The Natural History of Chronic Renal Failure: Results From an Unselected, Population-Based, Inception Cohort in Sweden

Marie Evans, MD, Jon P. Fryzek, PhD, Carl-Gustaf Elinder, MD, PhD, Sarah S. Cohen, MSc, Joseph K. McLaughlin, PhD, Olof Nyrén, MD, PhD, and C. Michael Fored, MD, PhD

• ***Background:*** **Mortality rates in patients with chronic renal failure (CRF) are high both before and after start of renal replacement therapy (RRT). However, few studies of mortality and progression have been performed in an unselected CRF population.** ***Methods:*** **We followed up a population-based inception cohort of 920 men and women aged 18 to 74 years who had CRF (serum creatinine level > 3.4 mg/dL [>300 μmol/L] for men and >2.8 mg/dL [>250 μmol/L] for women) for 55 to 79 months. Relationships between the outcomes (death and start of RRT) and independent variables under study (age, sex, primary renal disease, body mass index [BMI], and glomerular filtration rate [GFR] at entry) were explored by using Cox regression models.** ***Results:*** **Seven hundred thirty-nine patients (80%) started RRT during the follow-up period. As expected, GFR at entry was clearly linked to the incidence of RRT (*P* < 0.0001). Age was related inversely to incidence of RRT (adjusted relative risk for patients ≥65 years relative to patients <45 years, 0.72; 95% confidence interval, 0.57 to 0.90). Men progressed to RRT more often than women (adjusted relative risk, 1.59; 95% confidence interval, 1.35 to 1.88). BMI was unrelated to RRT incidence. By the end of follow-up, 389 patients with CRF (42%) had died, 89 of them (10%) before the start of RRT. The most common primary cause of death was cardiovascular disease (37.5%). Characteristics significantly related to a greater mortality rate included older age, diagnoses of diabetic nephropathy and nephrosclerosis, and low BMI.** ***Conclusion:*** **Preuremic characteristics (age, sex, primary renal diagnosis, BMI, and GFR) are predictive of prognosis in unselected patients with CRF.** ***Am J Kidney Dis*** **46:863-870.**

INDEX WORDS: Kidney failure; chronic; epidemiology; survival analysis; primary renal disease; body mass index (BMI); sex; renal replacement therapy.

THE INCIDENCE AND prevalence of end-stage renal disease (ESRD) are increasing worldwide. In the United States, the incidence rate of renal replacement therapy (RRT) is 333 per million population per year, whereas in Europe, the overall incidence rate is 117 per million population per year, with an annual increase of 4.8%.[1] In the United States, up to a 10-fold increase has been predicted in the prevalent population with diabetic renal disease during this decade. Already, the ESRD treatment program consumes 6.7% of the total Medicare budget in the United States.[2] Mortality is high in patients on RRT. The overall 5-year survival rate is approximately 40%, and life expectancy in dialysis patients is one fourth to one sixth that of the general population.[2] Survival in kidney transplant recipients is better. In Sweden, the mortality rate is 2.8% per year in transplant recipients compared with 27.7% in the general dialysis population.[3] However, in relation to the general population, patients with a kidney transplant still have considerably greater mortality.[2] A large number of clinical epidemiological studies have evaluated survival in patients already on RRT,[4] but individuals selected for dialysis therapy or a kidney transplant are only a subset of the entire population with chronic renal failure (CRF). Less is known about the natural history of CRF before ESRD.

Much effort has been made to understand factors that may influence progression from early CRF to ESRD.[5] Although studies showed that the progression rate varies among subgroups of patients with CRF, comparisons across studies

From the Department of Clinical Sciences, Nephrology Unit, Karolinska University Hospital, Huddinge; Department of Medicine, Clinical Epidemiological Unit, Karolinska University Hospital; Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; International Epidemiology Institute, Rockville, MD; and Vanderbilt University Medical Center, Nashville, TN.

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Address reprint requests to Marie Evans, MD, Nephrology Unit K56, Karolinska University Hospital SE-141 86, Huddinge, Sweden. E-mail: marie.evans@klinvet.ki.se

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are difficult to make because the studies differ substantially in methods (observational, interventional, subgroups) and outcome (decline in glomerular filtration rate [GFR], doubling of serum creatinine level, start of RRT).[6] Often, the patient groups included are parts of clinical trials and thus may be highly selected. Many mortality studies of pre-ESRD patients have similar problems. As a result, such outcomes as mortality and progression rates in patients of different underlying diagnoses, age, and sex are difficult to generalize to the entire CRF population.

To estimate time to RRT and death in an unselected population of patients with CRF, we followed up patients included in a nationwide, population-based, inception cohort study.

METHODS

Study Population

Cohort members were included during a 2-year period, May 20, 1996, to May 31, 1998, as part of a nationwide case-control study of risk factors for early CRF in Sweden[7] and followed up through 2002. Eligible patients were native Swedes aged 18 to 74 years with a serum creatinine level found to exceed 3.4 mg/dL (300 μmol/L) in men or 2.8 mg/dL (250 μmol/L) in women for the first time and permanently during the inclusion period. Patients were identified through 68 medical laboratories that covered practically all inpatient and outpatient care in Sweden. Each laboratory provided monthly lists of all serum creatinine measurements performed. These lists were reviewed by study staff in collaboration with the patients' physicians at each of the 60 hospitals throughout Sweden at which renal disease is treated. After reviewing patient medical records, it was determined whether the cause of serum creatinine level elevation could be CRF. Patients with increased serum creatinine levels caused by dehydration or acute renal failure (eg, prerenal failure, postrenal failure, and acute tubular necrosis), those with terminal malignant disease, and patients with kidney transplants were not eligible. If chronicity of renal failure was uncertain, a second creatinine measurement, 3 months after the first, was required for eligibility. To allow for day-to-day variation, thresholds for this second measurement were lower (2.8 mg/dL [250 μmol/L] for men, 2.3 mg/dL [200 μmol/L] for women).

Baseline Patient Data

All patients were identified by the National Registration Number, a unique identifier assigned to all Swedish citizens. Baseline characteristics of cohort members included age, sex, body mass index (BMI), underlying renal disease, and estimated GFR at study entry. Information on anthropometric measurements (as well as other lifestyle and medical factors) was obtained through a self-administered mailed questionnaire. Diagnoses of underlying conditions were based on medical information obtained during routine clinical workup. GFR was estimated by means of the abbreviated Modification of Diet in Renal Disease equation[8] using serum creatinine levels obtained from the medical laboratories during patient recruitment.

Outcome Data

Outcome measures included start of RRT (either dialysis or primary kidney transplantation) and death. The date of RRT start was obtained through the Swedish Registry of Renal Replacement Therapy (SRAU).[3] The decision to start RRT was made by the patients' nephrologists and based on routine clinical evaluation. The general Swedish recommendations for initiation of RRT follow the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF–K/DOQI) guidelines to a large extent.[9] Through linkage using the National Registration Number, the nationwide Cause of Death Register provided data on all cohort members' deaths, including date and causes. If cause of death was unavailable in the Cause of Death Register (because of a lag in time from death to registration), the information was obtained from the SRAU. In the standardized mortality ratio (SMR) analysis, we used mortality data from the Swedish National Board of Welfare only so that mortality of the inception cohort could be compared with that of the general population.

Analysis

Descriptive statistics were calculated to characterize the study population and their renal diseases. Patients were followed up from the date of their elevated serum creatinine level (inclusion in the original case-control study) through the date of the outcome of interest (death or RRT onset) or end of the study period (December 31, 2002), whichever came first. Cox regression models were used to explore the relationship between the independent variables under study (age, sex, BMI, primary renal disease, estimated GFR, transplantation during follow-up [only in mortality analysis]) and outcomes of interest (RRT and death). We used a modified World Health Organization classification of BMI (BMI of 15.3 to 20 kg/m^2 = underweight, BMI of 20.1 to 25 kg/m^2 = normal weight, BMI of 25.1 to 30 kg/m^2 = overweight, and BMI $>$ 30 kg/m^2 = obese). Patients were categorized into predefined groups according to age at entry and quartiles of estimated GFR. In the mortality analysis, we also used kidney transplantation (transplantation during follow-up, yes or no) as an independent variable. Crude and adjusted relative rates and 95% Wald confidence intervals (CIs) were calculated for each of the outcome variables, RRT and death. Mortality data were directly standardized against age- and sex-specific all-cause mortality for Sweden by inclusion year (1996 to 1998). All analyses were performed using SAS statistical software (version 9; SAS Institute, Cary, NC).

RESULTS

Between 1996 and 1998, a total of 1,189 eligible patients were identified. Sixty-nine of these patients died shortly after their eligibility status was determined and could not be included