Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: A global perspective

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We described the characteristics in a referred cohort of type II diabetic patients in the Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes study evaluating the global prevalence and determinants of microalbuminuria (MA). A cross-sectional study evaluating 32 208 type II diabetic patients without known albuminuria from 33 countries was performed. Overall, 8057 patients were excluded, either because of prior known proteinuria or non-diabetic nephropathy (3670), or because of invalid urine collections (4387). One single random urinary albumin/creatinine ratio was obtained in 24 151 patients (75%). The overall global prevalence of normo-, micro-, and macroalbuminuria was 51, 39, and 10%, respectively. The Asian and Hispanic patients had the highest prevalence of a raised urinary albumin/creatinine ratio (55%) and Caucasians the lowest (40.6), $P<0.0001$. HbA1c, systolic blood pressure (BP), ethnicity, retinopathy, duration of diabetes, kidney function, body height, and smoking were all independent risk factors of MA, $P<0.0001$. Estimated glomerular filtration rate was below 60 ml/min/1.73 m^2 in 22% of the 11 573 patients with available data. Systolic BP below 130 mmHg was found in 33 and 43% had an HbA1c below 7%. The frequency of patients receiving aspirin was 32%, statins 29%, and BP-lowering therapy 63%. A high prevalence globally of MA and reduced kidney function, both conditions associated with enhanced renal and cardiovascular risk, was detected in type II diabetic patients without prior known nephropathy. Early detection, monitoring of vascular complications, and more aggressive multifactorial treatment aiming at renal and vascular protection are urgently needed.

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In 1969, Keen *et al.*[1] first described microalbuminuria (MA) (an abnormal increase in the rate of urinary excretion of albumin to between 30 and 300 mg/24 h) in patients with diabetes mellitus. Five years later, Parving *et al.*[2] demonstrated that MA was associated with essential hypertension in non-diabetic subjects. In the early 1980s, several longitudinal studies in type I and type II diabetes documented that MA was a powerful independent risk factor for developing diabetic nephropathy.[3–5] Later, several prospective epidemiologic studies demonstrated that MA is an important risk factor for cardiovascular disease (CVD) in type II diabetic patients. A meta-analysis of these studies showed that the presence of MA doubles the risk of cardiovascular morbidity or mortality.[6] Observational studies in non-diabetic subjects have revealed that MA is also an independent powerful risk factor for fatal and non-fatal vascular events and all-cause mortality.[7,8] Conversely, a prespecified analysis revealed that reduction in urinary albumin excretion translates to reduction in cardiovascular events in hypertensive patients treated with blockade of the renin-angiotensin system.[9] Intervention studies aiming at improved glycemic control and blockade of renin-angiotensin system have both demonstrated that the development of diabetic nephropathy can be postponed in type II diabetic patients with normoalbuminuria and/or MA.[10–12] Despite the knowledge gained in relation to early identification and intervention in high-risk type II diabetic patients, diabetic nephropathy is still the leading cause of end-stage renal disease in most countries of the world.[13]

In 2003, the International Diabetes Federation and the International Society of Nephrology developed the theme, 'Diabetes could cost you your kidneys: Act Now!' We acted in collaboration with these two organizations and Bristol-Myers Squibb and Sanofi-Aventis to create a study on Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes (DEMAND). This cross-sectional global study describes the prevalence and risk factors for MA, and implementation of cardiovascular protective treatment in normo- and hypertensive type II diabetic patients without known proteinuria and/or

non-diabetic kidney disease. The study is clinic/medical center based and not population based.

RESULTS

The characteristics of the patients according to ethnic groups are shown in Table 1. Overall, the mean age was 61 years, the gender distribution 50/50, mean duration of diabetes 7.6 years, HbA1c 7.5% (but data missing in 37% of the patients), diabetic retinopathy present in 12%, 23% of the patients had a prior history of any CVD, and 26% had a history of smoking. Table 1 shows that the Hispanic group differs from the other groups by a lower male participation, higher HbA1c, family history of diabetes and CVD, presence of retinopathy, whereas prevalence of hypertension was lower. The Caucasian group had the lowest HbA1c but the highest frequency of hyperlipidemia and positive history of CVD. The African group was characterized by being youngest with the shortest known diabetes duration.

Diabetes treatments received by our patients are presented in Table 2. Only 9% received diet alone, whereas the remaining received oral hypoglycemic drugs and/or insulin. The Caucasian group was characterized by the highest frequency of antihypertensive treatment, number of antihypertensive agents, use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, lipid-lowering agents, and anticoagulant/platelet agents (Table 2). Among the 24 151 patients in our final data set, 19 574 (81%) had systolic blood pressure (BP) $\geqslant$130 mmHg and/or diastolic BP $\geqslant$80 mmHg; 859 (3.6%) had missing data about antihypertensive use. There is little difference in the fraction of patients not on antihypertensives among normo-, micro-, and macroalbuminuric patients (34, 29, and 30%, respectively. Antihypertensive drugs were prescribed to 63% of the patients who on average received 1.7 agents daily. Drugs blocking the RAS, followed by diuretics and calcium-channel blockers were most commonly used. The number of BP-lowering drugs increased with the level of systolic BP. The percentage of patients not receiving antihypertensive medication dropped from approximately 35% at a systolic BP level of 140 mmHg to approximately 10% at a systolic BP equal to 200 mmHg.

Table 1 | Characteristics of patients with type II diabetes by ethnic group

	Caucasian	African	Asian	Other	Hispanic	Missing[a]	Total	*P*-value
Demographic characteristics								
Number	9441 (39%)	490 (2%)	9111 (38%)	661 (2.7%)	1180 (4.9%)	3259 (13%)	24 151 (100%)	
Age (years)	63.2±11.2	54.4±10.7	59.9±11.6	60.4±12.2	57.1±11.8	63.1±11.6	61.4±11.7	<0.0001
Age (% missing)	202 (2.1)	6 (1)	97 (1)	16 (2.4)	28 (2.4)	238 (7.3)	587 (0.24)	<0.0001
Gender								
Male	4730 (50%)	253 (52%)	4.498 (49%)	357 (54%)	436 (37%)	1530 (47%)	11 804 (49%)	<0.0001
Female	4604 (49%)	235 (48%)	4572 (50%)	300 (45%)	745 (63%)	1643 (50%)	12 099 (50%)	
Missing	107 (1%)	2 (0.4%)	41 (0.5%)	4 (0.6%)	8 (0.7%)	86 (2.6%)	248 (0.1%)	
Region								
Europe	5792 (61%)	12 (2.4%)	94 (1%)	174 (26%)	36 (3%)	2216 (68%)	8324 (34%)	<0.0001
Asia	7 (0%)	2 (0.5%)	7844 (86%)	17 (2.6%)	0 (0%)	716 (22%)	8586 (36%)	
Africa	497 (5%)	359 (73%)	342 (3.8%)	62 (9.4%)	0 (0%)	71 (2.2%)	1331 (5.5%)	
North America	2095 (22%)	93 (19%)	325 (3.6%)	123 (19%)	922 (78%)	100 (3.1%)	3658 (15%)	
Central/South America	223 (2.4%)	22 (4.5%)	9 (0.1%)	189 (29%)	231 (19%)	61 (1.9%)	735 (3%)	
Oceania	827 (8.8%)	2 (0.4%)	497 (5.5%)	96 (15%)	0 (0%)	95 (2.9%)	1517 (6.3%)	
Clinical characteristics								
Height (cm)	166.5±10.0	165.5±9.2	161.8±8.8	163.2±9.8	158.3±9.5	165.1±9.9	164.0±9.8	<0.0001
Height (% missing)	132 (1.4)	24 (4.9)	123 (1.4)	11 (1.7)	13 (1.1)	121 (3.7)	424 (1.8)	<0.0001
BMI (kg/cm^2)	30.0±5.6	30.7±5.7	24.9±4.1	28.6±5.1	28.5±4.9	28.4±5.3	28.8±5.5	<0.0001
BMI (% missing)	186 (2)	25 (5.1)	148 (1.6)	25 (3.8)	18 (1.5)	146 (4.5)	548 (2.3)	<0.0001
Duration of diabetes (years)	7.8±6.2	6.7±5.1	7.1±6.1	7.9±6.2	8.2±6.5	8.1±6.2	7.6±6.2	<0.0001
Duration of diabetes (% missing)	689 (7.3)	20 (4.1)	746 (8.2)	47 (7.1)	32 (2.7)	233 (7.1)	1767 (7.3)	<0.0001
HbA1c (%)	7.2±1.5	8.2±2.1	7.8±1.8	7.8±1.7	8.2±1.8	7.5±1.6	7.5±1.6	<0.0001
HbA1c (% missing)	2092 (22)	158 (32)	5147 (56)	155 (23)	584 (49)	786 (24)	8922 (37)	<0.0001
Medical history								
Family history of diabetes	4876 (52%)	311 (63%)	3742 (41%)	383 (58%)	822 (69%)	1537 (47%)	11 671 (48%)	<0.0001
Retinopathy	942 (10%)	28 (5.7%)	1304 (14%)	82 (12%)	189 (16%)	398 (12%)	2943 (12%)	<0.0001
Diabetic foot	393 (4.2%)	13 (2.7%)	373 (4.1%)	43 (6.5%)	57 (4.8%)	176 (5.4%)	1055 (4.4%)	0.0005
History of hypertension	6442 (68%)	329 (67%)	4873 (53%)	376 (57%)	539 (45%)	2182 (67%)	14 741 (61%)	<0.0001
Family history of CVD	3422 (36%)	91 (19%)	1890 (21%)	213 (32%)	441 (37%)	885 (27%)	6942 (29%)	<0.0001
Smoking history	2749 (29%)	114 (23%)	2002 (22%)	187 (28%)	293 (25%)	933 (29%)	6278 (26%)	<0.0001
Hyperlipidemia	4702 (50%)	92 (19%)	3372 (37%)	321 (49%)	383 (32%)	1543 (47%)	10 413 (43%)	<0.0001
Positive history of any CVD	2843 (30%)	43 (8.8%)	1589 (17%)	113 (17%)	226 (19%)	733 (22%)	5547 (23%)	<0.0001

BMI, body mass index; CVD, cardiovascular disease.
[a]In this column, data on ethnicity are missing, whereas other data are available.

Table 2 | Medical treatment in patients with type II diabetes by ethnic group

	Caucasian	African	Asian	Other	Hispanic	Missing	Total	*P*-value
Treatment								
Glucose lowering								<0.0001
Diet alone	1237 (13%)	18 (3.7%)	619 (6.8%)	48 (7.3%)	78 (6.6%)	187 (5.7%)	2187 (9.1%)	
Oral hypoglycemic agent	5991 (63%)	314 (64%)	6917 (76%)	446 (67%)	866 (73%)	2361 (72%)	16 895 (70%)	
Insulin	1131 (12%)	92 (19%)	709 (7.8%)	77 (12%)	151 (13%)	273 (8.4%)	2433 (10%)	
Both	782 (8.3%)	58 (12%)	753 (8.3%)	72 (11%)	62 (5.2%)	340 (10%)	2.067 (8.6%)	
Missing	300 (3.2%)	8 (1.6%)	113 (1.2%)	18 (2.7%)	32 (2.7%)	98 (3.0%)	569 (2.4%)	
Antihypertensive treatment								
On any antihypertensive agent	6825 (72%)	307 (63%)	4691 (51%)	421 (64%)	627 (53%)	2343 (72%)	15 214 (63%)	<0.0001
Number of antihypertensive agents	1.8±0.92	1.8±0.85	1.5±0.71	1.6±0.82	1.4±0.64	1.8±0.84	1.7±0.85	<0.0001
Diuretics	2694 (29%)	157 (32%)	871 (9.6%)	127 (19%)	139 (12%)	928 (28%)	4916 (20%)	<0.0001
ACEI	4002 (42%)	179 (37%)	2027 (22%)	235 (36%)	417 (35%)	1277(39%)	8137 (34%)	<0.0001
ARB	1606 (17%)	59 (12%)	848 (9.3%)	133 (20%	91 (7.7%)	483 (15%)	3220 (13%)	<0.0001
ACEI or ARB	5431 (58%)	234 (48%)	2817 (31%)	360 (54%)	499 (42%)	1729 (53%)	11 070 (46%)	<0.0001
Beta blockers	1689 (18%)	38 (7.8%)	848 (9.3%)	61 (9.2%)	83 (7.0%)	604 (19%)	3323 (14%)	<0.0001
Calcium-channel blockers	2060 (22%)	99 (20%)	1909 (21%)	103 (16%)	101 (8.5%)	690 (21%)	4962 (21%)	<0.0001
Alpha blockers	248 (2.6%)	1 (0.2%)	159 (1.7%)	7 (1.1%)	15 (1.3%)	77 (2.4%)	507 (2.1%)	<0.0001
Other antihypertensive agents	248 (2.6%)	8 (1.6%)	399 (4.4%)	16 (2.4%)	9 (7.6%)	78 (2.4%)	758 (3.1%)	<0.0001
Lipid-lowering agents								
Statin	3731 (40%)	61 (12%)	1646 (18%)	223 (34%)	157 (13%)	1164 (36%)	6982 (29%)	<0.0001
Other lipid-lowering agents	643 (6.8%)	13 (2.7%)	989 (11%)	34 (5.1%)	77 (6.5%)	257 (7.9%)	2013 (8.3%)	<0.0001
On anticoagulant/antiplatelet agents	4349 (46%)	156 (32%)	2266 (25%)	272 (41%)	400 (34%)	1362 (42%)	8805 (36%)	<0.0001
On Aspirin	3708 (39%)	150 (31%)	1986 (22%)	242 (37%)	365 (31%)	1186 (36%)	7637 (32%)	<0.0001
On Warfarin	331 (3.5%)	3 (0.6%)	38 (0.4%)	8 (1.2%)	6 (0.5%)	80 (2.5%)	466 (1.9%)	<0.0001
On other anticoagulant/antiplatelet agents	402 (4.3%)	7 (1.4%)	283 (3.1%)	28 (4.2%)	38 (3.2%)	124 (3.8%)	882 (3.7%)	<0.0001

ACEI, angiotensin-converting enzyme inhibition; ARB, angiotensin receptor blocker.

Table 3 | Albuminuria, kidney function, and arterial blood pressure in patients with type II diabetes by ethnic group

	Caucasian	African	Asian	Other	Hispanic	Missing	Total	*P*-value
Laboratory variables								
Albuminuria								<0.0001
None	5576 (59%)	279 (57%)	4046 (44%)	354 (54%)	545 (46%)	1628 (50%)	12 428 (51%)	
Micro	3145 (33%)	177 (36%)	3942 (43%)	258 (39%)	521 (44%)	1325 (41%)	9368 (39%)	
Macro	720 (7.6%)	34 (6.9%)	1123 (12%)	49 (7.4%)	123 (10%)	306 (9.4%)	2355 (9.8%)	
Log 2 (albumin/creatinine ratio)	4.6±1.8	4.6±1.7	5.2±1.9	4.8±1.7	5.2±1.8	4.9±1.8	4.9±1.8	<0.0001
Serum creatinine (mg/dl)	0.98±0.32	1.00±0.38	1.00±0.39	0.97±0.30	1.08±0.98	1.04±0.40	1.00±0.40	<0.0001
Serum creatinine (% missing)	3642 (39)	275 (56)	5901 (65)	241 (36)	683 (57)	1576 (48)	12 318 (51)	<0.0001
MDRD GFR (ml/min)	78±24	97.4±30.0	79.0±27.3	81.4±26.3	75.1±29.5	74.8±25.6	78.2±26.0	<0.0001
MDRD GFR (% missing)	3746 (40)	276 (56)	5920 (65)	247 (37)	693 (58)	1696 (52)	12 578 (52)	<0.0001
Systolic BP (mmHg)	137.0±17	136.2±19.3	132.2±18.3	133.2±17.7	131.0±18.9	137.2±16.5	134.8±17.8	<0.0001
Systolic BP (% missing)	350 (3.7)	38 (7.8)	286 (3.1)	36 (5.4)	30 (2.5)	122 (3.7)	862 (3.6)	<0.0001
Diastolic BP (mmHg)	79.8±9.6	82.9±11.7	78.8±10.3	79.3±9.1	80.2±10.2	80.3±9.3	79.6±9.9	<0.0001
Diastolic BP (% missing)	360 (3.8)	37 (7.6)	297 (3.3)	38 (5.7)	29 (2.4)	124 (3.8)	885 (3.7)	<0.0001

BP, blood pressure; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease.

Only 37% of our patients received lipid-lowering drugs, and antiplatelet/anticoagulant agents were applied in a similar fraction of the patients.

Normoalbuminuria was demonstrated in 51%, MA in 39%, and the remaining 10% had macroalbuminuria (Table 3). The prevalence of abnormally elevated urinary albumin excretion was highest in Asian and Hispanic patients and the Caucasians had the lowest value, $P<0.0001$. Table 4 shows the odds ratio of micro-/macroalbuminuria, arranged in such a way that the first variable added is the one that has most explanatory value, followed by the second most explanatory. Several of the risk factors are modifiable, for example, HbA1c, systemic BP, and smoking.

Overall, estimated glomerular filtration rate (eGFR) averaged 78 ml/min/1.73 m^2 and 22% of the patients had renal insufficiency, that is eGFR <60 ml/min/1.73 m^2. The prevalence of renal insufficiency rose from normo- to micro- to macroalbuminuria (17, 27.5, and 30.7%, respectively). The total number of patients with chronic kidney disease was 58%. Conversely, the prevalence of any known CVD was similar in patients with normo-, micro-, and macroalbuminuria (21, 25, and 23%, respectively).

DISCUSSION

Our global cross-sectional study of type II diabetic patients without previously known proteinuria or kidney disease

Table 4 | Risk (odds ratio) of micro-/macroalbuminuria in patients with type II diabetes

Variables	Odds ratio	95% CI	*P*-value
HbA1c (per 1%)	1.13	1.11, 1.15	<0.0001
Systolic blood pressure (per 10 mmHg)	1.10	1.08, 1.12	<0.0001
Black vs Caucasian	1.48	1.20, 1.83	0.0002
Asian vs Caucasian	1.77	1.59, 1.97	<0.0001
Hispanic vs Caucasian	1.69	1.47, 1.94	<0.0001
Retinopathy	1.49	1.38, 1.62	<0.0001
Known duration of diabetes (per year)	1.02	1.01, 1.03	<0.0001
Estimated GFR (per 10 ml/min)	0.96	0.95, 0.98	<0.0001
Diabetic foot lesions	1.64	1.45, 1.86	<0.0001
Height (per 5 cm)	0.96	0.94, 0.97	<0.0001
Congestive heart failure	1.56	1.32, 1.84	<0.0001
Diastolic blood pressure (per 10 mmHg)	1.10	1.07, 1.14	<0.0001
Smoking	1.15	1.08, 1.22	<0.0001
Age (per 10 years)	1.04	1.01, 1.07	0.0034

CI, confidence interval; GFR, glomerular filtration rate.

based on medical records revealed that approximately 50% had micro- or macroalbuminuria, one-fifth had renal insufficiency, and 80% had elevated BP. This large clinic/medical center-based study demonstrates the high burden of renal disease in Asian and Hispanic subjects with type II diabetes compared with Caucasians. In addition, several potentially modifiable risk factors such as glycemic control, arterial BP, and smoking are associated with the presence of micro- and macroalbuminuria. Known diabetes duration is a well-established risk factor for vascular complications, and consequently our data must be regarded as rather conservative, as the average known duration was only 8 years.

Previous studies have established MA as a powerful independent predictor of microvascular lesions, CVD, cardiovascular mortality, and kidney disease including end-stage renal failure in patients with diabetes, hypertensive subjects, and even in the general population.[6–8,14] Our study shows a clear association of higher levels of albuminuria with an increased frequency of renal insufficiency, which we measured, but not of known CVD, of which we obtained only a history. It is likely that many more of these patients had asymptomatic CVD. However, patients with congestive heart failure had increased levels of albuminuria. The apparent discrepancy between congestive heart failure and CVD may be a chance finding, or reflects that cerebrovascular and peripheral arterial disease acts differently from cardiac disease in relation to micro-/macroalbuminuria.

Our study has several limitations. First, albumin/creatinine ratio was determined by a dipstick on the basis of a single random urine collection. However, the large number of samples collected and the high frequency with which a single urine collection showed a diagnostic abnormality should minimize the uncertainty associated with day-to-day differences in urinary albumin excretion. Second, our data do not permit examination of the generally accepted criterion for persistent MA, requiring that two out of three determinations are within the target range. However, other data suggest that this requirement only will reduce the point prevalence by one-fifth.[15] A third limitation is that our study is not population based and consequently our sampling frame is most well defined. Selection bias in relation to the participating centers and subsequently enrolled diabetic patients cannot be ruled out. However, it should be mentioned that our data dealing with the prevalence of abnormally elevated urinary albumin excretion (55%) in the Asian subset ($N = 9111$) are comparable with the high prevalence (58.6%) of micro- or macroalbuminuric observed in a cross-sectional study of 5549 type 2 diabetic patients from 10 Asian Countries or regions.[16] This study applied consecutive screening.

Our study confirms and extends previous observations suggesting a high prevalence of MA in several non-European groups throughout the world.[16,17] In addition, our study revealed an association between micro-/macroalbuminuria and several vascular risk factors, for example HbA1c, systolic/diastolic BP, smoking, and eGFR. Surprisingly, increased body mass index was not related to the presence of micro-/macroalbuminuria, which may be because of the high prevalence of micro-/macroalbuminuria in the Asian population who had the lowest body mass index.

Many physicians have difficulties in interpretation of serum creatinine, and consequently recent nephrology recommendations suggest that laboratories should provide GFR estimates as a regular laboratory test using standard validated prediction equations such as the modification of diet in renal disease (MDRD) formula.[18] Unfortunately, serum creatinine data were missing in half of our patients, but in the remaining subjects renal insufficiency was detected in 22%, increasing from normo- to macroalbuminuria. The finding of renal insufficiency in 17% of our normoalbuminuric patients was surprising, but support and extend data from Australia.[19] The causes of this loss in kidney function are poorly understood, but some data suggest that the MDRD formula underestimates the GFR, particularly in subjects with normal GFR.[20] Several recent studies suggest that reduced eGFR is a powerful independent risk factor of death, cardiovascular events, and hospitalization.[21–24] Furthermore, it should be stressed that there is an substantial rise in risk of all-cause mortality when eGFR (MDRD formula) falls below 60 ml/min/1.73 m^2 and downwards.[23] These findings document that quantification of renal function seems to provide an index of overall vascular health, even though the applied MDRD formula may underestimate GFR.

Type II diabetic patients have a risk of fatal and non-fatal cardiovascular events that is two to six times that in subjects without diabetes.[6,25,26] Patients with micro- and macroalbuminuria suffer the highest risk. This poor outcome is related to several modifiable risk factors such as hyperglycemia, hypertension, dyslipoproteinaemia, and increased platelet aggregability. Randomized double masked trials aiming at reducing these vascular risk factors in type II diabetes have demonstrated benefits in relation to large and small vessel

disease.[26–29] Whereas the previous studies investigated the effect of intensified intervention involving a single vascular risk factor, the Steno-2 study evaluated the effect on CVD of an intensified, targeted, multifactorial intervention aimed at several modifiable risk factors in patients with type II diabetes and MA.[30,31] The Steno-2 study revealed that multifactorial intervention reduced the risk of cardiovascular and microvascular events by about 50%.

The average HbA1c in DEMAND is lower than that reported in the intensified arm of the United Kingdom Prospective Diabetes Study (UKPDS) and Steno-2 study. However, values were missing in 37% of our patients, and patients with missing HbA1c values had an odds ratio of 1.25 for higher levels of albuminuria, clearly suggesting bias against higher values of HbA1c. In addition, standardization of HbA1c assay was not available.

Several guidelines suggest a target BP below 130/80 mmHg in type II diabetic patients and even lower in patients with micro-/macroalbuminuria.[32] The DEMAND study revealed that the majority of patients had BP above the recommended levels, and one-third of these patients did not receive BP-lowering therapy, despite the well-documented benefit on large and small vessel disease.[32] The majority of the treated patients received agents blocking the renin–angiotensin system. Angiotensin-conveting enzyme inhibition was most commonly used in all groups. As expected, the Asian group had the lowest utility of angiotensin-converting enzyme inhibitors, probably owing to their enhanced risk of coughing. Despite this side effect, the frequency of angiotensin receptor blockers was still low (9.3%) in the Asian group. Increased cost may partly explain the finding.

Several statin trials have demonstrated a beneficial effect on cardiovascular events, including ischemic stroke, in patients with type II diabetes without high levels of low-density lipoprotein-cholesterol.[28,29,33] Furthermore, these drugs are safe. Consequently, there is a strong argument that all subjects with type II diabetes warrant statin treatment.[34] Lipid-lowering therapy was only recorded in approximately one-third of the DEMAND patients, despite these patients having a high frequency of several conventional cardiovascular risk factors including micro- and macroalbuminuria. Only one-third of our patients received antiplatelet agents, despite a large meta-analysis clearly indicating a cardiovascular benefit in diabetes.[35]

The main strengths of our cross-sectional study included a large, multiracial referred cohort of type II diabetic subjects with validated identification of predefined primary and secondary end points. However, several limitations should be noted. First, we obtained only a single determination of urinary albumin/creatinine ratio and arterial BP. Second, bias was documented in relation to some of the missing variables, for example HbA1c and eGFR. Third, dosing of the different drugs was not obtained. Finally, serum creatinine assays were not calibrated to national and preferable international reference standards.

Conclusion

A high prevalence globally of micro- and macroalbuminuria and reduced kidney function, conditions associated with enhanced renal and cardiovascular risk, was detected in type II diabetic patients without prior known nephropathy. Early detection, monitoring of vascular complication, and more aggressive multifactorial treatment aiming at renal and vascular protection are urgently needed.

MATERIALS AND METHODS

Patients

Total number of patients was 32 208. Eligible patients were normo- or hypertensive women and men between 18 and 80 years, with type II diabetes mellitus (World Health Organization criteria) without prior known proteinuria and/or non-diabetic kidney disease. A history of kidney disease and/or proteinuria was recorded in 3670 patients leaving 28 538 appropriate patients. Invalid urine collections owing to fever, menstruation, pyuria, missing urine creatinine, or urine too dilute (see below) were observed in 4384. Three patients whose nationality and region were missing were also deleted. One single random albumin/creatinine ratio was obtained in 24 151 patients (75%). The DEMAND study is a multinational cross-sectional clinic/center-based study designed to evaluate the prevalence and determinants of micro- and macroalbuminuria in type II diabetic patients by random screening at each participating center during the interval from end of June to end of September 2003. The goal was to enroll 10 type II diabetic patients per center. The study was mainly performed in primary care settings. The study was endorsed and the center selected by local diabetes associations in collaboration with Bristol-Myers Squibb and Sanofi-Aventis. A total of 3137 physicians in 33 different countries in Asia, Europe, Central America, South America, North America, Africa, and Oceania participated. The study protocol was approved by the ethical committee of each clinic and all patients gave written informed consent. The study was overseen by a steering committee (present authors, except LGH), which contained two non-voting members who were employed by the two sponsoring pharmaceutical companies (Bristol-Myers Squibb and Sanofi-Aventis). The steering committee oversaw the study design, the conduct of the investigation, and the management, and analyses of the data. A writing subcommittee of the steering committee prepared this report (HHP, LGH).

Investigations

All participating general practitioners, physicians and nurses received the full study protocol and were instructed in performing the urinary albumin/creatinine test (single determination), and BP measurement with an appropriate cuff after approximately 10 min rest in the sitting position (single recording). Furthermore, demographic (age, gender, ethnicity, and region), clinical characteristics (height, body mass index, known diabetes duration, HbA1c, and serum creatinine), medical history (family history of diabetes/hypertension/CVD, retinopathy, diabetic foot lesion, history of any CVD, smoking, and hyperlipidemia), and simultaneous treatments (glucose lowering, antihypertensive agents, lipid-lowering drugs and antiplatelet/anticoagulant agents) on each patient were recorded on a single page clinical report form . Presence of CVD, that is coronary artery disease, myocardial infarction, left ventricular hypertrophy, congestive heart failure, stroke, transient ischemic attack, or peripheral vascular disease, was based on medical records and

information obtained during the interview. Standardized definitions of the different CVDs were not applied. Presence of hyperlipidemia was based on objective measurements as stated in the medical records. Presence of arterial hypertension was based on medical history of patient receiving BP-lowering therapy. A single random urine albumin/creatinine ratio was measured using Bayer reagent strip Multistix® 10SG. According to this semiquantitative strip test, normoalbuminuria is defined as albumin-to-creatinine ratio <30 mg/g, MA 30–299 mg/g, and macroalbuminuria $\geqslant 300$ mg/g. According to the manufacturer, the Multistix® 10SG test has a sensitivity of 84% and specificity of 91% for the albumin-to-creatinine ratio. Urine samples with concentrations of creatinine $\leqslant 10$ mg/dl were discarded as too dilute, as prespecified in the protocol.

We used the MDRD 4 variable formula (serum creatinine level, age, sex, and African race or not) to estimate the GFR (ml/min/1.73 m^2).[18] The stages of chronic kidney disease were defined according to the American National Kidney Foundation:[18] stage 1, eGFR $\geqslant 90$; stage 2, eGFR 60–89; stage 3, eGFR 30–59; stage 4, 15–29; and stage 5, eGFR <15 or dialysis. Patients belonging to stage 1 and 2 need to have structural or functional abnormalities of the kidney, for example, micro-/ macroalbuminuria, to be classified as having chronic kidney disease. A eGFR <60 ml/min/1.73 m^2 is defined as renal insufficiency.

Statistical analysis

Univariate comparisons of the impact of independent variables on the average levels of continuous and categorical dependent variables were made using one-way analysis of variance and the χ^2 statistic, respectively. A minimal multivariate model predicting the level of albuminuria (normal, micro-, or macroalbuminuria) was constructed using 'proportional odds' ordinal logistic models as realized by the function lrm for S.[36] Parallel models predicting the albumin/creatinine ratio (log transformed) as a continuous variable were built using ordinary linear regression models and gave comparable results. To build these models, independent variables were added to the model in the order in which they increased the total likelihood of the model, taken as a measure of explanatory power, until no further additions significantly ($P<0.05$) improved the likelihood, using the likelihood ratio test. All data management was performed using SAS for Windows version 9.0 (SAS Institute, Cary, NC, USA) and all analyses were performed using S-Plus version 6.2 for Windows (Insightful Corp., Seattle, WA, USA) by LG Hunsicker.

Role of the funding source

The sponsors of the study (Bristol-Myers Squibb and Sanofi-Aventis) contributed to the study design, data collection, and reviewed and commented on drafts. The sponsors had no role in data analysis (performed by LGH and HHP), data interpretation, or writing the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

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CONTRIBUTORS

Europe: Belgium, Germany, Greece, Netherlands, Hungary, Norway, Portugal, Romania, Slovakia, Spain, Turkey, United Kingdom.
North America: Canada, Mexico.
Central/South America: Chile, Columbia, Ecuador, El Salvador, Dominican Replublic, Venezuela.
Asia: China, Korea, Hong Kong, Indonesia, Saudi Arabia, Malaysia, Singapore, Taiwan, Thailand.
Africa: Kenya, Republic of South Africa.
Oceania: Australia, Philippines.

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