Low Incidence of End-Stage Renal Disease and Chronic Renal Failure in Type 2 Diabetes

A 10-year prospective study

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OBJECTIVE — Data on the incidence of end-stage renal disease (ESRD) and chronic renal failure from population-based studies in Caucasian type 2 diabetic patients are lacking. To provide such data, a population-based cohort of type 2 diabetic patients was identified in Casale Monferrato, Italy, and prospectively examined from 1991 to 2001.

RESEARCH DESIGN AND METHODS — During the follow-up period, patients were regularly examined with centralized measurements of plasma creatinine and HbA_{1c}. Independent predictors of progression to renal events were identified with multivariate Cox proportional hazards modeling, with sex, age, and individual follow-up time as confounders.

RESULTS — We followed 1,408 of 1,540 (91.4%) patients (average follow-up time 6.7 years, range 0.011–11.1); 10 new cases of ESRD and 72 of chronic renal failure (plasma values of creatinine ≥2.0 mg/dl) were identified, giving incidence rates/1,000 person-years of 1.04 (95% CI 0.56–1.94) and 7.63 (6.06–9.61), respectively. Cumulative risks for chronic renal failure adjusted for competing mortality were 6.1 and 9.3% after 20 and 30 years from diagnosis of diabetes, respectively. Incidence rates and cumulative risks of chronic renal failure defined by plasma creatinine values >1.5 mg/dl increased to 13.1/1,000 person-years, 8.6 and 14.8%, respectively. In Cox regression analysis, predictors of progression (after adjustment for confounders) were hypertension ($P = 0.078$), diastolic blood pressure ($P = 0.034$), BMI ($P = 0.03$), and albumin excretion rate (AER) ($P < 0.0001$).

CONCLUSIONS — We provide evidence that the individual risk of ESRD and chronic renal failure is low. AER and diastolic blood pressure are independent predictors of progression. These findings underline the relevance of primary prevention to reduce the number of diabetic patients with ESRD.

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In industrialized countries, diabetes is becoming the leading cause of end-stage renal disease (ESRD) (1). Preventing or delaying the progression of diabetic nephropathy is therefore becoming critical. Although the enrollment in ESRD programs is higher in patients with type 1 than type 2 diabetes, the number of subjects with type 2 diabetes is much greater; they therefore represent the majority of diabetic patients with ESRD. Despite the clinical and public health implications of ESRD, population-based studies on the incidence of ESRD in Caucasian type 2 diabetic patients are lacking. In fact, most of the studies suffer limitations due to the recruitment of selected ethnic groups at higher risk for diabetes and its complications than Caucasians (2–4) or cohorts that are clinic-based rather than population-based (5).

The aims of this prospective study are to assess incidence rates and predictive markers of ESRD and chronic renal failure among a large population-based cohort of Italian patients with known type 2 diabetes followed for 10 years (6–10).

RESEARCH DESIGN AND METHODS

— The study base consisted of 1,565 residents of Casale Monferrato, northwest Italy (93,477 inhabitants), in 1988 with known type 2 diabetes who attended a baseline examination in 1991–1992 to assess the prevalence of micro- and macroalbuminuria and cardiovascular risk factors and who were followed until 31 December 2001 (6–10). As described in detail elsewhere (6), at baseline all patients were interviewed and examined by trained investigators. Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg or treatment with antihypertensive drugs. Venous blood samples were collected in the fasting state for the determination of triglycerides, total cholesterol, HDL cholesterol (enzymatic-colorimetric method, after precipitation with Mn++), apolipoprotein (apo) A1 and apoB (turbidimetric method, BM/hitachi 717; BBR), and HbA_{1c} (HPLC; Daiichi, Menarini, Japan) (laboratory reference range 3.8–5.5%). Albumin excretion rate (AER) was calculated on the basis of urinary albumin concentration measured on a single timed

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Abbreviations: apo, apolipoprotein; AER, albumin excretion rate; CHD, coronary heart disease; ESRD, end-stage renal disease.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

overnight urine collection by nephelometric method (Behring Nephelometer Analyzer; Behring Institute, Marburg, Germany), after having excluded urinary tract infection, congestive heart failure, or other known causes of renal diseases. Of recruited patients, 765 were normoalbuminuric (AER <20 μg/min), 488 were microalbuminuric (AER 20–200 μg/min), and 268 were macroalbuminuric (AER >200 μg/min). Smoking was classified into one of three categories: never smoked, ex-smoker (if patient stopped smoking at least 1 month before the visit), and smoker. The date of diagnosis was retrieved and recorded for all enrolled patients.

During the follow-up period (1991–2001), patients were examined 3–4 times a year at either the diabetes clinic or by general practitioners, according to physician scheduled plans, with centralized measurements of plasma creatinine and HbA_{1c}. Cumulative individual averages of HbA_{1c} during follow-up were calculated.

Primary end points of the study were incidence of ESRD (need for dialysis) or chronic renal failure (two consecutive plasma creatinine values ≥2.0 mg/dl at least 2 months apart). The relevant time scale for the analysis was time since onset of the disease to development of chronic renal failure or ESRD or to last examination if the patient's plasma creatinine values remained <2.0 mg/dl. Censored observations were those of patients who died during follow-up or moved from the area. Incidence rates were calculated by dividing the number of new cases occurring during the study period by the number of person-years of observation. Differences in clinical characteristics between survivors and deceased subjects were assessed using the χ^2 test for categorical variables and the *t* test for continuous variables. Results are shown as means ± SD. Variables with skewed distribution (triglycerides and creatinine) were normalized using logarithmic transformation.

We recruited a prevalence cohort of patients, i.e., a heterogeneous cohort regarding duration of the disease and the stage of its complications. The baseline factors measured at enrollment could reflect more severe stages of the disease; the expected effect on our study would have been that the attained individual time of follow-up (the lag time between date of baseline examination and date of exit from the cohort) could have been lower for more severe patients. Therefore, to take into account the effect of the correlation between duration of disease and consequent severity affecting baseline factors and selective mortality, we introduced in the regression equations a categorical variable for individual attained time of follow-up. By doing so, we aimed to assess the predictive contribution of explanatory variables controlling for the length of follow-up.

All continuous variables were categorized in quartiles of their distribution. Age was categorized in 10-year age-groups (<60, 60–69, 70–79, and >79 years). RRs are shown in all tables, both adjusted and unadjusted for confounders (sex, age, and attained time of follow-up). Kernel density estimates of the hazard of chronic renal failure were estimated according to Breslow and Day (11). *P* values for trend were estimated according to Mantel Haenzel (12). Independent predictors of progression to chronic renal failure were identified with multivariate Cox proportional hazards modeling, with sex, age, and attained time of follow-up as confounders. The −2 log likelihood ratio test was used to test the significance of variables. A *P* value <0.05 was considered to indicate statistical significance. All analyses were performed with Stata (Stata Release 7.0; Stata, College Station, TX).

RESULTS — Of 1,565 patients in the cohort, 1,408 were followed, 50 patients were excluded at baseline (13 with chronic renal failure, 2 with ESRD, and 25 with missing creatinine values), and 117 were excluded because no creatinine measurement was available during follow-up (8 alive, 11 migrated, 1 lost, and 97 dead). Death certificates were analyzed, showing that renal insufficiency was reported as a contributor to cause of death in only two patients. Most of them died within a short period of time from the baseline examination (median lag 1.5 years). With respect to recruited patients, lost patients were older (75.4 ± 10.9 vs. 68.1 ± 10.5 years, $P < 0.0001$), had lower BMI (25.8 ± 4.1 vs. 27.4 ± 4.7 kg/m^2, $P = 0.001$) and HbA_{1c} (7.3 ± 1.8 vs. 8.1 ± 2.3%, $P = 0.0012$), and were more likely to be cared for by general practitioners (37.9 vs. 22.4%, $P < 0.0001$); no differences were found in other baseline variables.

Average duration of diabetes at entry (baseline examination) was 10.7 years (range 0.7–42.9), and average follow-up time from baseline examination was 6.7 years (range 0.011–11.1); <5% of subjects had follow-up times <1 year. During the follow-up period there were 620 censored cases; 58 of them moved out of the area and 562 died (31.9% among normoalbuminuric, 44.2% among microalbuminuric, and 58.2% among macroalbuminuric patients). They contributed to the person-years of observations in the cohort until the last available measurements of creatinine. Cardiovascular disease as a whole (ICD-9 390-459) accounted for 48.6% of deaths; frequencies of other main causes of death were as follows: malignant neoplasm (ICD-9 140-208) 20.5%; respiratory diseases (ICD-9 460-519) 6.6%, and digestive system diseases (ICD-9 520-579) 4.3%. Frequencies of death by attained time of follow-up (<1.50, 1.50–2.99, 3.00–4.50, 4.51–5.99, and ≥6.0 years) were 22.2, 19.2, 20.1, 18.1, and 20.3%, respectively. The distribution was stratified differently, however, among normo-, micro-, and macroalbuminuric patients; indeed, most macroalbuminuric patients died early, as 43 of 135 (31.8%) of deaths occurring among those with attained time of follow-up <1.50 years.

Table 1 shows baseline characteristics of the whole cohort and of those who died compared with those who survived at the end of follow-up. The latter were younger and had lower values of plasma total cholesterol and creatinine than those who died but higher plasma values of HDL cholesterol and apoA1.

Of 627 patients in the cohort treated for hypertension at baseline, 43.0% were treated with ACE inhibitors, either alone or in combination with other drugs, 6.4% with Ca^{2+}-antagonists, 20.4% with diuretics, 4.4% with β-blockers, 18.9% with vasodilators or α-adrenergic inhibitors, and 6.9% with two or more drugs in combination. Frequency of treatment for hyperlipidemia was 5.4%.

During the follow-up period, 10 patients developed ESRD in 9,588.94 person-years of observation, corresponding to an incidence rate of 1.04 per 1,000 person-years (95% CI 0.56–1.94). Of these 10 patients, only 1 patient was normoalbuminuric, 3 were microalbuminuric (RR 5.2, 95% CI 0.5–49.6), and 6 were macroalbuminuric (24.7, 3.0–205.2) at baseline.

Table 1—*Baseline features of the cohort of Casale Monferrato, by living status*

	Whole cohort	Survived	Dead	*P*
n	1,408	846	562	
Age (years)	68.1 ± 10.5	64.4 ± 9.8	73.4 ± 9.1	<0.0001
Men	614 (43.6)	356 (42.1)	258 (45.9)	0.16
Duration (years)	10.7 ± 6.9	10.0 ± 6.2	11.8 ± 7.7	<0.0001
BMI (kg/m^2)	27.4 ± 4.7	27.9 ± 4.7	26.5 ± 4.5	<0.0001
Hypertension	1,177 (84.1)	699 (82.8)	478 (86.0)	0.11
AER				
<20 (μg/min)	705 (51.0)	480 (58.2)	225 (40.4)	<0.0001
20–200	446 (32.2)	249 (30.1)	197 (35.4)	
>200	232 (16.8)	97 (11.7)	135 (24.2)	
Cared for by general practitioner	313 (22.4)	175 (20.9)	138 (24.7)	0.09
Treatment				
Diet	168 (12.0)	109 (12.9)	59 (10.6)	0.002
Oral hypoglycemic agents	998 (71.3)	617 (73.2)	381 (68.5)	
Insulin	233 (16.7)	117 (13.9)	116 (20.9)	
HbA_{1c} (%)	8.1 ± 2.3	8.0 ± 2.4	8.2 ± 2.2	0.04
Total cholesterol (mmol/l)	5.79 ± 1.24	5.60 ± 1.25	5.92 ± 1.22	<0.0001
HDL cholesterol (mmol/l)	1.42 ± 0.45	1.44 ± 0.48	1.38 ± 0.42	0.02
Triglycerides (mmol/l)	1.51	1.52	1.49	0.51
apoA1 (mg/dl)	134.88 ± 34.72	136.66 ± 35.23	132.16 ± 33.78	0.02
apoB (mg/dl)	103.70 ± 37.58	104.36 ± 37.95	102.69 ± 37.04	0.42
Creatinine (mg/dl)	1.02	1.00	1.06	<0.0001

Data are means ± SD or *n* (%).

Seventy-two new cases of chronic renal failure were identified in 9,434.8 person-years of observation, giving an overall crude incidence rate of 7.63 per 1,000 person-years (95% CI 6.06–9.61). This translates to cumulative risks for chronic renal failure adjusted for competing mortality of 6.1 and 9.3% after 20 and 30 years from diagnosis of diabetes, respectively. Risk for chronic renal failure increased with attained age (RR = 1.03 per year) and duration of disease (1.06 per year) (Fig. 1). Incidence rates and cumulative risks of chronic renal failure defined by lower plasma creatinine values (>1.5 mg/dl rather than >2 mg/dl) were also computed; using this lower cutoff, 121 incident cases were found, giving an incidence rate of chronic renal failure of 13.1 per 1,000 person-years, whereas cumulative risks adjusted for competing mortality were 8.6 and 14.8% after 20 and 30 years from diagnosis of diabetes, respectively. As shown in Table 2, risks for chronic renal failure were higher in insulin-treated patients, hypertensive patients, and those in the upper quartiles of systolic and diastolic blood pressure. Cumulative individual averages of HbA_{1c} during follow-up were associated with an increased risk for chronic renal failure. A strong effect of micro- and particularly macroalbuminuria was evident, even after adjustment for confounders, which caused a reduction in RR from 11.89 to 5.52 for the latter; in fact, mortality risk in macroalbuminuric subjects was the highest in the cohort. Results were similar when AER quartiles were considered, with values <11.0 μg/min as reference (adjusted odds ratio 1.33, 1.55, and 4.95, respectively, for AER values of 11–18.33, 18.34–44.14, and >44.14 μg/min, $P < 0.0001$). Regarding

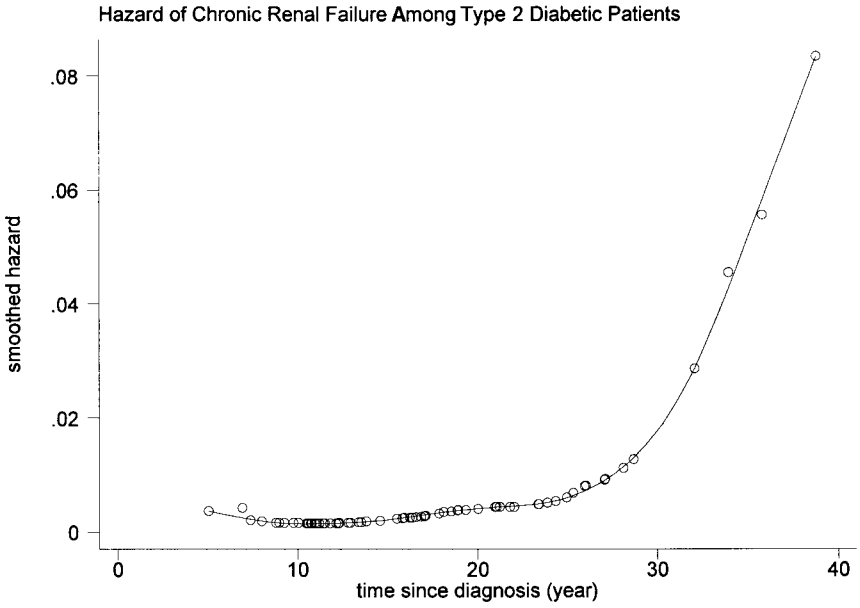

Figure 1—*Kernel density estimate of the hazard of chronic renal failure in the Casale Monferrato cohort of type 2 diabetic patients*

Table 2—*Incidence/1,000 person-years of chronic renal failure in the Casale Monferrato cohort of type 2 diabetes, by selected variables at baseline examination (1991–1992)*

	Incident cases (*n*)	Incidence rate/1,000 person-years	RR (95% CI)	*P*	Adjusted RR (95% CI)	*P*
Sex				0.30		0.31
Women	36	6.80	1.00		1.00	
Men	36	8.69	1.28 (0.81–2.03)		1.28 (0.79–2.06)	
BMI (kg/m^2)				0.16*		0.046
<24.2	11	5.29	1.00		1.00	
24.2–26.7	18	7.98	1.51 (0.71–3.20)		1.91 (0.88–4.12)	
26.8–30.0	19	7.97	1.51 (0.72–3.17)		2.15 (1.00–4.61)	
>30.0	23	9.16	1.73 (0.84–3.55)		2.76 (1.30–5.83)	
Antidiabetic treatment				0.0002*		0.14
Diet	5	4.81	1.00		1.00	
Oral drugs	42	6.06	1.26 (0.50–3.18)		1.40 (0.55–3.59)	
Insulin	24	16.70	3.47 (1.32–9.09)		2.26 (0.82–6.19)	
Smoking				0.75*		0.84
Never	44	7.26	1.00		1.00	
Ex	16	8.40	1.16 (0.65–2.05)		0.95 (0.46–1.96)	
Current	10	7.68	1.06 (0.53–2.10)		1.21 (0.55–2.63)	
Hypertension				0.002		0.009
No	2	1.32	1.00		1.00	
Yes	69	8.73	6.59 (1.62–26.89)		6.75 (1.63–28.01)	
Systolic blood pressure (mmHg)				0.0001*		0.0004
<140	8	3.77	1.00		1.00	
140–149	11	5.74	1.52 (0.61–3.78)		1.68 (0.66–4.26)	
150–169	16	5.59	1.48 (0.63–3.46)		1.75 (0.72–4.21)	
>169	36	14.35	3.81 (1.77–8.19)		4.10 (1.85–9.09)	
Diastolic blood pressure (mmHg)				0.004*		0.0016
<80	5	3.94	1.00		1.00	
80–85	16	5.69	1.44 (0.53–3.93)		1.44 (0.52–4.03)	
86–92	21	7.46	1.89 (0.71–5.01)		2.05 (0.75–5.57)	
>92	29	11.51	2.92 (1.13–7.54)		4.08 (1.53–10.88)	
AER				<0.0001*		<0.0001
Normoalbuminuria	14	2.74	1.00		1.00	
Microalbuminuria	20	6.76	2.47 (1.25–4.89)		1.86 (0.93–3.73)	
Macroalbuminuria	38	32.53	11.89 (6.44–21.94)		5.52 (2.90–10.51)	
HbA_{1c} cumulative average (%)				0.005*		0.13
<6.34	11	4.18	1.00		1.00	
6.34–7.57	14	5.98	1.43 (0.65–3.15)		1.34 (0.60–2.99)	
7.58–8.80	24	11.64	2.78 (1.36–5.68)		2.29 (1.10–4.77)	
>8.80	23	9.73	2.33 (1.13–4.77)		1.53 (0.73–3.24)	

RRs were adjusted for sex, age, and attained time of follow-up (the lag time between date of baseline examination and date of exit from the cohort). *Based on the Mantel-Haenszel test for trend.

baseline lipids (Table 3), an increased risk was found to be associated with high values of triglycerides or low values of HDL cholesterol levels at baseline.

In multiple Cox regression analysis, variables independently associated with chronic renal failure after adjustment for age, sex, attained individual time of follow-up, and cumulative individual averaged HbA_{1c} were hypertension (P = 0.078), diastolic blood pressure (P = 0.034), BMI (P = 0.03), and micro- and macroalbuminuria ($P < 0.0001$). The RRs for micro- and macroalbuminuria were 1.72 (95% CI 0.84–3.52) and 4.94 (2.25–9.68), respectively. The effect of HbA_{1c} cumulative individual average was not significant after inclusion in models of AER categories.

CONCLUSIONS — This prospective population-based study provides evidence that, although type 2 diabetes is becoming the leading cause of ESRD in Caucasians, the individual risk for chronic renal failure or ESRD is relatively low, as most patients died before reaching the terminal phase of renal function. In our cohort, only 10 of 1,408 patients followed for 10 years developed ESRD, giving an incidence rate of 1.0 per 1,000 person-years, whereas cumulative risks for chronic renal failure adjusted for competing mortality were 6.1 and 9.3% after 20 and 30 years from diagnosis of diabetes, respectively. Previous estimates have

Table 3—*Incidence/1,000 person-years of chronic renal failure in the Casale Monferrato cohort of type 2 diabetes, by plasma lipids at baseline examination (1991–1992)*

	Incident cases (*n*)	Incidence rate/1,000 person-years	RR (95% CI)	*P*	Adjusted RR (95% CI)	*P*
Total cholesterol (mmol/l)				0.068*		0.74
<4.97	21	9.90	1.00		1.00	
4.97–5.69	20	8.49	0.86 (0.46–1.58)		1.04 (0.56–1.96)	
5.70–6.49	17	7.10	0.72 (0.38–1.36)		0.97 (0.50–1.88)	
>6.49	14	5.46	0.55 (0.28–1.08)		0.73 (0.36–1.46)	
HDL cholesterol (mmol/l)				0.0007*		0.04
<1.14	31	14.71	1.00		1.00	
1.14–1.34	13	5.52	0.37 (0.20–0.72)		0.46 (0.24–0.90)	
1.35–1.60	14	5.94	0.40 (0.21–0.76)		0.57 (0.30–1.09)	
>1.60	13	5.02	0.34 (0.18–0.65)		0.45 (0.23–0.88)	
apoA1 (mg/dl)				0.37*		0.92
<111	19	8.70	1.00		1.00	
111–128	19	8.02	0.92 (0.49–1.74)		0.98 (0.51–1.89)	
129–152	17	7.10	0.82 (0.42–1.57)		0.87 (0.45–1.71)	
>152	16	6.57	0.76 (0.39–1.47)		0.81 (0.41–1.60)	
apoB (mg/dl)				0.21*		0.61
<75	16	6.82	1.00		1.00	
75–99	13	5.11	0.75 (0.36–1.56)		0.74 (0.35–1.57)	
100–125	23	10.36	1.52 (0.80–2.88)		1.19 (0.61–2.31)	
>125	19	8.40	1.23 (0.63–2.40)		0.97 (0.49–1.93)	
Triglycerides (mmol/l)				0.022*		0.03
<1.06	10	4.34	1.00		1.00	
1.06–1.43	20	8.46	1.95 (0.91–4.17)		2.11 (0.97–4.59)	
1.44–2.03	14	5.94	1.37 (0.61–3.08)		1.38 (0.60–3.17)	
>2.03	27	11.26	2.60 (1.26–5.36)		2.67 (1.27–5.62)	

RRs were adjusted for sex, age, and attained time of follow-up (the lag time between date of baseline examination and date of exit from the cohort). *Based on the Mantel-Haenszel test for trend.

been provided only in selected populations at high risk of ESRD. These findings suggest that increasing prevalence of type 2 diabetes is likely to be the main cause of the increasing trend of ESDR in diabetic patients claimed in most dialysis centers in western countries (1). This pattern is mainly due to: *1*) the increasing prevalence of risk factors for diabetes (obesity and lifestyle changes); *2*) demographic changes of the underlying population; and *3*) reduced mortality risk of diabetic patients (13).

No previous population-based study of Caucasian patients with type 2 diabetes has provided prospective data on the association between categories of AER and risk of progression. This study provides evidence that risk of progression to chronic renal failure is fourfold higher in macroalbuminuric than in normoalbuminuric patients, independent of age, duration of disease, and attained time of follow-up. The study base of this report is a prevalent rather than incident cohort, thus including patients at different stages of the disease. However, even taking into account confounders, such as duration of disease and attained time of follow-up, which are related to incidence of complications and mortality, RR for chronic renal failure remained almost fourfold higher in macroalbuminuric patients and twofold higher in microalbuminuric than in normoalbuminuric patients. A linear increase of risk is evident across quartiles of AER (reference category AER <11.0 μg/min). This finding is consistent with a role of albuminuria per se as a risk factor of progression (14). Proteins filtered through the glomerular capillary have intrinsic renal toxicity, which together with other independent risk factors (such as hypertension) can have a contributory role in the progression of renal damage. Interestingly, in this cohort the predictive role of average glycemic control during follow-up was no more significant after inclusion in AER models, suggesting that in an advanced stage of diabetes (mean duration of diabetes at entry, 10 years) the role of increased AER is stronger than that of glycemic control.

Recent trials have provided evidence that incidence and progression of diabetic nephropathy can be prevented by improving glycemic control, reducing blood pressure, and using ACE inhibitors or angiotensin-II receptor antagonists (15). We confirmed that diastolic blood pressure is a predictor of progression. However, low individual estimates of risk of both chronic renal failure and ESRD in type 2 diabetes should underline the relevance of primary versus secondary prevention programs (16,17) to reduce the number of people at risk of diabetic nephropathy. Indeed, assuming even a modest benefit from risk factor modification in the population, the number of subjects in whom the progression to renal disease and particularly cardiovascular diseases that can be delayed or prevented is large.

No universally accepted definition of chronic renal failure in diabetic patients is

available in the literature, so estimates are dependent on the cutoff values of creatinine used. Incidence rate of chronic renal failure in the Casale Monferrato Study compares with estimates obtained from the World Health Organization Multinational Study (6.3/1,000 person-years, undefined cutoff values) (5) and with those estimated in Rochester, MN (1.33/1,000 person-years, defined as plasma creatinine values ≥4.0 mg/dl) (18). In the Casale Monferrato Study, the incidence rate for chronic renal failure, computed using a lower cutoff, (plasma creatinine values >1.5 mg/dl rather than ≥2 mg/dl), increased to 13.1 per 1,000 person-years, whereas cumulative risks adjusted for competing mortality were 8.6 and 14.8% after 20 and 30 years from diagnosis of diabetes, respectively.

Consistent with other studies (19), we found that the risk for chronic renal failure was associated with lipid abnormalities at baseline, such as high triglycerides and low HDL cholesterol level. However, when we analyzed the contribution of each risk factor after adjusting for all the others in a multivariate model, AER categories, hypertension, and diastolic blood pressure remained independent risk factors, whereas associations with HDL cholesterol and triglycerides disappeared. This finding suggests that they are neither determinant nor intermediate factors but only markers of progression to renal failure.

A two- to threefold increased mortality risk, mainly for cardiovascular diseases, in proteinuric compared with nonproteinuric patients has been observed in clinic- and population-based studies (20). The effect of this selective mortality on our study was that the individual attained follow-up time of patients with macroalbuminuria was lower than that of micro- and normoalbuminuric patients, and estimates of risk would have been strongly biased if this confounding effect was not considered. For instance, the RR for chronic renal failure in the macroalbuminuric group reduced from 11.9 to 5.5 after adjustment for confounders. This point is critical in order to state the strength of predictors and to compare results of different studies on this issue.

In conclusion, this prospective population-based study provides the first evidence that, although type 2 diabetes is becoming the leading cause of ESRD in Caucasians, the individual risk for ESDR or chronic renal failure is relatively low and that AER values and diastolic blood pressure are the strongest predictors of progression.

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