Magnitude of end-stage renal disease in IDDM: A 35 year follow-up study

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Magnitude of end-stage renal disease in IDDM: A 35 year follow-up study. Significant improvements were made during the last two decades in the treatment of IDDM patients. To assess the risk of ESRD in a population that was exposed to these improvements, we determined the cumulative incidence of ESRD in a cohort of 142 white patients who were aged less than 21 years when they came to the Joslin Diabetes Center in 1959 with recently diagnosed IDDM. The first case of ESRD occurred after 13 years of IDDM, and a total of 25 cases have developed by 35 years' duration (cumulative incidence 21.3%). Median survival after the diagnosis of ESRD for the 16 patients who began dialysis was only 3.5 years. A strong predictor of the development of ESRD was the level of glycemic control during the first two decades of IDDM. ESRD developed in 36.3% of patients in the worst tertile for glycemic control but only in 14.4% and 9.2% of those in the middle and best tertiles. In comparison with two population based studies, the onset of ESRD in the Joslin Cohort was postponed by about five years. This advantage is more plausibly attributable to differences arising after the diagnosis of diabetes than to referral of less severe cases of IDDM to the Joslin Diabetes Center. What differences in diabetes care accounted for the postponement of ESRD cannot be discerned from comparisons among published studies, but likely candidates include Joslin's long-term advocacy of good glycemic control and the prompt implementation of new clinical interventions, such as antihypertensive treatment.

Diabetic nephropathy, one of the most serious late complications of juvenile-onset insulin-dependent diabetes mellitus (IDDM), develops in one out of three patients [1, 2]. In a majority of those affected, it progresses to end-stage renal disease (ESRD) and requires renal replacement therapy [1, 2]. Coronary atherosclerosis is accelerated in nephropathy, so most succumb to coronary artery disease despite renal replacement therapy, and these deaths account for much of the premature mortality in IDDM [3].

Few data have been acquired from recent cohort studies of the occurrence of ESRD in IDDM. Such studies are necessary to assess the effectiveness of improvements that have been made during the last three decades in the care for patients with IDDM. These include tools to improve glycemic control such as the introduction of measurements of hemoglobin A_{1c} [4], antihypertensive treatment to retard progression of proteinuria to ESRD

[5, 6], and hemodialysis and renal transplant to maintain those who developed ESRD [7]. Contemporary estimates of the risk of ESRD in IDDM are also critical for the development of new preventive programs [8, 9]. The cost and effectiveness of any new program must be measured against the cost and effectiveness of existing programs. For example, recent clinical trials have demonstrated, in very select populations, that both intensive glycemic control and treatment with ACE inhibitors reduce the risk of diabetic nephropathy [10-13]. It remains to be determined, however, how much these new therapeutic protocols will reduce the overall risk of ESRD when implemented in the care of all patients.

This report describes the occurrence of ESRD in the cohort of patients who came to the Joslin Diabetes Center in 1959 with a recent diagnosis of IDDM. They have been followed until January 1, 1994. During this interval, the majority of the cohort remained in the care of the Joslin Diabetes Center, an institution in which control of hyperglycemia has been emphasized in patient care. In the 1970's and 1980's this cohort was also exposed to antihypertensive treatment and had access to treatment with replacement renal therapy [5-7, 14].

Methods

All patients ($N = 142$) with newly diagnosed IDDM, aged < 21 years, who came to the Joslin Clinic during an 18 month interval centered around 1959 were included in the present study. Additional eligibility criteria were that all were Caucasian residents of Massachusetts at the time of their first visit to the clinic in that interval. Previously, this cohort had been followed up to 1981 as a part of an earlier investigation [2, 3].

For each individual, the medical records at the Joslin Clinic were examined for any evidence of renal function impairment. Individuals who had their last Joslin Clinic visit before January 1, 1994, were interviewed by phone regarding doctor-diagnosed kidney disease, hemodialysis, or kidney transplantation. In cases of death, information was sought from private physicians, autopsy reports, and death certificates regarding the circumstances of the death and all conditions present at that time. Information from all these sources was used to determine whether a patient had developed ESRD and, if so, the date of its onset.

Patients were diagnosed as having ESRD if they underwent long-term dialysis, or if they died due to other causes but had renal failure (serum creatinine $\geq$ 5.0 mg/dl or 440 μmol/liter) documented at least one month prior to death. ESRD onset was

Table 1. Characteristics of the 1959 cohort according to gender

Characteristic	Men $N = 77$	Women $N = 65$	Total $N = 142$
Age at diagnosis of IDDM *years*	11.2 ± 5.9	11.7 ± 4.8	11.4 ± 5.4
Visited Joslin Clinic after 1991 %	28.5	35.4	31.7
Did not visit Joslin after 1991 but alive as of 1 Jan 1994 %	41.6	32.3	37.3
Dead as of 1 Jan 1994 %	27.3	24.6	26.1
Status unknown as of 1 Jan 1994 %	2.6	7.7	4.9
ESRD diagnosed before 1 Jan 1994[a] %	18.2	16.9	17.6

[a] 19 of the 25 patients with ESRD began dialysis, 16 of whom entered Medicare's ESRD Program; the remaining 6 died in years 1976, 1979, 1987, 1990, 1990, and 1991 (see text for details).

Fig. 1. *Cumulative incidence of end-stage renal disease (ESRD) according to duration of IDDM and according to age at onset of IDDM.* Closed rectangles represent those diagnosed between ages 11 and 20 years; open circles represent those diagnosed before age 11 years. Asterisks indicate point at which the two curves are significantly different ($P = 0.04$).

the date that dialysis began or the date of death for those not undergoing dialysis. Patients who developed ESRD were matched against the file of registrants in the Medicare's End-Stage Renal Disease Program to find out what proportion of patients from our cohort were registered. The matching data were full name, date of birth, place of birth, and Social Security Number if available. Instances of imperfect but nearly complete matches were investigated until the discrepancies were resolved or the mismatch was confirmed by additional data.

An index of the frequency of hyperglycemia, the same as used in the previous study of persistent proteinuria and glycemic control, was used in the present study to determine the relationship between levels of glycemic control during the first 20 post-pubertal years of diabetes and the development of ESRD [2]. Briefly, the index is the proportion of clinic visits in which severe hyperglycemia was present. Hyperglycemia was considered severe on the date of a clinic visit if a patient had a fasting blood glucose value ≥ 180 mg/dl, or during postprandial intervals < 1.4 hours, 1.5 to 2.4 hours, 2.5 to 3.4 hours, or ≥ 3.5 hours a blood glucose value ≥ 240, or 220, or 200 or 180 mg/dl, respectively. The index was calculated by five-year intervals of age from age 10 to 30 years. Specifically, the index of hyperglycemia was the number of clinic visits with severe hyperglycemia during a five-year age interval divided by the total number of clinic visit during that interval. If the number of clinic visits during an interval was less than four, the corresponding index of hyperglycemia was considered missing. If no index of hyperglycemia was available for any interval between ages 10 and 30 years, the patient was considered a non-attender (26 of 142 patients, 18.3%). Otherwise, the patient was classified according to the average of the intervals for which the index was calculated.

Incidence and cumulative incidence rates were used to measure the frequency of the occurrence of end-stage renal disease. The cumulative incidence rates were calculated over specific time intervals using life table methods [15, 16]. In this study two end points (death and ESRD) were considered, and patients contributed person years of follow up until the year of the occurrence of these end points. Patients who were traced to the present and did not have either end point contributed person years until January 1, 1994. Patients who were untraced contributed person years until the year of the last clinic visit or hospitalization when serum creatinine was measured. Differences among incidence rates were tested by a chi-square test [16]. Differences among cumulative incidence rates were tested by log-rank tests [15, 16].
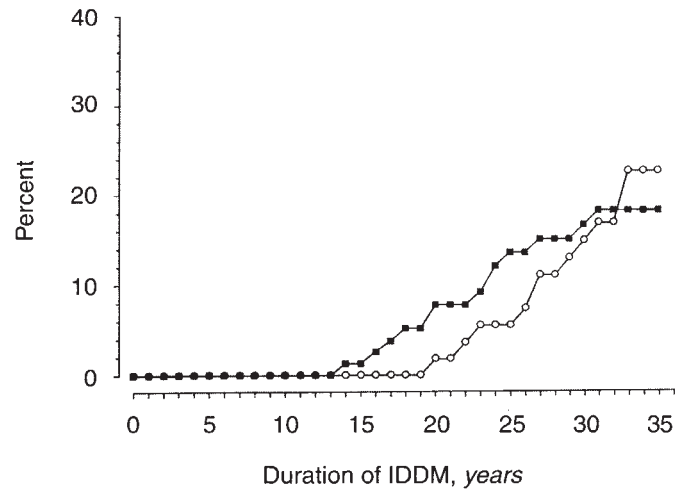
Results

Risk of ESRD

Characteristics of the study group according to sex are shown in Table 1. The average age at onset of IDDM was 11 (range 0 to 20) years for males and 12 (range 0 to 20) years for females. As of 1 January 1994, 31.7% of the entire cohort of patients were still visiting the Joslin Clinic (at least 1 visit after January 1, 1991), 26.1% were dead, 4.9% were untraced, and the remaining 37.3% were alive but in the care of other medical facilities. No significant difference between males and females was observed for the characteristics shown in Table 1.

The first case of ESRD occurred in 1973 and began dialysis in December of that year. Since then, ESRD has developed in a total of 25 patients, 17.6% of the cohort. Of these, 16 (64%) began dialysis and were registered in the Medicare End Stage Renal Disease Program. Another three began dialysis but died promptly and were not registered. The remaining six individuals had renal failure as defined by serum creatinine level but were not put on dialysis before they died. One refused dialysis and the others were either too ill due to other medical problems or died suddenly before dialysis began.

Figure 1 shows the cumulative incidence of ESRD according to duration of diabetes in two subgroups defined by age at onset of IDDM. The first cases of ESRD occurred after 13 years of diabetes in the 82 patients with diabetes diagnosed between age 11 and 20 years. After 35 years of diabetes, ESRD had developed in 13 of them, giving a cumulative incidence of 18.3% $\pm$ 4.6%. In the 60 patients with diabetes diagnosed before age 11, the first case of ESRD did not occur until after 19 years of diabetes, about six years later than the previous group. After 35 years of diabetes, ESRD had developed in 12 patients in this subgroup, giving a cumulative incidence of 22.7% $\pm$ 5.8%. Therefore, the risk in the long run was similar regardless of age of onset of IDDM, but in the window 18 and 19 years of IDDM, the risk was significantly higher in those with IDDM diagnosed after age 11 than those diagnosed at younger ages ($P = 0.04$). When exposure to diabetes

Table 2. Incidence of ESRD according to post-pubertal duration of IDDM

Post-pubertal duration of IDDM *years*	Person-years	Incidence rate/1000
0–9	1371	—
10–14	672	1.5 (1)[a]
15–19	636	12.6 (8)
20–24	574	10.4 (6)
25–29	450	17.8 (8)
30–34	310	6.4 (2)
Total	4012	6.2 (25)

[a] Number of cases of ESRD

before age 11 years was disregarded so that the cumulative incidence of ESRD was computed according to post-pubertal duration of diabetes, the two curves were virtually identical (data not shown). In the total group, the cumulative incidence rate of ESRD after 35 years of post-pubertal duration of IDDM was 21.3% ± 3.9%.

The incidence rate of ESRD during specific intervals of post-pubertal duration of diabetes is presented in Table 2. The first case occurred between the 10th and 14th year of post-pubertal diabetes (incidence rate 1.5/1000 person-years). The incidence rate then increased with duration of diabetes, reaching a peak of 17.8/1000 person-years between the 25th and 29th year, and declined afterwards to 6.4/1000 person-years. While the decline is not statistically significant with the small number of person-years of follow-up after 30 years post-pubertal duration, it is consistent with the decline in the incidence rate of proteinuria in long duration diabetes.

Association of glycemic control and the risk of ESRD

An index of severe hyperglycemia, the same as that in the previous study of this cohort [2], was used to examine the relationship of the risk of ESRD to glycemic control. Stated simply, severe hyperglycemia was defined as a blood sugar above the 66th percentile of all clinic blood sugars, specific to a time since last meal (see above). The index of hyperglycemia was the proportion of a patient's clinic visits in which the blood sugar was in the severe hyperglycemia range. The group was divided into tertiles according to the index of hyperglycemia (lowest = 0% to 11.9%, middle = 12.0% to 25.0%, and highest ≥ 25.1%) to calculate the cumulative incidence rate of ESRD over 35 years of IDDM according to glycemic control (Fig. 2). Those with the poorest control (severe hyperglycemia on more than 1 of 4 clinic visits) had a significantly higher risk of ESRD 36.3% ± 8.7% (*P* = 0.02) than the middle and best tertiles (14.4% ± 6.0% and 9.2% ± 5.1%, respectively). No index of hyperglycemia can be calculated for non-attenders (the 26 patients who never attended clinic more than three times in any five-year interval between age 10 and 30 years). For them, the cumulative incidence of ESRD after 35 years of post-pubertal IDDM was 31.3% ± 12.0%, similar to the clinic attenders who had the poorest glycemic control but not significantly different from the group of attenders as a whole (19.9% ± 4%; *P* = 0.39).

Association between ESRD and mortality

Out of 25 individuals who developed ESRD (at an average age of 35 ± 5.6 years), 18 had died as of January 1, 1994, at an average
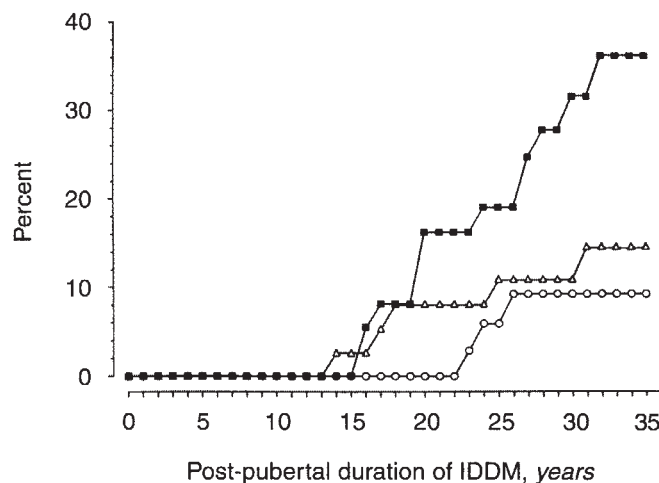

Fig. 2. *Cumulative incidence of ESRD according to duration of IDDM and according to tertile of the index of hyperglycemia.* Closed rectangles represent the tertile with the highest index of severe hyperglycemia (*N* = 37); open triangles represent the middle tertile (*N* = 39), and open circles represent the third (*N* = 40) with the lowest index of hyperglycemia. The differences among the curves are statistically significant, *P* = 0.017. The remainder of the group (*N* = 26) were non-attenders, so no index of hyperglycemia could be calculated. Their curve was very similar to that for the tertile with the highest index of hyperglycemia.

age of 38 ± 6.5 years. Survival in this group was very poor, 50% of these patients survived 2.5 years after diagnosis of ESRD and 25% survived 8.5 years. Survival was slightly better if consideration was restricted to patients who began dialysis, some of whom subsequently had a renal transplant. Half of these patients survived 3.5 years and 25% survived nine years.

In addition to the 18 deaths that were preceded by ESRD, 19 deaths occurred in the absence of ESRD. Three occurred before the age of 20 (2 DKA and 1 suspected suicide). Among the remaining 16 (average age 38 ± 7.4 years), there were 12 due to coronary artery disease (including sudden death), 2 to cerebrovascular disease, and 2 due to other causes. As was found for ESRD, exposure to diabetes before age 11 did not contribute to mortality. Cumulative mortality due to all causes in this cohort was 29.0% ± 4.2% after 35 years of post-pubertal duration of IDDM. If renal replacement therapy were not available and patients had died at the time of the diagnosis of ESRD, cumulative mortality would have been worse, 33.4% ± 4.2%.

Comparisons with other studies

Reports from two studies have published incidence rates of ESRD in IDDM patients that can be compared to this study. Both studied geographically-defined populations. In one study, the investigators showed that the cumulative incidence of ESRD up to 20 years duration of IDDM was significantly later among whites in Allegheny County, Pennsylvania, than in patients in Japan [17]. In comparison with these two populations, the cumulative risk in the present study was even later (Fig. 3). Interestingly, the cumulative risk in the half of the Joslin Cohort with the worst hyperglycemia (the highest tertile of the index of hyperglycemia combined with non-attenders), was superimposable on the Allegheny County curve (reaching 12% at 25 years rather than 23 years, data not shown), whereas the cumulative risk in the half of the cohort with
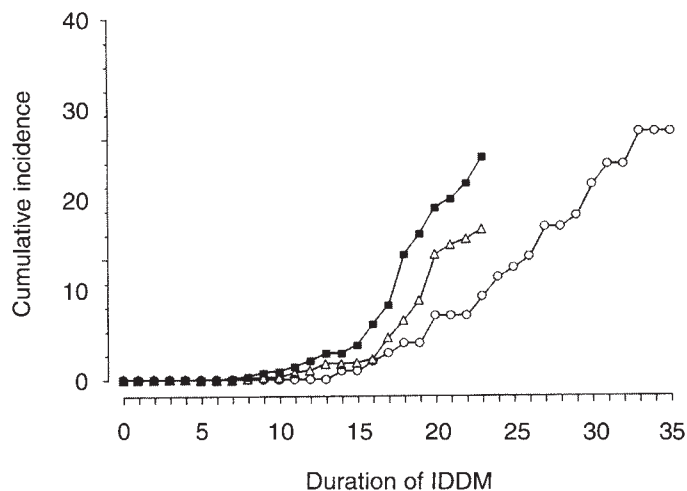
Fig. 3. *Cumulative risk of dialysis according to follow-up time in patients with IDDM in Japan (filled rectangles), Allegheny County, PA, (open triangles), and the present Joslin cohort study (open circles).* The average durations of diabetes at the beginning of follow-up in the Japanese and Allegheny County studies were 3.5 and 4.4 years, respectively. Therefore, four years were added to the published follow-up times to make them approximate duration of IDDM. Similarly, for this figure, the Joslin Cohort was plotted according to duration of diabetes rather than post-pubertal duration.

Fig. 4. *Age specific incidence rates of diabetic ESRD in Southeastern Michigan among black patients with IDDM (filled rectangles) and among white patients with IDDM (open triangles), and in the Joslin cohort of white patients with IDDM (open circles).* The six out of 25 Joslin patients who did not begin dialysis, died at ages 30, 31, 31, 38, 44, and 46 years. If they are withdrawn from the analysis, the incidence rate for the Joslin cohort is even lower than the Michigan rates.

less frequent hyperglycemia (the lower 2 tertiles of the index of hyperglycemia) had only reached 11.4% by the end of follow-up.

In the second study, investigators estimated the age-specific incidence rate of ESRD in two populations, black and white patients with IDDM in Southeastern Michigan, and showed that the incidence rate peaked earlier (and higher) in blacks than in whites (ages 25 to 29 compared to 30 to 34 years) [18]. It peaked five years later yet (ages 35 to 39 years) in the Joslin Cohort (Fig. 4). In all three populations, the incidence rate fell off steeply after the peak, a pattern consistent with the exhaustion of a pool of susceptible individuals within each population. An indication of the size of the susceptible pool is given by the cumulative incidence rate of ESRD up to age 50 years, calculated from these age-specific rates: 34.9% in Michigan blacks, 28.6% in Michigan whites, and 21.5% in the white Joslin Cohort. In the half of the Joslin Cohort with the worst hyperglycemia (the highest tertile of the index of hyperglycemia combined with non-attenders), the cumulative incidence up to age 50 years was 36.2% ± 7.5%, while it was only 11.4% ± 3.8% ($P = 0.003$) in those with less frequent hyperglycemia (the lower two tertiles of the index of hyperglycemia). The cumulative risk of 36.2% was quite close to that in the two Michigan populations.

Discussion

Significant improvements have been made during the last two decades in the treatment of IDDM patients at risk of ESRD, as well as in the treatment of patients with ESRD. In the present study, we examined the cumulative incidence of ESRD in a cohort of white patients who came to the Joslin Diabetes Center in 1959 with recently diagnosed, juvenile-onset IDDM and who were followed until January 1, 1994. During the first 20 years of diabetes, a majority of these patients were under the care of the Joslin Diabetes Center, an institution where control of hypergly-
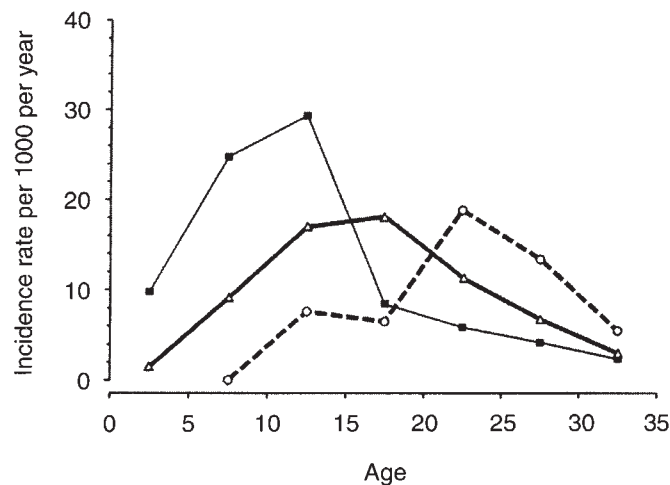
cemia has been a main goal of patient education and care. During the 1970s and 1980s these patients were exposed to antihypertensive treatment and had access to renal replacement therapies through Medicare's ESRD Program once they developed ESRD. Despite improvements in the treatment of hypertension, almost one fourth of these juvenile-onset IDDM patients developed ESRD during 35 years of diabetes. Although the majority of affected patients were enrolled in the Medicare ESRD Program, median survival after the beginning of dialysis was only 3.5 years.

The pattern of occurrence of ESRD according to duration of IDDM in our cohort parallels the previously described pattern of occurrence of persistent proteinuria, just shifted about 10 years later [1, 2]. The first case of ESRD occurred after 13 years of diabetes, and then the incidence rate increased to a peak in the interval 25 to 29 years of diabetes and subsequently declined.

A strong predictor of the development of ESRD in our cohort during the third and fourth decade of IDDM was the level of glycemic control during the first two decades of IDDM. The risk of ESRD in the tertile with the poorest glycemic control (highest tertile) was almost threefold higher than in the middle tertile, and fourfold higher than the tertile with the best glycemic control (lowest tertile). Patients in the highest tertile presented for clinic appointments with severe hyperglycemia at least once out of every four visits, while the rest of the patients were more consistent in keeping below that range. This fourfold gradient for the risk of ESRD is slightly steeper than the gradient we reported previously for persistent proteinuria [2]. Recognizing the crudeness of this index of severe hyperglycemia as an indicator of glycemic control, one can expect an even steeper gradient if the analysis could have been based on the level of hemoglobin A_{1c}. An implication of a very steep gradient is that a threshold may exist in the dose response relationship.

Although we found a strong relationship between the frequency of severe hyperglycemia and the risk of ESRD, it is not clear how

much this "pattern" of poor glycemic control can be changed and how much it is controlled by the same genetic factors that determine susceptibility to diabetic nephropathy. Two facts argue against a common genetic determinant of poor glycemic control and susceptibility to diabetic nephropathy. The first is that the cumulative risk of ESRD in the half of the study group with poorest glycemic control was 36.2%, nearly the same as the prevalence of susceptibility to nephropathy in all patients with IDDM [2]. If both poor glycemic control and susceptibility to nephropathy were due to the same genetic determinants, one would expect a much higher risk of nephropathy in the subgroup with poorest glycemic control. The second argument against this hypothesis is based on the recent DCCT results. In highly motivated patients, intensive diabetes treatment results in improved glycemic control to such a degree that 90% of the study group is able to maintain a hemoglobin A1c below 8.1%, a threshold for risk of microalbuminuria [19]. If this can be accomplished in ordinary IDDM patients, the majority of cases of ESRD in IDDM patients would be prevented or delayed. Such an effect on the risk of persistent proteinuria seems to have been accomplished in one Swedish community [20].

In agreement with previous reports, in which the risk of persistent proteinuria was high among non-attenders [2, 21], we found that patients in this study who attended clinic infrequently had a very high risk of ESRD. According to a recent study, levels of glycosylated hemoglobin are significantly higher in such patients at the time of their clinic visits, as well as when they are not attending the clinic [22]. Moreover, these patients are from lower socioeconomic strata or dysfunctional families. Another study suggests that patients who attend clinic infrequently have health beliefs that downplay the value of physician-patient interchanges [23]. All of these findings point to the critical need for the development of new strategies to engage IDDM patients in preventive programs (such as intensive diabetes treatment) against ESRD.

New strategies for engaging IDDM patients with nephropathy in therapeutic programs to retard progression to ESRD are equally important. Since the early 1980s, antihypertensive treatment of patients with persistent proteinuria has been advocated [5, 6]. Such treatment was implemented at the Joslin Diabetes Center in the early 1970s, so the patients in the 1959 Cohort who remained under the care of the clinic were exposed to this treatment [14]. Most likely, the non-attenders were not treated for hypertension, and this may account for some of the excess ESRD among that group. The superiority of ACE inhibitors over conventional antihypertensive drugs in reducing the risk of ESRD in patients with diabetic nephropathy has recently been demonstrated in clinical trials. This improvement can be translated into patient care only if the disengaged patients are targeted for early screening and therapeutic programs.

A majority of the patients in our study who developed ESRD entered the Medicare ESRD Program. The main reason for ESRD patients in this cohort not being entered into the Medicare ESRD program was their death within months of the diagnosis of ESRD. While some of them had other medical problems more pressing than their renal failure, the prompt demise of many of them was not anticipated. Mainly, this reflects the high risk of coronary disease in this population, particularly after the age of 35 years [24]. An important implication is that the registrations of diabetic patients in Medicare's ESRD Program underestimates

the number of incident cases of ESRD. This problem of underestimation also extends to the population-based studies in Allegheny County [17] and Southeastern Michigan [18]. In both studies, the end point was the date when renal replacement therapy began. In the Joslin cohort, six patients with ESRD did not begin dialysis. If they are withdrawn from the analysis, the cumulative risk after 35 years of IDDM decreases to 16.0%, and the disparity with the other studies is even larger.

Finally, these differences between the incidence rate of ESRD in the Joslin Cohort and other populations have important implications regarding the potential for reducing the devastating impact of diabetic renal disease. While the lifetime risk of ESRD in white patients with IDDM at Joslin Diabetes Center was similar to that in other locales, the distribution of onsets of ESRD was delayed about five years relative to Allegheny County and Southeastern Michigan. In contrast, within Michigan, the distribution of age at onset of ESRD among blacks was shifted even earlier by five years than that among whites. The fact that the lifetime risk of ESRD in the Joslin Cohort was similar as that in whites elsewhere [1, 18], indicates that patients who came to the Joslin Diabetes Center at the diagnosis of IDDM were not less susceptible to ESRD, therefore the delayed onset of ESRD must be related to the setting of the treatment. Patients in the Joslin Cohort became engaged with the medical care system from the onset of their diabetes. Although a certain proportion of them became disengaged later, most were exposed to the education programs of this center that advocated strict control of glycemia. By contrast, the data from Allegheny County and Southeastern Michigan included many patients who, from the onset of their diabetes, were remote from close medical follow-up and held diverse attitudes toward medical expertise. The position of black patients with IDDM in Figure 4 is consistent with their being even more remote from close medical follow-up, perhaps for cultural as well as economic reasons. If this interpretation of the differences among distributions of onset of ESRD is valid, these differences indicate that relatively simple measures (in comparison with the intensive diabetes treatment achieved by the DCCT) are required to postpone significantly the devastating impact of ESRD on the population of patients with IDDM.

The strengths and shortcomings of our study should be mentioned. Data on the experience of patients of the Joslin Diabetes Center were based on a fixed cohort of newly diagnosed IDDM patients, some of whom were referred to the center most likely because their diabetes was especially difficult to control from the outset. This cohort was followed for 35 years with nearly complete follow-up and documentation of renal status as of 1 January, 1994. Hence, the delayed risk of ESRD in the Joslin Cohort relative to the other studies likely reflects an effect of their exposure to the Center's educational and therapeutic protocols, as well as the early introduction of new measures to control hyperglycemia and hypertension. It must be recognized, however, that the center did not have an active policy to retain patients under its care during the relevant decades, and its education program did not achieve "fair" glycemic control in at least one third of the population. If the Center had intensified the treatment of diabetes in the subset of this cohort with the worst hyperglycemia and improved their glycemic control, it is likely that the onset of ESRD would have been postponed 10 years in that subgroup.

Acknowledgments

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