

The statistical analysis was performed with assistance from Dr Bergemann and Mr Mast, Institute for Medical Informatics and Biostatistics, Basle.

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(Accepted 15 April 1993)