Cardiovascular Risk Factors and Disease Management in Type 2 Diabetic Patients With Diabetic Nephropathy

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OBJECTIVE — The purpose of this study was to assess the prevalence of cardiorenal risk factors, their management in a routine clinical setting, and the actual achievement of international guideline targets in a large cohort of type 2 diabetic patients with diabetic nephropathy.

RESEARCH DESIGN AND METHODS — A multicentric cross-sectional study was performed in the Campania region in Italy to evaluate cardiorenal risk factors and their management in light of international guidelines. Overall, 28,550 diabetic patients were screened in the 21 participating centers; 847 (348 male and 449 female) patients with type 2 diabetes and a clinical diagnosis of diabetic nephropathy were recruited.

RESULTS — Of these subjects, 749 had microalbuminuria and 98 had macroalbuminuria. Targets for blood pressure, HbA_{1c}, LDL cholesterol, HDL cholesterol, and triglycerides were reached in, respectively, 17.5, 32.3, 30.7, 47, and 55.2% of the patients. Chronic renal failure (glomerular filtration rate <60 ml/min) was revealed in 41% and anemia in 23.8% of the patients.

CONCLUSIONS — This is the first study to investigate a large cohort of type 2 diabetic patients with early and moderate diabetic nephropathy strictu sensu. Notably, impaired renal function can be often diagnosed in these patients even in the presence of microalbuminuria. Thus, clinical diagnosis of diabetic nephopathy allows us to identify a group of patients at very high cardiorenal risk, for whom care is really difficult. We suggest that a correct diagnosis of diabetic nephropathy should always be made and that sodium intake and anemia should be routinely evaluated in these patients.

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Diabetic nephropathy in patients with type 2 diabetes has a cumulative prevalence of 30–40% (1) and is currently the leading cause of end-stage renal disease (ESRD) in Western countries. Diabetic patients with renal damage are at higher risk of fatal and nonfatal cardiovascular events (1), and, as a consequence, diabetic nephropathy has also become an economic issue (2).

Epidemiological studies have demonstrated that the factors strictly correlated to the progression of nephropathy in diabetic patients are arterial blood pressure, glycemic control, lipid levels, proteinuria levels, obesity, anemia, and cigarette smoking, with most of these critically influencing mortality (3,4). Nevertheless, what is emerging is the fact that physicians must treat the global cardiovascular risk rather than a single risk factor to achieve maximal renal and cardiovascular protection. Consequently, the number and strictness of the targets have increased, together with the difficulty of reaching them.

Data from interventional studies in type 2 diabetic populations with overt (5,6) or also early nephropathy (7), who are expected to have a very high prevalence of cardiovascular risk factors (8), indirectly suggest that new targets are hard to achieve even in the groups receiving intensive therapy. However, no study has specifically evaluated the implementation of guidelines in patients with renal damage followed outside the experimental setting of clinical trials.

The most important studies (7,9,10) investigating type 2 diabetic patients with microalbuminuria and even with overt nephropathy (6) did not specify whether subjects had typical diabetic nephropathy. In fact, it has been demonstrated (11) that microalbuminuria in type 2 diabetes is associated in only 30% of the subjects with typical diabetic nephropathy, with the remaining subjects showing nontypical renal damage or normal/nearly normal renal histology. In particular, in type 2 diabetes, severe diabetic retinopathy in the presence of microalbuminuria appears only in true diabetic nephropathy. This point is crucial because patients with diabetic nephropathy are clinically characterized by a more rapid decline in renal function over time (12). Similar data have also been collected in diabetic patients with frank proteinuria (13). As a consequence, the diabetic populations studied previously can be defined as being affected with nephropathy, but actually only some of them had nephropathy secondary to diabetes. We designed this study to investigate the prevalence of cardiorenal risk factors, their management in routine clinical settings, and the achievement of international guideline targets in a large population of type 2 diabetic patients with diabetic nephropathy.

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*A complete list of NID-2 Study Group members can be found in the APPENDIX.

Abbreviations: AER, albumin excretion rate; ESRD, end-stage renal disease; GFR, glomerular filtration rate.

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

RESEARCH DESIGN AND METHODS

— This was a multicentric cross-sectional study. The study group covered 21 outpatient clinics in Campania, Italy, caring for diabetic patients. Three centers were in academic institutions, 3 were in public hospitals, and 15 were in specialist clinics.

Eligible patients were type 2 diabetic subjects with diabetic nephropathy who had regularly received outpatient care in the participating centers for at least 1 year. Inclusion criteria were type 2 diabetes, age ≥40 years, therapy with diet and/or oral hypoglycemic agents during the first 3 years of diagnosis of diabetes, persistent albumin excretion rate (AER) ≥30 mg/day in at least two of three determinations during the last 6 months, and severe diabetic retinopathy as judged by fundus oculi examination and fluorangiography, when necessary, performed by a blinded expert ophthalmologist. Specifically, severe diabetic retinopathy was defined as severe nonproliferative diabetic retinopathy, characterized by vascular closure, or a proliferative diabetic retinopathy, characterized by the growth of new blood vessels on the retina and posterior surface of the vitreous. This last criterion was chosen as the hallmark of diabetic nephropathy, thus excluding other possible causes for the increased AER, because renal biopsies are generally not indicated for diagnostic purposes in microalbuminuric diabetic patients. Exclusion criteria were diagnosis of the diabetes at <30 years of age, insulin therapy during the first 3 years of diagnosis of the disease, severe liver or heart failure, and known neoplastic or psychiatric disease. All consecutive subjects seen at the centers during a 6-month period from November 2002 to May 2003 and in accordance with the selection criteria were recruited for the study.

The study design called for two examinations 1–2 months apart; the first one was for screening and enrollment, and the second one became the study visit. For each patient, a medical history was taken, including blood pressure measurements at the first referral to the center. Laboratory data were collected at the study visit. The study visit included blood pressure monitoring as a mean of three measurements taken in a sitting position after 10 min of rest and with current drug regimens. Adherence to therapy was also assessed by questionnaire. Glomerular filtration rate (GFR) was estimated through the Cockroft-Gault equation and 24-h creatinine clearance; the values of creatinine clearance were corrected for a standard body surface area of 1.73 m^2. Daily salt intake (grams per day) was calculated by dividing 24-h urinary sodium excretion by 17. Patients were defined as ex-smokers if they had ceased smoking for >6 months.

The study was approved by the ethical committee of the Second University of Naples. All the patients gave their written informed consent for the collection and analysis of the data.

Twenty-one outpatient clinics in the Campania region of Italy (a geographic area characterized by a homogeneous prevalence of type 2 diabetes) were randomly chosen among all the regional clinics. In the design and implementation process, an effort was made to ensure consistency across the 21 centers in terms of data specification, data collection tools, and methods and the analysis and reporting of results. Blood pressure was measured according to European Society of Hypertension-European Society of Cardiology recommendations (14), with the use of validated mercury sphygmomanometers. Laboratory tests were performed at each investigative site. All the laboratories checked internal quality and participated in a control program for external quality by sending random blood and urine samples to a central laboratory (intra- and interassay variabilities were <0.5%).

Target definitions

Based on guidelines from the American Diabetes Association (15), Joint National Committee VII (16), and European Society of Hypertension–European Society of Cardiology (14), we considered the following recommended targets: <130/80 mmHg for blood pressure, <7% for HbA_{1c} (A1C), <100 mg/dl for LDL, >40 mg/dl (men) and >50 mg/dl (women) for HDL, and <150 mg/dl for triglycerides. The diagnosis of anemia was established according to World Health Organization criteria (Hb <13 g/dl in men and <12 g/dl in women).

Statistical analysis

Patients were analyzed all together and then after grouping according to targets for blood pressure. Student's *t* test for independent samples was used to compare measured variables among subjects who were or were not meeting their targets and between the micro- and macroalbuminuric groups. Multivariate logistic regression analysis was used to test the influence of the following variables: age, sex, BMI ≥30 kg/m^2, duration of hypertension, GFR <60 ml/min, and urinary sodium excretion >100 mmol/day on the achievement of target blood pressure, considered as dependent variable. Nonparametric tests were used to compare proportions. ANOVA or a Kruskal-Wallis test, when indicated, was used to compare the outcomes from the different sites. All statistical testing was two tailed. A *P* value <0.05 was considered statistically significant. Statistical Package Software System 8.0 for Windows (SPSS, Chicago, IL) was used.

RESULTS

— Overall, 28,550 diabetic patients were screened in the 21 participating centers. A total of 4,688 patients were initially excluded because of the diagnosis of type 1 diabetes (n = 1,412), age <40, diagnosis of the disease at <30 years of age, insulin therapy during the first 3 years of the disease (n = 542), severe liver or heart failure, or known neoplastic or psychiatric disease (n = 1,203) (for at least 1 year). Patients who were not regularly examined in the outpatient clinic (n = 1,531) were also excluded. Of 23,862 remaining patients, 23,015 were negative for microalbuminuria and/or background diabetic retinopathy. Specifically, 6,049 patients had microalbuminuria but not severe diabetic retinopathy. Following the strict selection criteria, 847 (398 male and 449 female) Caucasian patients were finally eligible for the study. The mean number of enrolled patients for each center was 40 (range 12–68).

The high compliance of the selected patients, who regularly received outpatients care for at least 1 year, together with the cross-sectional design of the study, allowed us to avoid dropouts. The main clinical and laboratory characteristics of the subjects are shown in Table 1.

The duration of follow-up from the first referral visit was equal to a mean of 6.9 years. Most of the patients were overweight (43.7%) or slightly obese (26.2%); the remaining were normal weight (17.9%), moderately obese (9%), and severely obese (3.2%).

More than half of the population (57.6%) were nonsmokers, whereas 158 (18.8%) were ex-smokers, and 198 (23.6%) were still smoking cigarettes. Acute myocardial infarction and transient ischemic attack/stroke were registered in 128 of 847 (15.1%) and 80 of 847 (9.4%) patients, respectively; 13 subjects experi-

Table 1—*Clinical characteristics and laboratory parameters of the participants*

Age (years)	65.7 ± 8.7
Men (%)	47
BMI (kg/m^2)	29.3 ± 4.9
Systolic blood pressure (mmHg)	136.7 ± 13.5
Diastolic blood pressure (mmHg)	78.6 ± 6.8
Duration of hypertension (years)	8.5 ± 6.7
Cigarette smoking (%)	23.6
At least one cardiovascular event (%)	23.0
Left ventricular hypertension (%)	30.9
Hospitalization in the last year (%)	21.8
Family history for cardiovascular event (%)	27.7
A1C (%)	7.5 ± 1.3
Serum creatinine (mg/dl)	1.2 ± 0.6
Total cholesterol (mg/dl)	196.5 ± 40
LDL cholesterol (mg/dl)	118.6 ± 34.9
HDL cholesterol (mg/dl)	47.5 ± 11.8
Triglycerides (mg/dl)	151.6 ± 77.5
Serum uric acid (mg/dl)	5.2 ± 1.4
Hemoglobin (g/dl)	13.2 ± 1.4
Micro-/macroalbuminuric (*n*)	749/98
GFR (ml/min per 1.73 m^2)	72.7 ± 24.7
Urinary sodium excretion (mmol/day)	169.8 ± 78.7

Data are means ± SD unless otherwise indicated. Cardiovascular event includes acute myocardial infarction, transient ischemic attack, or stroke.

enced both. Left ventricular hypertrophy was diagnosed in 261 (30.9%) of the patients by either a 12-lead electrocardiogram or echocardiography, according to criteria of American Society of Echocardiography (17).

In our study, 148 (17.5% [95% CI 14.9–20.0]) of patients had target systolic and diastolic blood pressure measurements at the study visit; the systolic goal was reached less frequently than the diastolic target. Systolic blood pressure, indeed, was found to be on target in 211 (24.9% [22.0–27.8]) subjects, whereas diastolic blood pressure was found to be on target in 359 (42.4% [39.1–45.7]) subjects. Blood pressure measurement at the first referral visit to the center revealed that the targets were both reached in only 71 (8.4%) patients, with a mean value of 145/83 mmHg.

In microalbuminuric patients, the mean value of AER was 116 mg/day (range 30–290); in macroalbuminuric patients the mean value of AER was 585 mg/day (300–2,900). A consistent number of patients (359 of 847, 42.4%) had mildly decreased GFR (60–89.9 ml/min). Chronic renal failure (GFR <60 ml/min) was revealed in 41% patients (347 of 847), with most of them (36.5%) showing moderate dysfunction (GFR 30–59.9 ml/min). Interestingly, chronic renal failure was observed in 38.1% of microalbuminuric and 61.8% of macroalbuminuric patients. It is notable that only 92 of 367 (25.1%) of the patients with overt nephropathy (GFR <60 and/or AER >300 mg/day) were followed by a nephrology specialist.

Anemia was revealed in 202 of 847 (23.8%) patients. The distributions of anemic patients according to renal function and the level of albuminuria are shown in Fig. 1. The proportions of anemic patients within those with normal or mildly decreased GFR were similar in both micro- and macroalbuminuria ranges. Conversely, the proportions was statistically higher ($P < 0.001$) in both micro-and macroalbuminuric patients with a moderately decreased GFR when compared with patients with normal or mildly decreased GFR.

Total cholesterol was <200 mg/dl in 491 of 847 (57.9%) patients. Triglycerides and HDL cholesterol were on target in 468 of 847 (55.2%) and 398 of 847 (47%) patients, respectively. In contrast, LDL cholesterol was on target in 30.7%. Glucose metabolism control, as judged by A1C value, was on target (i.e., <7%) in 32.3% of patients, with optimal values (i.e., <6.5%) in 19.7% patients and very bad control (i.e., ≥10%) in only 5.1%.

Antihypertensive treatment was accurately evaluated. After the exclusion of normotensive patients (i.e., those with blood pressure <130/80 mmHg without therapy, $n = 25$), the remaining patients were treated with at least three drugs (223 of 822, 27.1%), two drugs (269 of 822, 32.7%), one drug (252 of 822, 30.7%), or no drug (78 of 822, 9.5%). ACE inhibitors and/or angiotensin receptor blockers were prescribed in 74.5% of the patients. Loop diuretics were prescribed in 13.2% of patients, at a mean dose of 41.7 ± 75.6 mg/day of furosemide. Dietary salt restriction, based on urinary sodium excretion ≤100 mmol/day, was observed only in 18.7% of patients overall and in 15.7% of patients with GFR <60 ml/min. Patients who reached blood pressure targets were more often treated with calcium channel blockers (41.3 vs. 24.3%, $P < 0.001$), α-blockers (12.0% vs. 5.4%, $P < 0.001$), and loop diuretics (14.3 vs. 7.4%, $P < 0.05$) than those who were treated with other antihypertensive agents. Conversely, the uses of other antihypertensive drugs were similar in the two groups. Other chronic treatments included β-cell–stimulating agents (48.9%), metformin (45.8%), insulin (41.4%), oral hypoglycemic agents and insulin (16.3%), hydroxymethylglu-

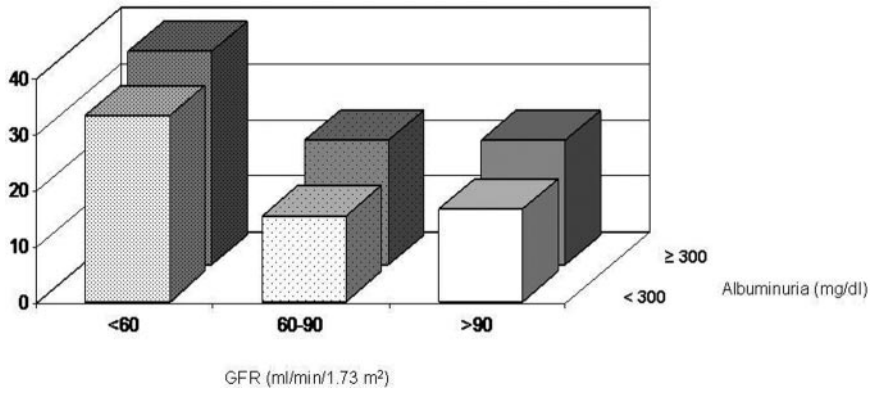

Figure 1—*Prevalence of anemic patients according to World Health Organization criteria in the patients after grouping for renal function and level of albuminuria.*

Table 2—*Comparison between patients at target and not at target for blood pressure (top) and between micro- and macroalbuminuric patients (bottom)*

	Target	No target	*P*
n	148	699	
Age (years)	63.3 ± 9.2	66.3 ± 8.6	<0.001
BMI (kg/m^2)	28.0 ± 4.1	29.6 ± 5.0	<0.001
Duration of hypertension (months)	94.1 ± 68.2	103.7 ± 82.5	0.214
A1C (%)	7.5 ± 1.3	7.5 ± 1.3	0.982
Total cholesterol (mg/dl)	192.2 ± 38.9	197.5 ± 40.2	0.133
LDL cholesterol (mg/dl)	115.7 ± 35.0	118.8 ± 36.0	0.267
HDL cholesterol (mg/dl)	47.6 ± 10.6	47.5 ± 12.1	0.879
Triglycerides (mg/dl)	140.4 ± 63.4	154.0 ± 80.1	0.114*
Hemoglobin (g/dl)	13.1 ± 1.3	13.2 ± 1.5	0.433
GFR (ml/min per 1.73 m^2)	77.1 ± 25.2	71.8 ± 24.6	0.038
AER (mg/day)	120.6 ± 142.0	159.8 ± 229.8	0.042*
Urinary sodium excretion (mmol/day)	157.4 ± 66.3	172.5 ± 81.0	0.035
Number of drugs	1.6 ± 1.1	1.9 ± 1.2	0.002

	Microalbuminuric	Macroalbuminuric	*P*
n	749	98	
Age (years)	65.7 ± 8.8	66.3 ± 8.6	0.501
BMI (kg/m^2)	29.3 ± 4.9	29.2 ± 4.9	0.816
Systolic blood pressure (mmHg)	136.3 ± 13.1	140.3 ± 14.6	0.011
Diastolic blood pressure (mmHg)	78.5 ± 6.7	79.1 ± 8.0	0.473
A1C (%)	7.5 ± 1.3	7.7 ± 1.3	0.244
Total cholesterol (mg/dl)	195.9 ± 39.0	201.6 ± 46.9	0.262
LDL cholesterol (mg/dl)	118.1 ± 35.1	119.9 ± 41.7	0.510
HDL cholesterol (mg/dl)	47.5 ± 11.8	48.2 ± 11.9	0.521
Triglycerides (mg/dl)	119.4 ± 74.4	168.3 ± 96.9	0.053*
Hemoglobin (g/dl)	13.2 ± 1.4	12.7 ± 1.8	0.002
GFR (ml/min per 1.73 m^2)	74.5 ± 24.1	60.1 ± 25.8	<0.001
Urinary sodium excretion (mmol/day)	169.2 ± 78.9	174.1 ± 78.0	0.613

Data are means ± SD. *Mann-Whitney test.

taryl-CoA reductase inhibitors (52.9%), and antiplatelet agents (43.2%).

The comparisons of clinical and laboratory parameters after grouping for blood pressure target achievement at the study visit and between micro- and macroalbuminuric patients are shown in Table 2. In multiple logistic regression analysis, when the achievement of the blood pressure target was considered a dependent variable, only BMI ≥30 kg/m^2 ($P = 0.04$, odds ratio 1.77 [95% CI 1.01–3.07[) and urinary sodium excretion >100 mmol/day ($P < 0.01$, 2.25 [1.25–4.05]) were predictive of not achieving the target, whereas sex, age (10 years), duration of hypertension (2 years), and GFR <60 ml/min were not.

CONCLUSIONS — We originally identified a population with early or moderate diabetic nephropathy strictu sensu from a larger cohort of patients with type 2 diabetes to study the prevalence as well as the management of major cardiorenal risk factors. This study originally evaluated parameters, such as hemoglobin and urinary sodium excretion, that are usually overlooked and also suggests them as possible targets of a multifactorial intervention.

Target intervention against multiple risk markers is, today, the primary way to reduce cardiovascular disease, even in patients with diabetic neuropathy. Nevertheless, intervention trials have shown (7,18,19) that following the guideline is overly ambitious and corresponds to idealism rather than clinical reality.

In our study, the assessment and treatment of hypertension highlight problems with its control, with only 24.9 and 42.4% of the patients reaching the recommended targets for systolic and diastolic blood pressure, respectively (17.5% for both). We observed for the first time that age, BMI, AER, and urinary sodium excretion were higher, whereas GFR was lower in type 2 diabetic patients with diabetic nephropathy who were not on target for blood pressure compared with those who were.

These findings could suggest the importance of weight, AER, and urinary sodium excretion reduction in controlling blood pressure in diabetic patients with diabetic nephropathy. In particular, for dietary salt restriction, patients with diabetic nephropathy develop sodium-sensitive hypertension as renal dysfunction progresses because urinary sodium excretion decreases (20), and, conversely, a low sodium intake improves the efficacy of antiproteinuric drugs (19). Similarly, the mean daily dose for loop diuretics seems inadequate, in light of the reduced number of functioning nephrons, lower renal blood flow, accumulation of organic acids, and proteinuria that characterize patients with chronic kidney disease (21).

Triglycerides and HDL cholesterol values were much more often within recommended ranges than LDL cholesterol. The target of 100 mg/dl was achieved in 30.7% of the overall population, but most of them did not receive pharmacological treatment. Actually, only 17.2% of the treated patients were at target. As for glycemic control, again, the established target of 7% for A1C was reached in only 31.2% of patients.

As already stated, there are no studies specifically designed to evaluate the control of risk factors for renal and cardiovascular disease among diabetic patients with diabetic nephropathy but only in generic diabetic populations (22–24). Previous data showed that in microalbuminuric diabetic subjects, GFR is generally well preserved. In our study, chronic renal failure (GFR <60 ml/min) was revealed in 41% patients. Specifically, we found that 38.1% of the microalbuminuric patients had chronic renal failure. These original results seem to confirm the fact that our population has classical diabetic nephropathy, with more severe renal damage than a diabetic population with generic microalbuminuria. In other words, we selected patients with an especially severe form of microangiopathy. On the other hand, these findings support the need to screen not only for microalbuminuria but also for diabetic nephropathy by the simple and inexpensive clinical method.

A number of investigators have pointed out the role of anemia as a risk factor for nephropathy and cardiovascular disease in diabetic subjects. Recent data (4) suggest that hemoglobin is an in-

dependent risk factor for progression of nephropathy to ESRD in type 2 diabetes and that even mild anemia (Hb <13.8 g/dl) increases the risk for this progression. In our study, 23.8% of patients were anemic. Patients with more pronounced renal failure had a greater likelihood of being anemic, as well as those with higher levels of albuminuria compared with those with lower levels.

The present study is limited by the analysis of prescription of rather than adherence to therapy; however, the possibility that patients were not compliant with prescribed therapy is plausibly reduced by the selection of patients with regular follow-up in the same clinic. On the other hand, this potential bias becomes less important when considering that prescribed therapy was per se largely inadequate.

In summary, clinical diagnosis of diabetic nephropathy strictu sensu allows the identification of a group of patients at very high cardiorenal risk, for whom care is really difficult. Notably, impaired renal function can be often diagnosed in these patients even in the presence of microalbuminuria. Therefore, we suggest that type 2 diabetic patients with diabetic nephropathy should always be identified according to clinic criteria. Moreover, sodium intake and anemia should be routinely evaluated in these patients, together with the other cardiorenal risk factors.

The well-known dichotomy between controlled clinical trials and ambulatory practice is an obstacle to overcome by implementing the guidelines to manage diabetic subjects. Based on these results, it seems opportune to evaluate the feasibility and efficacy in routine practice of an intensive multifactorial intensive treatment on cardiovascular and renal outcome in type 2 diabetic patients with diabetic nephropathy.

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APPENDIX

NID-2 (Nephropathy in Diabetes-Type 2) Study Group

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