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Awareness of albuminuria in an Italian population-based cohort of patients treated with hypoglycemic drugs

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Abstract

Background: **Albuminuria is a powerful predictor of renal and cardiovascular outcomes in type 2 diabetes and a good indicator of the evolution of renal disease. Our aim was to obtain information concerning the identification of albuminuria as well as the utilization of antihypertensive, lipid-lowering and antiplatelet drugs in patients with diabetes.**

Methods: **Subjects were enrolled from individuals registered with 3 Italian local health units by querying the drugs reimbursable, hospital laboratory investigation and hospital discharge databases. The determination of albumin to creatinine ratio (ACR) throughout 2007 and 2008 was defined as the index date. Patients who received at least 2 prescriptions of hypoglycemic drugs in the 12 months before the index date were classified as diabetics. We looked also for prescriptions of antihypertensive, lipid-lowering and antiplatelet drugs.**

Results: **Among a population of 701,133 subjects, we identified 29,350 patients with diabetes (4.2% of the cohort). ACR had been determined in 5,644 diabetic subjects (19.2% of that cohort). The prevalence of determination of ACR in nontreated subjects was 16.0%, while in treated subjects, it ranged from 13.6% to 34.9% according to different schedules of treatment. Drugs acting on the renin-angiotensin system were prescribed in more then 80% of diabetics. The ratio of angiotensin receptor blockers to angiotensin-converting enzyme inhibitors regimen was 0.64 in subjects without determination of ACR, 0.88 in subjects with normal albuminuria, 1.02 in subjects with microalbuminuria and 1.43 in subjects with macroalbuminuria.**

Conclusions: **Our methodology can easily be applied to obtain an epidemiological view of albuminuria and pharmacological treatments of diabetics in a general population.**

Key words: *Albuminuria, Angiotensin receptor blockers, Antihypertensive therapy, Type 2 diabetes*

Introduction

The presence of albuminuria is a well-known and powerful predictor of poor renal outcomes in patients with type 2 diabetes mellitus (1-3). Albuminuria has also been shown more recently to be a predictor of poor cardiovascular outcomes in this population (4-6). While there are no randomized trials demonstrating that screening for albuminuria in diabetic patients improves clinical outcomes, the American Diabetes Association recommends that patients with type 2 diabetes be tested for albuminuria at the time of initial diabetes diagnosis and yearly thereafter (7). Despite these recommendations, there are few orchestrated strategies of screening for albuminuria, and there is evidence that diabetic patients are often not screened for albuminuria and that the presence of abnormal levels of albuminuria may go unidentified. It has become increasingly clear that albuminuria should not only be measured in all patients with type 2 diabetes, but also that steps should be taken to suppress albuminuria to prevent future renal and cardiovascular adverse events (8). There are emerging data that reduction of albuminuria leads to reduced risk of adverse renal and cardiovascular events (9-11). Initiation of angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) therapy should be considered in patients with microalbuminuria or overt proteinuria (12, 13). The level of albuminuria should be followed up during treatment, and doses of the ACE-I or ARB should be titrated upward to maximize the beneficial effect on albuminuria. To our knowledge, no data are available concerning the awareness of albuminuria in diabetic patients in Italy. Thus, the aim of the present survey was to obtain information concerning the identification of albuminuria as well as the utilization of antihypertensive (AH), lipid-lowering (LL) and antiplatelet (AP) drugs in diabetic patients, by querying the electronic records of 3 local health units in 3 Italian regions: the Survey on Medications Adherence in Cardiovascular Kidney Prevention (SMACK) study.

Subjects and methods

Data source

The study subjects were enrolled from individuals registered with 3 local health units (LHUs) located in northern and central Italy who were permanently eligible over the study period. The ethics committees of the 3 LHUs approved this study. The LHU is a body delegated by the national health system to serve a specific geographical area, generally a province, providing health care. The LHU, being a point of delivery for the central health system, has an administrative/accounting-type archive that is used conventionally for recording the amounts that pharmacies are entitled to receive from the LHU by way of refund in respect of drugs reimbursable by the Italian National Health System and dispensed free of charge. This archive has been structured in such a way as to enable a patient-oriented reading: the prescriptions recorded are attributed in each case to the patient-recipient. The data available in each prescription include the patient's national health number, the prescribing physician's number, the Anatomical Therapeutic Chemical (ATC) code of the drug purchased, the number of packs, the number of units per pack, the dosages, the unit cost per pack and the prescription date. The identification of the patient given by the personal health number, cross-checked with the registry office, hospital laboratory investigation database and hospital discharge database, allows the information to be integrated with date of birth and sex, date and results of laboratory tests, and any record of previous hospitalizations for cardio-cerebrovascular (CV) diseases.

Study design

The SMACK study was a retrospective cohort study, which included all subjects aged 18 years or more living in the area of the 3 LHUs considered. Patients who died or moved away during the follow-up period were excluded from the study. During the study period, from 1 January 2007 to 31 December 2008, we looked for the determination of albumin to creatinine ratio (ACR) in a morning urine sample in the diabetic patients. The performance date was defined as the index date. Patients who received at least 2 prescriptions for hypoglycemic drugs (ATC code A10) in the 12 months before the index date were classified as diabetics. In the 12 months before the index date (and in the 12 months before the study period in diabetic patients without determination of ACR) we looked also for at least 2 prescriptions for AH drugs (diuretics [ATC code C03], beta-blockers [ATC code C07], calcium channel blockers [ATC code C08], ACE-I [ATC code C09A/B], ARB [ATC code C09C/D], LL drugs [ATC code C10], AP drugs [ATC code B01AC] and cardiac drugs [ATC code C01]). Moreover, we looked for hospitalizations for CV diseases (ICD-9 codes: 401-405, for arterial hypertension; 410, acute myocardial infarction; 411-414, coronary disease; 428, heart failure; 430-438, cerebral circulatory dysfunction; 440-442, arteriosclerosis of the main arteries and aneurysm; and 584-585, chronic kidney disease) in the 24 months before the index date or before the study period in diabetic subjects with or without the determination of ACR.

ACR values <30 mg/g creatinine were defined as normal, ACR values falling between 30 and 299 mg/g creatinine were identified as in the microalbuminuria range, while ACR values ≥300 mg/g creatinine were defined as macroalbuminuria (12). AH treatment was defined as ARB-based if at least a prescription for ARB, with or without other AH drugs, was present; as ACE-I–based if at least a prescription for ACE-I, with or without other AH drugs but not ARB, was present; and as no renin-angiotensin system (RAS) blockade, if prescriptions for AH drugs, but not ARB or ACE-I, were present.

Statistical analysis

We summarized data as mean values with standard deviations for continuous variables and as numbers (percentages) of subjects for categoric variables. Statistical significance of proportions was calculated using the 2-sided chi-square test; statistical significance of averages was calculated using analysis of variance (ANOVA). A p value <0.05 was considered significant. All statistical analysis were conducted using SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Among a population of 701,133 subjects aged 18 years or more living in the area of the 3 LHUs considered, we identified 29,350 individuals with diabetes (4.2% of the whole cohort). The characteristics of the diabetic cohort compared with the nondiabetic cohort are shown in Table I. Diabetic patients compared with nondiabetic patients were significantly older, with an higher prevalence of previous hospital admissions for CV reasons, as well as a higher prevalence of treatment with AH, LL, AP and cardiac drugs.

In Table II, we report the prevalence of diabetic and nondiabetic subjects treated with a unique class of drugs (AH or LL or AP), as well as with associations of different classes of drugs. In the diabetic cohort, 5,172 patients (17.6% of the whole cohort) and 510,303 patients in the nondiabetic cohort (76.0% of the whole cohort) had not received any prescription for the 3 classes of drugs considered. Diabetic patients were significantly more treated than nondiabetic patients, with the 3 classes of drugs considered either as monotherapy or as an association of 2 or 3 drugs.

ACR had been determined in 5,644 diabetic patients (19.2% of the whole diabetic cohort). In 22,017 diabetics treated with AH drugs, the ACR had been determined in 4,289 subjects (19.5% of that cohort); and in 8,966 diabetics treated with LL drugs, ACR had been determined in 2,542 subjects (28.4% of that cohort). The relationships among different pharmacological schedules of treatment and determination of ACR are reported in Table III. In diabetic patients who did not received any pharmacological treatment with AH and/or LL and/or AP drugs, compared with treated diabetics, the ACR had less frequently been determined (16.0% vs. 19.9%, respectively). ACR was significantly more frequently determined in treated patients independently from the schedule of treatment (monotherapy or therapy with 2 or 3 drugs) except in patients treated with monotherapy based on AP or AH drugs and in patients treated by an association of AH and AP drugs. The prevalence of determination of

TABLE I
CHARACTERISTICS AND PHARMACOLOGICAL TREATMENTS OF THE PATIENTS EVALUATED

	Diabetic	Nondiabetic	p Value, ≤
Patients, no.	29,350	671,783	
Age, mean (SD)	70.3 (12.5)	50.1 (19.1)	0.001
Sex, % male	50.2	48.0	0.001
Patients treated with AH drugs, no. (%)	22,017 (74.9)	147,944 (22.0)	0.001
Patients treated with LL drugs, no. (%)	8,966 (30.5)	27,673 (4.1)	0.001
Patients treated with AP drugs, no. (%)	11,593 (39.5)	51,259 (7.6)	0.001
Patients treated with cardiac drugs, no. (%)	4,520 (15.4)	21,682 (3.2)	0.001
Patients with previous CV event, no. (%)	4,751 (16.2)	21,189 (3.2)	0.001

AH = antihypertensive; AP = antiplatelet; CV = cardio-cerebrovascular; LL = lipid-lowering.

ACR in untreated patients was 16.0%, while in pharmacologically treated subjects, the prevalence of determination of ACR ranged from 13.6% in diabetics treated with AH drugs to 34.9% in diabetics treated with the association of LL and AP drugs.

In the 5,644 diabetic patients with recorded ACR, 4,521 patients (80.1%) had a normal level of albuminuria (ACR <30 mg/g), 967 patients (17.1%) had microalbuminuria (ACR between 30 and 299 mg/g) and 156 patients (2.8%) had macroalbuminuria (ACR ≥300 mg/g). The exposure to the 3 different AH drug regimens evaluated (based on ARB, on ACE-I or on no RAS blockade) was significantly different (p<0.001) in diabetics with known ACR compared with diabetics with unknown ACR (Tab. IV). In patients treated with a drug acting on the RAS, the ratio of ARB/ACE-I regimens was 0.64 in the subjects without determination of ACR (a

TABLE II
DIABETIC AND NONDIABETIC SUBJECTS PHARMACOLOGICALLY TREATED

	Diabetic	Nondiabetic	p Value, ≤
Patients treated with AH drugs, no. (%)	8,984 (30.6)	97,147 (14.5)	0.001
Patients treated with LL drugs, no. (%)	810 (2.8)	4,212 (0.6)	0.001
Patients treated with AP drugs, no. (%)	933 (3.2)	7,793 (1.2)	0.001
Patients treated with LL + AH drugs, no. (%)	2,791 (9.5)	8,862 (1.3)	0.001
Patients treated with LL + AP drugs, no. (%)	418 (1.4)	1,531 (0.2)	0.001
Patients treated with AH + AP drugs, no. (%)	5,295 (18.0)	28,867 (4.3)	0.001
Patients treated with LL + AH + AP drugs, no. (%)	4,947 (16.9)	13,068 (1.9)	0.001

AH = antihypertensive; AP = antiplatelet; LL = lipid-lowering.

TABLE III
PRESENCE OF AT LEAST A DETERMINATION OF ACR IN DIABETIC PATIENTS ACCORDING TO MODALITY OF PHARMACOLOGICAL TREATMENT

	Diabetics with determination of ACR	Diabetics without determination of ACR	p Value, ≤
No treatment, no. (%)	830 (14.7)	4,342 (18.3)	0.001
Treatment with LL drugs, no. (%)	213 (3.8)	597 (2.5)	0.001
Treatment with AH drugs, no. (%)	1,226 (21.7)	7,758 (32.7)	0.001
Treatment with AP drugs, no. (%)	166 (2.9)	767 (3.2)	0.257
Treatment with LL + AH drugs, no. (%)	715 (12.7)	2,076 (8.8)	0.001
Treatment with LL + AP drugs, no. (%)	146 (2.6)	272 (1.1)	0.001
Treatment with AH + AP drugs, no. (%)	880 (15.6)	4,415 (18.6)	0.001
Treatment with LL + AH + AP drugs, no. (%)	1,468 (26.0)	3,479 (14.7)	0.001

ACR = albumin to creatinine ratio; AH = antihypertensive; AP = antiplatelet; LL = lipid-lowering.

total of 14,866 diabetics), 0.88 in the subjects with normal albuminuria (a total of 2,984 diabetics), 1.02 in subjects with microalbuminuria (a total of 740 diabetics) and 1.43 in subjects with macroalbuminuria (a total of 134 diabetics).

Discussion

Microalbuminuria is the earliest indicator of diabetic kidney disease, as well as a good indicator of the evolution of renal disease since it may revert to normoalbuminuria, persist or progress to macroalbuminuria or proteinuria. The present survey conducted in a study sample of patients treated with hypoglycemic drugs recruited from the general population showed (a) a record of ACR equal to 19.2%, (b) microalbuminuria and macroalbuminuria prevalences of 17.1% and 2.8%, respectively, among patients with known ACR, and (c) a high exposure to AH treatment with a prevalent use of drugs acting on the RAS system.

In our survey, the awareness of albuminuria of about 20% could be an underestimation. We have looked in the laboratory database for ACR only, while other methods to evaluate albuminuria (i.e., urine dipstick test, total excretion in 24-hour urine and excretion in a morning sample not related to creatinine excretion) could be used. Given the importance of albuminuria, we have chosen to evaluate ACR, which is today considered the best practice (7, 12, 14, 15). Regarding the absolute value of ACR, because the results of existing studies on this issue are based on different subject characteristics (age range, inclusion of type 1 and/or type 2 diabetes, ethnicity, etc.) or setting (general practice, diabetics surgery, etc.), comparisons with regard to the prevalence of microalbuminuria and macroalbuminuria are difficult. In the Third National Health and Nutrition Examination Survey, the prevalence of albuminuria among subjects with type 1 and 2 diabetes was 28.1% for microalbuminuria and 6.1% for macroalbuminuria (16), whereas in a study from Germany, the prevalence of microalbuminuria and macroalbuminuria in type 2 diabetic patients was 19% and 5.2%, respectively (17). In a previous survey from Italy (18), the prevalence of albuminuria was 49.7% in known type 2 diabetic patients (32.1% microalbuminuria, 17.6% macroalbuminuria).

In the present study, 74.9% of patients treated with hypoglycemic drugs were prescribed with AH drugs. Compared with subjects not treated with AH drugs, treated subjects were older, had suffered an higher number of previous CV events and were more treated with LL, AP and cardiac drugs. This finding is plausible and in agreement with findings from controlled studies (12, 19, 20) that showed that the treatment of hypertension is a crucial target to interfere with the progression of diabetic nephropathy toward chronic kidney diseases and CV morbidity and mortality. Among AH drug users, a high percentage of patients were treated with drugs acting on the RAS, or ACE-I or ARB, as recommended by international guidelines for diabetic patients (7, 12, 21). Moreover, the prevalence of use of drugs acting on the RAS seems to be related to evaluation of albuminuria, while the prescription of an ARB regimen rather than an ACE-I regimen seems to be higher in subjects with known ACR compared with subjects with unknown ACR, and seems to increase according to the increase of ACR levels. This finding in clinical practice is not surprising since clinical trials have shown the efficacy of ARBs in preventing the progression of microalbuminuria (11, 22).

The SMACK study had some limitations that need to be considered. It was cross-sectional in design, thus longitudinal trends in the management of the disease cannot be taken into account. Since only diabetic patients on hypoglycemic drugs were included, results should not, therefore, be applied to undiagnosed and untreated diabetic patients. Furthermore, a single random urine sample was used to define the ACR level, thus data on the reproducibility of albumin excretion were not available. Finally, this selection may have underestimated the awareness of albuminuria because other methods of measurement have not been taken into account. However, the present study also has some strengths. The study was based on participants recruited from the general population through analysis of the database of drugs purchased by the national health system, thus considering subjects managed by general practitioners as well as diabetologists. Moreover, the link between ad-

TABLE IV
AH REGIMENS IN DIABETIC PATIENTS ACCORDING TO PRESENCE OR NOT OF ACR RECORD

	Diabetics with ACR	Diabetics without ACR
ARB-based regimen, no. (%)	1,853 (43.2)	5,821 (32.8)
ACE-I–based regimen, no. (%)	2,005 (46.7)	9,045 (51.0)
No RAS blockade, no. (%)	431 (10.0)	2,862 (16.1)

ACE-I = angiotensin-converting enzyme inhibitor; ACR = albumin to creatinine ratio; AH = antihypertensive; ARB = angiotensin receptor blocker; RAS = renin-angiotensin system.

ministrative databases and laboratory database is simple to perform and does not require an epidemiological organization, and thus the cost is very low. Furthermore, the present paper contains data on the treatment with AH drugs, which are one of the most important therapeutic approaches in diabetic patients.

Since diabetes represents one of the prevalent problems in all health systems, we believe that our methodology can be applied to obtain an epidemiological view of albuminuria and AH treatment, and the method we have applied can help to improve care for diabetic patients in the general population.

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