Journal of Internal Medicine 2000; **248**: 333–341

Prognosis of persons with type 1 diabetes on intensified insulin therapy in relation to nephropathy

I. MÜHLHAUSER[1,2], P. T. SAWICKI[1], M. BLANK[1], H. OVERMANN[1], R. BENDER[1,3] & M. BERGER[1]

From the [1]Department of Nutrition and Metabolic Diseases (WHO-Collaborating Centre for Diabetes), University of Düsseldorf, Düsseldorf; [2]Department of Health Science and Education, University of Hamburg, Hamburg; and [3]Institute of Epidemiology and Medical Statistics, School of Public Health, University of Bielefeld, Bielefeld, Germany

Abstract. Mühlhauser I, Sawicki PT, Blank M, Overmann H, Bender R, Berger M (University of Düsseldorf, Düsseldorf; University of Hamburg, Hamburg; and University of Bielefeld, Bielefeld, Germany). Prognosis of persons with type 1 diabetes on intensified insulin therapy in relation to nephropathy. *J Intern Med* 2000; **248:** 333–341.

Objective. To study the prognosis of persons with type 1 diabetes in relation to the degree of nephropathy at initiation of intensified insulin therapy.

Design. Ten years follow-up of a cohort of 3674 patients who had participated in a 5-day group treatment and teaching programme for intensification of insulin therapy between September 1978 and December 1994.

Setting. Ten diabetes centres in Germany.

Subjects. A total of 3674 patients (insulin treatment before age 31), age at baseline 27 ± 10 years, with a diabetes duration of 11 ± 9 years. Patients were divided into three groups according to baseline renal parameters (group I, normal proteinuria, $n = 1829$; group II, microproteinuria, $n = 1257$; group III, at least macroproteinuria, $n = 367$).

Main outcome measures. End-stage diabetic complications (blindness, amputations, renal replacement therapy), standardized mortality ratios (SMR) and causes of death.

Results. Outcome measures were documented for 97% of patients; 251 (7%) had died. During follow-up, 1% of patients in group I, 4% in group II, and 47% in group III had at least one end-stage diabetic complication. SMR for men: nephropathy group I, 2.2 (95% CI = 1.5–3); group II, 3.2 (2.3–4.3); group III, 11.5 (8.8–14.7). SMR for women: group I, 2.5 (1.5–3.8); group II, 3.5 (2.2–5.3), group III, 27 (19.8–35.9). Causes of death for men and women combined: group I (total 58 deaths) – cardiovascular, 21 (36%); hypoglycaemia, 1; ketoacidosis, 3; violent deaths, 17 (29%); others, 16; group II (66 deaths) – cardiovascular, 25 (38%); hypoglycaemia, 2; ketoacidosis, 2; violent deaths, 14 (21%); others, 23; group III (114 deaths) – cardiovascular, 68 (60%); hypoglycaemia, 2; ketoacidosis, 5; infections, 15 (13%); violent deaths, 5 (4%); others, 19.

Conclusions. Patients with microproteinuria have only a slightly worse prognosis than patients with normal proteinuria during the first 10 years after initiation of intensified insulin therapy. Excess mortality amongst patients who started intensified insulin therapy is mainly due to those with manifest clinical nephropathy.

Keywords: causes of death, intensified insulin therapy, late complications, mortality, prognosis, type 1 diabetes.

Introduction

Life expectancy of type 1 diabetic patients is decreased in comparison with the general population. The excess mortality is mainly due to cardiac death of patients who develop diabetic nephropathy [1–4]. The care of patients with type 1 diabetes has changed during the last 20 years. The introduction of intensified insulin therapy was associated with significant improvements in glycaemic control, but also increases in the risk of severe hypoglycaemia [5]. Thus, prognosis and causes of death might have changed during the last years.

Available cohort studies on the prognosis of type 1

diabetes are limited by the failure to distinguish the types of diabetes, small and selected groups of patients, high attrition or incomplete description of patient groups [6–13]. In addition, previous studies have been performed under the conditions of conventional insulin therapy [2, 3, 14].

Since 1978, the standard therapy for persons with type 1 diabetes at the diabetes centre of the university hospital of Düsseldorf has included participation of all patients in a structured 5-day in-patient group treatment and teaching programme for intensification of insulin therapy. Efficacy and safety of this intervention have been documented in various national and international controlled studies, including one randomized controlled trial [15]. Effective translation of the programme to non-specialized general hospitals has been documented [16]. At present, the programme has been implemented in more than 120 hospitals in Germany [17]. In a recent cross-sectional population based survey in North-Rhine, Germany, it was shown that ≈ 80% of adult type 1 diabetic patients are on intensified insulin therapy, and about two-thirds of patients have participated in such a structured group treatment and teaching programme for intensification of insulin therapy [18].

In the present study, a cohort of 3674 persons with type 1 diabetes who initially had all participated in the same structured treatment and teaching programme for intensification of insulin therapy were followed over a mean period of 10 years. The aim of the present analyses was to study the prognosis of these patients in relation to the baseline degree of nephropathy.

Patients and methods

Study cohort

This included all 3674 persons with type 1 diabetes (ketosis-prone) who were treated with insulin before the age of 31 and who participated in the 5-day treatment and teaching programme for intensification of insulin therapy at the diabetes centre of the Düsseldorf university hospital between September 1978 and December 1994 or at one of nine cooperating general hospitals (n = 590) during 1985–86 [16]. The intervention programme has been described in detail [15–20]. Exclusion criteria were pancreoprive and gestational diabetes. Ascertainment included comparison of various patient registries, i.e. hospital and diabetes ward admission registries, education programme participation registries, and archives of patient discharge reports.

Data files

Procedures and methods used have been described repeatedly in previous evaluation studies [16, 18–20]. Baseline data were drawn from patient records – retrieved for all but 104 patients – and patient discharge reports. In cases of missing data, files were supplemented whenever possible by screening outpatient records or research protocols of previous clinical evaluation studies. Informed consent of patients to use their data for clinical research was obtained during their hospital stay.

The initial medical examination includes a standardized general and diabetes-specific case history, physical examination, and clinical chemistry analysis using routine laboratory methods. The general and diabetes-specific baseline documentation sheets were extended and improved during the recruitment period, e.g. with respect to the assessment of smoking history or socioeconomic status. However, in order to obtain complete data of as many patients of the cohort as possible, for various parameters, the less optimal assessment method had to be used. In addition, some laboratory methods had changed during the recruitment period. Thus, individual values have been converted to the most recent method or the method used in the majority of patients applying conversion equations from the respective laboratories.

Social status classification

The social class score was an additive variable of the highest educational level achieved and/or the present or last employment level, resulting in a score ranging from 0 to 16, higher scores indicating lower levels of social class. For descriptive purposes, the cohort was divided into three levels of social status: high (scores 0–6), middle (scores 7–8) and low (scores 9–16).

Glycosylated haemoglobin

This was measured using the thiobarbiturate method from 1978 to June 1987 and thereafter

using the HPLC method. In the 590 patients from the nine general hospitals, the microcolumn method was used [16]. Values were converted to the Diamat® HPLC method (reference range 4.3–6.1%) as described previously [19]. This procedure was cross-checked by using so-called relative HbA1c values as described by Müller *et al.* [17]. The relative HbA1c is the calculated ratio between the measured glycosylated haemoglobin value and the respective mean normal value. Results were almost identical for both conversion procedures. Severe hypoglycaemia was defined as a hypoglycaemia necessitating treatment with glucagon or glucose injection.

Foot complications

Examination of the feet included palpation of pulses and screening for sensation loss using the Rydel–Seiffer tuning fork as described by Liniger *et al.* [21]. Patients were grouped according to (neuropathic) foot complications: (i) vibration sensation score at the first metatarsal $\geq 6/8$ bilaterally, no ulcer, no amputation; (ii) vibration sensation score $< 6/8$, no ulcer, no amputation; (iii) acute or healed ulcer or amputation.

Nephropathy

Protein concentration was measured by the laser turbidimetric method [22] in a 24-h urine sample. In cases where a 24-h urine sample was not provided, a first morning urine sample was used. Patients were grouped according to renal parameters [18–20]: (i) normal proteinuria: proteinuria ≤ 50 mg L^{-1} and serum creatinine ≤ 133 μmol L^{-1} – corresponding to an albuminuria excretion of < 20 mg day^{-1} [22]; (ii) microproteinuria: proteinuria 51–499 mg L^{-1} and serum creatinine ≤ 133 μmol L^{-1} – corresponding to microalbuminuria of 20–300 mg day^{-1} [22]; (iii) macroproteinuria: proteinuria ≥ 500 mg L^{-1} and serum creatinine ≤ 133 μmol L^{-1} – corresponding to macroalbuminuria of more than 300 mg day^{-1} [22]; (iv) increased serum creatinine: serum creatinine > 133 μmol L^{-1}; (v) renal replacement therapy.

Hypertension

Blood pressure was measured according to WHO recommendations, including the use of a large cuff in patients with increased upper arm circumferences. Hypertension was inferred if hypertension was documented as a diagnosis or if antihypertensive medication was prescribed.

Smoking

Patients were classified as current smokers or current non-smokers.

Alcohol consumption

Patients were classified according to self-reported consumption of alcoholic beverages as never, occasionally or regularly drinking.

Macrovascular complications

If one or more of the following clinically manifest macrovascular complications were documented the patient was considered to have 'any macrovascular complications': history of angina pectoris, myocardial infarction, coronary bypass surgery or angioplasty, cerebral infarction, claudicatio intermittens, peripheral bypass operation or angioplasty.

Retinopathy

Until 1987, all subjects were seen by an ophthalmologist. Thereafter, non-mydriatic photography was performed as described elsewhere [18, 19]. In all subjects, a macula-centred photograph was obtained of one eye. If there was any hint of retinopathy on this first photograph, a picture of the other retina was taken as well. In cases where the pupils did not sufficiently dilate, whenever possible, pharmacological mydriasis was induced with 1% tropicamide eye drops. Patients with significant lesions were additionally seen by an ophthalmologist. All available eye examination results were used in order to rate the degree of retinopathy for each patient. In cases where the degree of retinopathy differed between both eyes, and in cases where the findings differed between methods, the higher degree of retinopathy was used. Patients were grouped according to the degree of retinopathy: (i) no retinopathy; (ii) non-proliferative retinopathy without macular involvement, no history of laser therapy; (iii) advanced: preproliferative or prolifera-

tive retinopathy, macula involvement, macula oedema, history of laser therapy, advanced diabetic eye disease, blindness of one eye due to diabetes; (iv) blindness due to diabetes defined as legal blindness or best visual acuity ≤ 0.1.

Follow-up

Between August 1996 and September 1998, all patients were sent a letter and asked to report on blindness, amputations and renal replacement therapy and to state the date (month/year) when this happened using a structured documentation sheet. In cases where there were missing data, patients were contacted again by phone or mail. Vital status was ascertained from municipal residents' registries and personal contact of patients, relatives and family physicians. For patients who had died, all available sources of information were used to obtain data on end-stage complications, such as hospital and outpatient records, necropsy reports, death certificates, and contact with family physicians and relatives.

The study was approved by the Ethical Committee of the University of Düsseldorf.

Causes of death were ascertained by using various sources of information, i.e. death certificates, necropsy reports including medicolegal necropsy, hospital records and physician records, and by contacting relatives and family physicians on circumstances of death when deemed necessary. A classification of all reported events of death was made by a clinical review committee of two to three diabetologists – one of them not involved in the study – a medical student and a paramedical clinical researcher based on all available information [23]. The review committee determined a leading cause of death based upon the following list of 11 possible causes according to the International Classification of Diseases (ICD9):

1 Cardiac death (ICD9: 410 −428, 798), including acute myocardial infarction (death within 30 days after a critical ischaemic myocardial event, and/or acute rupture of myocardium at any time), heart failure (death due to congestive heart failure, without an acute ischaemic event during the last 30 days), sudden death (no potentially fatal or critical event or disease present at least 1 h before death), or fatal dysrhythmia at any time and unexpected death (no critical event or disease present at least 24 h before death).

2 Cerebrovascular death (ICD9: 430–434), including ischaemic cerebral event and intracranial haemorrhagic event.

3 Pulmonary death (ICD9: 453, 490–496, 500–508), including pulmonary embolism, fatal obstructive and other pulmonary disease, but excluding malignoma and pulmonary infections.

4 Gastrointestinal death (ICD9: 530–537, 550–553, 560, 571, 577, 578), including pancreatitis, liver cirrhosis, intestinal perforation and gastrointestinal bleeding.

5 Renal death (ICD9: 580–589), including death due to uraemia of any cause including denial or cessation of dialysis treatment.

6 Diabetes treatment-associated death (ICD9: 271 276), including hypoglycaemia, ketoacidosis, hyperosmolar coma and death within 4 weeks after pancreas transplantation.

7 Surgery-associated death (ICD9: E870–876), including in-hospital death during or after a maximum of 1 week after surgery for a non-critical disease.

8 Infection caused death (ICD9: 001–0139, 320–326, 390–392, 422, 480–487): any septicaemia or fatal infection, including diabetic foot syndrome, tuberculosis, pneumonia, meningitis, myocarditis and other infectious diseases.

9 Neoplasma (ICD9: 140–239): any fatal malignant disease.

10 Violent death (ICD9: E800–876, E880–999), including fatal accidents, suicide, violence and intoxication.

11 Unknown cause of death (ICD9: 799).

Statistical analysis

Standardized mortality ratios (SMRs) were calculated by using the male and female population of North-Rhine Westphalia as reference populations. The population and mortality data of North-Rhine Westphalia on a 1-year basis for age and calendar year were made available from the State Office for Data Processing and Statistics of North-Rhine Westphalia, Düsseldorf. Significance tests and 95% confidence intervals (CIs) for the SMRs were calculated by using Byar's approximation to the exact Poisson test and the exact Poisson limits [24].

Results

Vital status could be documented for 3570 (97%) of the 3674 patients, and data on blindness, amputations and renal replacement therapy for 3549 (97%), 3550 (97%) and 3554 (97%) patients, respectively. For 104 (3%) patients, vital status could not be reliably assessed: 44 patients could not be traced and 60 patients who were registered at the local communities could not be contacted. These 104 patients who were lost to follow-up had a shorter diabetes duration, less severe diabetic complications, slightly higher HbA1c levels, fewer had a history of severe hypoglycaemia, and more of them were smokers.

Baseline data of the patients according to the nephropathy group at baseline are summarized in Table 1; 117 of the 3570 patients could not be included because of missing data. Of the 367 patients with clinical nephropathy, 220 had macroproteinuria with normal serum creatinine levels, 123 had increased serum creatinine levels, and 24 were on renal replacement therapy. The follow-up period (time up to re-examination or death) for the 3570 patients was 10.3 ± 3.4 years. During this period 251 (7%) patients died; 229 (6.4%) had at least one end-stage diabetic complication: 45 (1.3%) became blind, 71 (2%) had a total of 104 amputations, and 162 (4.6%) started renal replacement therapy. At follow-up, a cumulative 67 (1.9%) patients were blind, 91 (2.5%) had a total of 133 amputations, and 186 (5.2%) had renal replacement therapy. End-stage diabetic complications in relation to the baseline nephropathy groups for the 3453 patients with complete data are shown in Table 2.

Table 1 Baseline characteristics according to nephropathy group

Characteristic[a]	Normal proteinuria (n = 1829)	Microproteinuria (n = 1257)	At least macroproteinuria (n = 367)
Women	872 (47.7%)	694 (55.2%)	164 (44.7%)
Age (years)	26.1 ± 8.7	28.2 ± 10	33.5 ± 9.7
Diabetes duration (years)	8.4 ± 8.3	11.4 ± 9.9	19.7 ± 8.5
Social status			
Low	531 (32.2%)	342 (30.7%)	135 (40.1%)
Middle	332 (20.1%)	228 (20.5%)	64 (19%)
High	785 (47.6%)	543 (48.8%)	138 (40.9%)
Smokers	736 (41.5%)	513 (42.2%)	175 (48.9%)
Body mass index (kg m^{-2})	22.4 ± 3.0	22.8 ± 3.2	23.3 ± 3.3
HbA1c (%)	8.1 ± 1.9	8.3 ± 1.9	8.4 ± 1.7
History of severe hypoglycaemia	393 (21.7%)	330 (26.5%)	121 (34.2%)
Serum cholesterol (mmol L^{-1})	5.16 ± 1.14	5.44 ± 1.3	7.0 ± 2.0
HDL cholesterol (mmol L^{-1})	1.39 ± 0.42	1.41 ± 0.43	1.34 ± 0.43
Blood pressure (mmHg)	117 ± 13/74 ± 9	119 ± 13/75 ± 9	137 ± 20/84 ± 11
Hypertension	44 (2.4%)	93 (7.4%)	214 (58.3%)
Antihypertensive medication	30 (1.6%)	70 (5.6%)	193 (52.3%)
Retinopathy group			
None	1474 (80.6%)	805 (64.1%)	76 (20.8%)
Non-proliferative	292 (16.0%)	303 (24.1%)	85 (23.2%)
Advanced	62 (3.4%)	143 (11.4%)	188 (51.4%)
Blindness	1 (0.05%)	4 (0.3%)	17 (4.6%)
Amputations	2 (0.1%)	4 (0.3%)	11 (3%)
Foot complications group			
None	1662 (90.9%)	1032 (82.1%)	157 (42.8%)
Neuropathy	162 (8.9%)	209 (16.6%)	187 (51.0%)
Ulcer or amputation	5 (0.3%)	16 (1.3%)	23 (6.3%)
Macrovascular complications	21 (1.1%)	41 (3.3%)	57 (15.5%)

[a]For definition of variables, see 'Methods' section.
Numbers may not add up to 3453 because of missing data. Percentages relate to the respective number of patients with complete data (not shown).

Table 2 End-stage diabetic complications during 10 years of follow-up according to nephropathy group at initiation of intensified insulin therapy

	Normal proteinuria (n = 1829)	Microproteinuria (n = 1257)	At least macroproteinuria (n = 367)
At least one end-stage diabetic complication	20 (1.1%) (n = 1820)	49 (3.9%) (n = 1246)	152 (46.9%) (n = 324)
Blindness[a]	8 (0.4%) (n = 1820)	15 (1.2%) (n = 1246)	20 (5.8%) (n = 344)
Amputations[b]	10 (0.5%) (n = 1822)	21 (1.7%) (n = 1250)	38 (10.5%) (n = 361)
Renal replacement therapy[c]	10 (0.5%) (n = 1822)	19 (1.5%) (n = 1250)	127 (37.2%) (n = 341)

[a]For patients with follow-up data who were not blind at baseline.
[b]For patients with follow-up data with or without amputations at baseline.
[c]For patients with follow-up data who were not on renal replacement therapy at baseline.

Causes of death for men and women combined are summarized in Table 3. In group I, 3.2% patients had died; in 21 (36%) patients, cause of death was cardiovascular, while 17 (29%) had violent deaths. In group II, 5.3% patients had died: cardiovascular, 25 (38%); violent deaths, 14 (21%). In group III, 31.1% patient died: cardiovascular, 68 (60%); infections, 15 (13%); violent deaths, 5 (4%).

The SMR for women (n = 1794, 103 observed cases of death, expected 17 cases of death) was 5.7 (95% CI = 4.6–6.9), and for men (n = 1776, 148 observed cases of death, expected 37 cases of death) was 3.9 (3.3–4.6). SMRs according to nephropathy group at initiation of intensified insulin therapy are shown in Table 4.

Discussion

The present study shows that amongst patients with type 1 diabetes who start intensified insulin therapy during the first 10 years, the prognosis of patients with microalbuminuria is only slightly worse when compared with those with normoalbuminuria, with SMRs between 2.2 and 3.5, whereas patients with overt nephropathy have a substantially worse prognosis, with SMRs of 27 for women and 11.5 for men. Over the 10-year observation period, 1% of patients with normoalbuminuria, 4% of those with microalbuminuria, but 47% of those with overt nephropathy at baseline suffered at least one end-stage diabetic complication, i.e. blindness, amputation or renal failure. Up to now, there are no other studies available that have followed a sufficiently large number of subjects on intensified insulin therapy for a period long enough to analyse end-stage complications and standardized mortality in relation to baseline nephropathy.

Rossing *et al.* [3] studied predictors of mortality in

Table 3 Death and causes of death during follow-up according to nephropathy group at initiation of intensified insulin therapy

	Normal proteinuria (n = 1829)	Microproteinuria (n = 1257)	At least macroproteinuria (n = 367)
Death	58 (3.2%)	66 (5.3%)	114 (31.1%)
Causes of death			
Cardiac death	19	24	51
Cerebrovascular death	2	1	17
Violent death	17	14	5
Diabetes treatment-associated death	4	4	10
Infection-caused death	3	6	15
Surgery-associated death	2	3	2
Renal death – uraemia	1	0	3
Malignoma	5	6	4
Other causes	0	3	1
Unknown cause of death	5	5	6

Table 4 Standardized mortality ratios (SMRs) in relation to nephropathy at baseline

	Nephropathy group		
	Normal proteinuria	Microproteinuria	At least macroproteinuria
Women			
SMR	2.5	3.5	27.0
95% CI	1.5–3.8	2.2–5.3	19.8–35.9
	(n = 872)	(n = 694)	(n = 164)
Men			
SMR	2.2	3.2	11.5
95% CI	1.5–3	2.3–4.3	8.8–14.7
	(n = 957)	(n = 563)	(n = 203)

conventionally treated patients in relation to baseline nephropathy at a tertiary referral centre in Denmark. Over a period of 9.2 years, from 1984 to 1994, they followed 939 adults who were aged 40 or under at the onset of type 1 diabetes and who had a diabetes duration of at least 5 years. During follow-up, 15% of the patients with normoalbuminuria, 25% of those with microalbuminuria and 44% of those with diabetic nephropathy died. In the present study, over a period of 10 years, 3% of patients with normoalbuminuria, 5% of those with microalbuminuria and 31% of those with overt nephropathy died. When interpreting the differences between the Danish study and the present study, various differences in study populations and assessment methods have to be considered. Patients in the Danish were $\approx$ 10 years older and had had diabetes for $\approx$ 10 years longer; they had somewhat higher HbA1c levels ($\approx$ 9%) and more patients were smokers ($\approx$ 60%), whereas a comparable percentage (52%) of patients with overt nephropathy were given antihypertensive drug therapy.

Several other studies have examined SMRs in conventionally treated patients with type 1 diabetes mellitus. However, comparison of the various cohorts is hampered by substantial differences in case mix. In addition, SMRs depend on changing life expectancies of the respective background populations. In the present study, SMRs were still 2.2–2.5 even for patients who had normal albuminuria at initiation of intensified insulin therapy.

Cardiovascular disease was the underlying cause of death in 36–38% of patients with normal and microalbuminuria, but in 60% of patients with overt nephropathy. In the Danish study by Rossing *et al.* [3], cardiovascular disease was a major cause of death in 34–40% of patients in all three groups, whereas end-stage renal disease was the cause of death in 35% of patients who had overt nephropathy at baseline. In contrast to the Danish study, violent death was more frequent in the present study amongst patients with normal or microalbuminuria, whereas end-stage renal disease was a rare cause of death even in patients with overt nephropathy. Variance in patient subgroup characteristics, definition and ascertainment of causes of death might explain most of these differences between the two studies.

The present study has several limitations which should be taken into account when interpreting the results. The study cohort is centre- rather than population-based. In comparison to the general population of adult persons with type 1 diabetes of the respective geographical area of North-Rhine, the adult portion of the study cohort ($>$ 18 years old) is $\approx$ 7 years younger and diabetes duration is $\approx$ 7 years shorter, whereas baseline prevalences of end-stage diabetic complications are comparable [18]. Only a single baseline assessment was performed. For the diagnosis of nephropathy, only one measurement, rather than repeated measurements, of proteinuria was available. Thus, some misclassification of patients to the various nephropathy groups is likely. In addition, duration of microproteinuria or overt nephropathy before initiation of intensified insulin therapy are not known for subjects of the present study. Since, after the initial intervention, patients were primarily treated by their family physicians, systematic follow-up measurements of blood pressure, cholesterol levels or HbA1c levels are not available for the total patient group. However, such data are available for representative subgroups of the present cohort, including a study population of 636 patients who were repeatedly re-

examined for up to 6 years of follow-up. In these studies, it has been shown that glycosylated haemoglobin values improved by about 1% after participation of the patients in the treatment and teaching programme [15, 16, 19, 20]; during follow-up, insulin therapy was further intensified as reflected by the number of daily insulin injections [16]. On the other hand, blood pressure control was poor [19, 20, 25] and ACE inhibitors were not used for treatment of microalbuminuria in type 1 diabetic patients without hypertension according to a population-based study carried out between 1994 and 1996 in the reference region of North-Rhine [18]. Finally, due to event rates being too small amongst the nephropathy subgroups, the study refrained from analysing predictors of outcome within groups taking account of differences in patient characteristics between the three nephropathy groups.

In conclusion, the main message of the present study is that patients with microalbuminuria do not face a substantially worse prognosis than that faced by patients with normal microalbuminuria during the first 10 years after initiation of intensified insulin therapy.

Acknowledgements

This study has been funded by a grant of the Public Health Research Group of North-Rhine Westphalia (project II-1, no. 701 400043). We thank the Peter-Klöckner Stiftung (Duisburg) for generous financial support (grants to MB).

References

1 Andersen AR, Christiansen JS, Andersen JK, Kreiner S, Deckert T. Diabetic nephropathy in Type 1 diabetes: an epidemiological study. *Diabetologia* 1993; **25**: 496–501.

2 Borch-Johnsen K, Andersen PK, Deckert T. The effect of proteinuria on relative mortality in Type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1985; **28**: 590–96.

3 Rossing P, Hougaard P, Borch-Johnsen K, Parving HH. Predictors of mortality in insulin dependent diabetes: 10 year observational follow up study. *Br Med J* 1996; **313**: 779–84.

4 Tuomilehto J, Borch-Johnson K, Molarius A *et al.* Incidence of cardiovscular disease in Type 1 (insulin-dependent) diabetic subjects with and without diabetic nephropathy in Finland. *Diabetologia* 1998; **41**: 784–90.

5 The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the diabetes control and complications trial. *Diabetes* 1997; **46**: 271–86.

6 Garcia MJ, McNamara PM, Gordon T, Kannell WB. Morbidity and mortality in diabetics in the Framingham population. *Diabetes* 1974; **23**: 105–11.

7 Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirtyone. *Diabetologia* 1978; **14**: 371–77.

8 Dorman JS, Laporte RE, Kuller LH *et al.* The Pittsburgh insulin-dependent diabetes mellitus (IDDM) morbidity and mortality study. *Diabetes* 1984; **33**: 271–76.

9 Diabetes Epidemiology Research International Mortality Study Group. International evaluation of cause-specific mortality and IDDM. *Diabetes Care* 1991; **14**: 55–60.

10 Lehnsten K, Becker B, Willich SN, Rjasanowski I, Michaelis D, Fischer U. Mortalität bei insulinpflichtigem Diabetes mellitus in Abhängigkeit von Geschlecht, Manifestationsalter und Diabetesdauer. *Diab Stoffw* 1995; **4**: 297–303.

11 Klein R, Klein BEK, Moss SE, Cruickshanks KJ, Brazy PC. The 10-year incidence of renal insufficiency in people with Type 1 diabetes. *Diabetes Care* 1999; **22**: 743–51.

12 Moss SE, Klein R, Klein BEK. Ten-year incidence of visual loss in a diabetic population. *Ophthalmology* 1994; **101**: 1061–70.

13 Moss SE, Klein R, Klein BEK. The 14-year incidence of lower-extremity amputations in a diabetic population. *Diabetes Care* 1999; **22**: 951–59.

14 Klein R, Moss SE, Klein BEK, DeMets DL. Relation of ocular and systemic factors to survival in diabetics. *Arch Int Med* 1989; **149**: 266–72.

15 Berger M, Mühlhauser I. Implementation of intensified insulin therapy – a European perspective. *Diabetic Med* 1995; **12**: 201–208.

16 Jörgens V, Grüßer M, Bott U, Mühlhauser I, Berger M. Effective and safe translation of intensified insulin therapy to general internal medicine departments. *Diabetologia* 1993; **36**: 99–105.

17 Müller UA, Femerling M, Reinauer KM *et al.* Intensified treatment and education of type 1 diabetes as clinical routine. A nationwide quality-circle experience in Germany. *Diabetes Care* 1999; **22**: B29–34.

18 Mühlhauser I, Overmann H, Bender R *et al.* Social status and the quality of care for adult people with Type 1 diabetes mellitus – a population based study. *Diabetologia* 1998; **41**: 1139–50.

19 Mühlhauser I, Bender R, Bott U *et al.* Cigarette smoking and progression of retinopathy and nephropathy in Type 1 diabetes. *Diabetic Med* 1996; **13**: 536–43.

20 Sawicki PT, Bender R, Berger M, Mühlhauser I. Non-linear effects of blood pressure and glycosylated haemoglobin on progression of diabetic nephropathy. *J Intern Med* 2000; **247**: 131–38.

21 Liniger C, Albeanu A, Bloise D, Assal JP. The tuning fork revisited. *Diabetic Med* 1990; **7**: 859–64.

22 Sawicki PT, Heinemann L, Berger M. Comparison of methods for determination of microalbuminuria in diabetic patients. *Diabetic Med* 1989; **6**: 412–15.

23 Start RD, Bury JP, Strachan AG, Cross SS, Underwood JCE. Evaluating the reliability of death in published clinical research, *Br Med J* 1997; **314**: 271.

24 Breslow NE, Day NE. *Statistical Methods in Cancer Research, II. The Design and Analysis of Cohort Studies.* Lyon: International Agency for Research on Cancer, 1987.

25 Weyer C, Sawicki PT. Optimierung antihypertensiver Therapie bei Diabetes. *Diab Stoffw* 1998; **7**: 49–59.

Received 16 March 2000; revision received 29 June 2000; accepted 18 July 2000.

Correspondence: Prof. Dr med. Ingrid Mühlhauser, Medizinische Klinik der Universität Düsseldorf, Klinik für Stoffwechselkrankheiten und Ernährung, Moorenstraße 5, D-40225 Düsseldorf, Germany (fax: 0211 8118772; e-mail: Ingrid_Muehlhauser@uni-hamburg.de).