Prevalence and risk factors for microalbuminuria in a cross-sectional study of type-2 diabetic patients in Indonesia : a subset of DEMAND study

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Abstrak

Tujuan *Mikroalbuminuria (MA) adalah prediktor kuat untuk nefropati diabetik serta morbiditas dan mortalitas kardiovaskular pada pasien DM tipe 2. Studi ini bertujuan untuk mengumpulkan informasi mengenai prevalensi dan faktor risiko untuk MA pada pasien Indonesia dengan DM tipe 2.*

Metode *Studi DEMAND adalah survei potong lintang 1 hari mengenai prevalensi MA dan faktor risikonya pada pasien DM tipe 2. Studi ini melaporkan hasil survei yang dilakukan di Puskesmas di Indonesia dari Juni sampai Desember 2003. Pasien hipertensi dan normotensi dewasa laki-laki dan perempuan dengan DM tipe 2 tanpa diketahui adanya proteinuria dan/atau penyakit ginjal diikutsertakan dalam studi. Pasien yang diketahui hamil, sedang haid atau menderita demam akut tidak diikutsertakan dalam studi. Uji albumin urin/kreatinin dilakukan satu kali pada semua pasien.*

Hasil *Seluruhnya ada 770 pasien yang memenuhi syarat untuk dianalisis. Sekitar 80% pasien menderita mikro-/ makroalbuminuria, sedangkan insufisiensi ginjal ditemukan pada kira-kira 36% dari 433 pasien yang ada datanya. Target HbA1c (<7%) dicapai hanya oleh 40% dari 118 pasien yang mempunyai nilai HbA1c. Kebanyakan obat anti diabetes yang diresepkan adalah oral (82%), sedangkan insulin digunakan hanya oleh 14% pasien. Target tekanan darah (< 130/80 mmHg) dicapai hanya oleh 9% pasien. Pasien yang menerima antihipertensi 52%, statin 18%, dan aspirin 26%. Antihipertensi yang paling banyak dipakai adalah penghambat RAS (45%), sedangkan diuretik digunakan oleh 7% pasien. Riwayat DM dalam keluarga ditemukan pada 43% pasien, riwayat retinopati 16%, kaki diabetik 9%, dan riwayat merokok pada 20% pasien.*

Kesimpulan *Data ini menunjukkan bahwa Indonesia mempunyai frekuensi penyakit ginjal diabetik asimtomatik yang tertinggi di antara berbagai negara yang ikut studi DEMAND di dunia. Deteksi dini, pemantauan komplikasi vaskular, dan pengobatan multifaktorial yang lebih agresif yang ditujukan untuk proteksi ginjal dan vaskular sangat dibutuhkan untuk pasien Indonesia dengan DM tipe 2.* ***(Med J Indones 2009; 18: 124-30)***

Abstract

Aims Microalbuminuria (MA) is a strong predictor of diabetic nephropathy and cardiovascular morbidity and mortality in patients with type-2 DM. The present study aimed to gather information on the prevalence and risk factors for MA in Indonesian patients with type-2 DM.

Methods The DEMAND study was an international open cross-sectional 1-day survey on microalbuminuria prevalence and its risk factors in type-2 diabetic patients. This study reports the results of the Indonesian survey which was performed in primary care practice in Indonesia from June to December 2003. Normotensive or hypertensive adult patients of both genders with type-2 DM without known proteinuria and/or kidney disease were recruited into the study. Patients with known pregnancy, having menstruation or acute fever were excluded. A single urinary albumin/creatinine test was carried out in all patients.

Results A total of 770 patients were eligible for analysis. Approximately 80% of the patients had micro-/ macroalbuminuria, while renal insufficiency was detected in about 36% of the 433 patients with available data. Target HbA1c (< 7%) was reached by only 40% of the 118 patients who had HbA1c values. Most antidiabetic treatment prescribed was oral (82%), while insulin was used by only 14% of patients. Goal BP (< 130/80 mm Hg) was achieved in only 9% of patients. The frequency of patients receiving antihypertensives was 52%, statins 18%, and aspirin 26%. The most frequently used antihypertensives were RAS blockers (45%), while diuretics were used in 7 % of the patients. The family history of DM was found in 43% of patients, the history of retinopathy in 16%, diabetic foot 9%, and history of smoking in 20% of patients.

Conclusion These data reveal that Indonesia has one of the highest frequencies of silent diabetic kidney disease seen in any national group in the global DEMAND Study. Early detection, monitoring of vascular complications, and more aggressive multifactorial treatment aiming at renal and vascular protection are urgently needed for Indonesian patients with type-2 diabetes. **(Med J Indones 2009; 18: 124-30)**

Key words: *microalbuminuria, type-2 DM, Indonesia, DEMAND study*

Microalbuminuria (MA) is defined as an abnormal increase in the rate of urinary excretion of albumin to between 30 and 300 mg/24 h. It was first described in patients with diabetes mellitus by Keen et al.[1] in 1969. MA was also found in benign essential hypertension non-diabetic patients, but not in patients treated effectively for hypertension[2]. Later, it was demonstrated that MA strongly predict the development of clinical diabetic nephropathy in both type-1 and type-2 diabetes mellitus[3,4]. In 1997, a systematic overview of the literature showed that MA is a strong predictor of total and cardiovascular mortality and cardiovascular morbidity in patients with type-2 DM[5]. In non-diabetic patients, MA is also an independent predictor of vascular disease (coronary and peripheral) and all-cause mortality[6]. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients treated with an angiotensin–receptor blocker[7]. In hypertensive patients with type-2 DM and MA, an angiotensin-receptor blocker can delay the development of diabetic nephropathy, and this renoprotective effect was independent of the blood-pressure lowering effect[8]. In patients with type-2 DM and hypertension but with normoalbuminuria, an angiotensin-receptor blocker can decrease the incidence of MA[9].

In 2003, Parving et al. in collaboration with the International Diabetes Federation and the International Society of Nephrology and Bristol-Myers Squibb and Sanofi-Aventis created a study on Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes (DEMAND)[10].

This cross-sectional global study aimed to gather information on the prevalence and risk factors for MA in patients with normo-and hypertensive type-2 DM without known proteinuria and/or non-diabetic kidney disease seen in primary care practice in various countries world-wide, including Indonesia, and to establish the correlation between the prevalence of MA and well-known cardiovascular risk markers or factors, and also to increase physician awareness on the major importance of urinary albumin screening in order to improve patient's care. The data presented here were data from Indonesia.

METHODS

Patients

Normotensive or hypertensive men and women, aged between 18 and 80 years, with type-2 DM (World Health Organization criteria) without prior known proteinuria and/or non-diabetic kidney disease were recruited into the study. Excluded from the study were patients with type-1 DM, menstruation period, known pregnancy, and acute fever.

Concomitant medications such as cimetidine (may cause falsely elevated results with the creatinine test used in this study) and drugs containing azo dyes, nitrofurantoin and riboflavin (cause abnormal urine colour, and therefore may affect the readability of the reagent strips for urinalysis and cause false interpretation) were prohibited. Contamination of the urine specimen with soaps, detergents, antiseptics, or skin cleansers or the use of urine preservatives other than boric acid (1.0 g/L) may also affect test results, and therefore was also restricted.

Study design and procedure

The present study was the Indonesian subset of DEMAND study. The DEMAND study was a multinational open cross-sectional 1-day survey designed to evaluate the prevalence and risk factors of micro- and macroalbuminuria in type-2 diabetic patients seen in primary care settings by random screening at each participating center during the interval from June to September 2003. Each center should enroll at least 10 eligible patients. The study was endorsed and the centers 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. In Asia, 8 countries participated, including China, Hong Kong, Indonesia, Korea, Malaysia, Singapore, Taiwan, and Thailand.

The study protocol was approved by the ethical committee of the Medical Faculty, University of Indonesia, and written informed consent was obtained from each patient before screening.

All participating physicians and nurses received the full study protocol and the instructions to measure the urinary albumin and creatinine (single determination) and BP after 10 min rest in the seated position (single recording).

Patient data (gender, age, height, weight), medical diagnosis (type-2 DM : family history, duration, HbA$_{1c}$ the last 6 months, diabetic retinopathy and diabetic foot; hypertension : history, duration; cardiovascular risk : family history, history of smoking, hyperlipidemia), and concomitant drug therapy (antidiabetics,

antihypertensives, lipid lowering drugs and antiplatelet/anticoagulants) of each patient were recorded on a single page case report form.

Presence of CVD, that is left ventricular hypertrophy, coronary artery disease, myocardial infarction, congestive heart failure, stroke, transient ischemic attack, or peripheral vascular disease, was obtained from medical records and anamnesis during the interview. Presence of hyperlipidemia was also obtained from the medical records, while presence of hypertension was obtained from medical history of receiving antihypertensives.

A single urinary albumin and creatinine levels were determined using Bayer reagent strip Multistix® 10 SG. According to this semiquantitative strip test, normoalbuminuria is defined as albumin-to-creatinine ratio < 30 mg/g, MA 30-300 mg/g, and macroalbuminuria > 300 mg/g. According to the manufacturer, the Multistix® 10 SG test has 88% accuracy, 84% sensitivity, and 91% specificity for albumin-to-creatinine ratio.

The estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) was calculated using the Modification of Diet in Renal Disease 2 (MDRD 2) formula.[10] The stages of chronic kidney disease (CKD) were defined according to the American National Kidney Foundation: stage 1, eGFR ≥ 90; stage 2, 60–89; stage 3, 30–59; stage 4, 15–29; and stage 5, eGFR < 15 or dialysis[10]. Patients in stages 1 and 2 need to have structural or functional abnormalities of the kidney, for example, micro-/macroalbuminuria, to be classified as having kidney damage and mild stage of CKD. An eGFR < 60 mL/min/1.73 m^2 is defined as moderate stage of CKD.

Statistical analysis

Descriptive statistics (number of patients and its percentage of the total, mean and standard deviation, distribution of data) were used to analyze all data in the present study. Statistical tests were used only in the global DEMAND study to compare data from various countries, but not in the subsets of the study.

RESULTS

A total of 770 patients were eligible to be included in this Indonesian subset of DEMAND global study. The demographics, clinical characteristics and medical history of the patients are presented in Table 1. There were more females than males, and most of the patients were in the age group of 40s to 60s with a mean of 57 years. The mean BMI was almost 25. The mean duration of diabetes was 6.7 years. Diabetic retinopathy was present in 16.5% of patients, almost 16% of patients had a history of CVD, and almost 20% had a history of smoking. Only 15% of patients had HbA_{1c} recorded. Among these patients, the mean HbA_{1c} was 8.1%, and only 40% of these patients reached target level (< 7%).

Table 1. Characteristics of patients with type-2 DM

Demographic characteristics	**n**	**(%)**
Number	770	(100)
Gender		
Male	360	(46.75)
Female	409	(53.12)
Missing	1	(0.13)
Age (yrs) Mean ± SD	57.0 ± 9.9	
Age by decades		
20s	2	(0.26)
30s	30	(3.90)
40s	149	(19.35)
50s	269	(34.94)
60s	236	(30.65)
70s	63	(8.18)
80s	6	(0.78)
Missing	15	(1.95)
Clinical characteristics		
BMI (kg/m^2) Mean ± SD	24.7 ± 4.0	
BMI (Missing)	14	(1.82)
Duration of DM (yrs) Mean ± SD	6.7 ± 5.6	
Duration of DM (Missing)	35	(4.55)
HbA_{1c} (%) Mean ± SD	8.1 ± 2.1	
HbA_{1c} at target (< 7%)	47	(6.10)
Not at target (≥ 7%)	71	(9.22)
HbA_{1c} (Missing)	652	(84.68)
Medical History		
Family history		
Family history of DM	329	(42.73)
Family history of CV disease	91	(11.82)
Personal history		
History of retinopathy	127	(16.49)
History of diabetic foot	67	(8.70)
History of CV disease	121	(15.71)
History of hyperlipidemia	262	(34.03)
History of smoking	151	(19.61)

BMI = body mass index
CV = cardiovascular

Medical treatments received by patients are presented in Table 2. Only 2.5% of patients did not take any antidiabetic drug. Most patients (81.5%) took oral antidiabetics, while the rest received insulin and oral

+ insulin combination. Almost 50% of patients did not receive any antihypertensive drug, while around 45% received an ACEI or an ARB. Only 24% of patients took lipid lowering drugs (mostly statins by more than 18% of patients). Among 262 (34%) patients with hyperlipidemia, lipid lowering drugs were taken by 70% of the patients, mostly statins were taken by 54% of the patients. Antiplatelets/anticoagulants were given to about 29% of patients (mostly aspirin to about 26% of patients).

Table 2. Medical treatment in patients with type-2 DM

Treatment	n	(%)
Antidiabetics		
None	19	(2.47)
Oral	628	(81.56)
Insulin	56	(7.27)
Oral + insulin	53	(6.88)
Missing	14	(1.82)
Antihypertensives		
None	367	(47.66)
Diuretics	54	(7.01)
ACEIs	322	(41.82)
ARBs	30	(3.90)
ACEIs or ARBs	349	(45.32)
α-blockers	18	(2.34)
CCBs	90	(11.69)
Others	11	(1.43)
Lipid lowering drugs		
Statins	141	(18.31)
Others	44	(5.71)
Antiplatelets/Anticoagulants		
Aspirin	200	(25.97)
Warfarin	4	(0.52)
Other antiplatelets/anticoagulants	20	(2.60)

ACEI = angiotensin-converting enzyme inhibitor
ARB = angiotensin receptor blocker
CCB = calcium channel blocker

Micro/macroalbuminuria was demonstrated in 80% of patients, microalbuminuria in 60%, while the remaining 20% had macroalbuminuria (Table 3). The estimated glomerular filtration rate (eGFR) averaged 68 mL/min/1.73 m^2 (data missing in 44% of patients). Among the 433 patients having eGFR values, 157 patients (36%) had moderate stage of CKD, that is eGFR < 60 mL/min/1.73 m^2. Systolic BP reached target level (< 130 mm Hg) in 30% of patients, while diastolic BP reached target level (< 80 mm Hg) in only 12% of patients, resulting BP goal (SBP < 130 and DBP < 80 mm Hg) achieved in only 9% of patients.

Table 3. Albuminuria, kidney function, and blood pressure in patients with type-2 DM

Variable	n	(%)
Albuminuria		
None	158	(20.52)
Micro	460	(59.74)
Macro	152	(19.74)
Log2 (Albumin/creatinine ratio)		
(mg albumin/g creatinine)	70.8	
[95% confidence interval]	[6.0 – 835]	
Serum creatinine (mg/dL) Mean ± SD	1.15 ± 0.57	
Serum creatinine (Missing)	331	(42.99)
MDRD2 eGFR (mL/min) Mean ± SD	68 ± 24	
MDRD2 eGFR group midpoint (mL/min)		
20	20	(2.60)
40	67	(8.70)
60	161	(20.91)
80	113	(14.68)
100	50	(6.49)
120	15	(19.48)
140	2	(0.26)
160	5	(0.65)
Missing	337	(43.77)
Systolic BP (mm Hg) Mean ± SD	137 ± 20	
Systolic BP at target (< 130 mm Hg)	227	(29.48)
Systolic BP not at target (≥ 130 mm Hg)	520	(67.53)
Systolic BP (Missing)	23	(2.99)
Diastolic BP (mm Hg) Mean ± SD	84 ± 10	
Diastolic BP at target (< 80 mm Hg)	94	(12.21)
Diastolic BP not at target (≥ 80 mm Hg)	651	(84.55)
Diastolic BP (Missing)	25	(3.25)
BP goal achieved (SBP < 130 mm Hg and DBP < 80 mm Hg)	71	(9.22)
BP goal not achieved	676	(87.79)
BP goal (Missing)	23	(2.99)

eGFR = estimated glomerular filtration rate
MDRD = modification of diet in renal disease
BP = blood pressure

DISCUSSION

This cross-sectional survey of type-2 DM patients from Indonesia without previously known proteinuria or kidney disease based on medical records − as a subset of DEMAND study − revealed that about 80% of the patients had micro- or macroalbuminuria, which were much higher than among either global (approximately 50%) or Asian patients (56%).[11]

This data from Indonesia showed that both micro-albuminuria (about 60%) and macroalbuminuria (about 20%) were much higher than either global data (about 40% and 10%, respectively) or Asian data (43% and 12%, respectively) of DEMAND study.[11] The prevalence of albuminuria was indeed highest in Asian and Hispanic patients (55% and 54%, respectively), and lowest in Caucasians (40.6%).[11]

In this Indonesian data, renal insufficiency was detected in about 36% of patients with available eGFR values, and this prevalence was much higher compared to 22% of global patients and 23% of Asian patients.[11] These data were in agreement with the serum creatinine levels, which averaged 1.15 mg/dL in the Indonesian patients, and 1.00 mg/dL in both Asian and global patients.[11] The very high prevalence of micro- and macroalbuminuria and renal insufficiency found among these diabetic Indonesian patients not known previously to have proteinuria or kidney disease was in fact one of the highest frequencies of silent diabetic kidney disease seen in any national group in the DEMAND Study. More regular and earlier testing of MA to detect the presence of diabetic kidney disease is clearly warranted.

Previous studies have established MA as a powerful independent predictor of both renal outcomes and cardiovascular events in diabetic and non-diabetic patients.[3-6] Testing for albuminuria is simple and inexpensive, and can be used to systematically screen those at immediate risk.[12] The 2007 guidelines of the European Society of Hypertension and the European Society of Cardiology have now include MA in routine testing.[13]

In addition to the high prevalence of micro- and macroalbuminuria, the present study also showed high prevalence of several vascular risk factors, for example HbA_{1c} (not at target in 60% of the 15% of patients who had HbA_{1c} values), BP (not at target in about 90% of patients), smoking (in almost 20% of patients), and eGFR (mean 68 mL/min in 56% of patients who had eGFR values). The Steno-2 study showed that intensive multifactorial intervention in patients with type-2 DM and MA (stepwise implementation of behaviour modification, and pharmacological therapy targeting hyperglycemia, hypertension, dyslipidemia, and MA) slowed progression to nephropathy and progression of retinopathy and autonomic neuropathy after 3.8 years of follow-up, and reduced the incidence of macrovascular complications and mortality after 7.8 years of follow-up.[14,15] The Steno-2 study revealed that multifactorial intervention in patients with type-2 DM and MA reduced the risk of cardiovascular and microvascular events by about 50%.[15]

Cigarette smoking is a strong and modifiable risk factor for macrovascular disease in patients with diabetes,[16] and all diabetic patients who smoke should quit smoking.[17] In the present study, almost 20% of patients had a history of smoking.

The mean HbA_{1c} in the present study was lower than that in the Steno-2 study. However, values were missing in 85% of our patients. Only 40% of the 15% of patients who had HbA_{1c} values achieved target HbA_{1c} (< 7%). This poor glycemic control was due to the management of glycemia was less aggressive than desired. Insulin was not used in those patients with the highest HbA_{1c} levels.

The 7th report of the Joint National Committee on prevention, detection, evaluation and treatment of BP recommends a target BP below 130/80 mm Hg in type-2 diabetic patients.[18] The DEMAND Study showed that most of the patients had BP above the recommended level, and 37% of these patients did not receive any antihypertensive therapy[11]. In the present study, only 9% of the patients achieved this BP goal, and 48% of these patients did not receive BP-lowering therapy, which were common among Asian patients (49% did not receive BP-lowering therapy).[11] In fact, Asian patients received the lowest number of antihypertensive agents (average 1.5) among the other ethnics in the DEMAND Study (average 1.7).[11] In line with the guideline,[18] the most frequently used drugs for hypertension associated with diabetes were RAS blockers (ACEIs and ARBs), in all groups. The Asian group had the lowest utility of ACEIs or ARBs (31%), while the Caucasian had the highest utility (58%).[11]

The guideline also mention that if the BP is 20/10 mm Hg higher than the goal, a combination of drugs should be used,[18] and that a diuretic generally should be one of the drug combination[18] used for the management of hypertension in diabetic patients.[17] In fact, hypertension in patients with kidney disease is hard to control without use of diuretics. And yet, diuretics were underused in the present study (only 7%), and also in Asian subset of patients (almost 10%).[11] The Caucasians and Africans had the highest utility of diuretics (29% and 32%, respectively).[11] In order to reach target BP values of < 130/80 mm Hg, hypertensive patients with chronic kidney disease should receive aggressive BP therapy, often with 3 or more drugs.[18] With advanced renal disease (eGFR < 30 mL/min/1.73 m^2), increasing doses of loop diuretics are usually needed in the drug combination.[18]

Several statin trials have demonstrated a beneficial effect on cardiovascular events, including ischemic stroke, in patients with type-2 DM without high levels of LDL-cholesterol.[19-21] Since these drugs are safe, there is a strong argument that all patients with

type-2 DM warrant statin treatment.[22] Statins were only taken by 29% of patients in the DEMAND Study, by 18% of patients in Asian subset,[11] and also by 18% of Indonesian patients. Even in patients with a history of hyperlipidemia, only 54% of the Indonesian patients received statins. The Caucasian had the highest utility of statins (40%), while the African and Hispanic had the lowest utility (12-13%).[11]

A large meta-analysis of the use of antiplatelet agents clearly indicated a CV benefit in diabetes.[23] However, only one-third of patients in the DEMAND Study, one-fourth of patients in the ASIAN subset,[11] and almost 30% of Indonesian patients received antiplatelets.

The present study has several limitations.[11] Firstly, a single determination of urinary albumin/creatinine ratio did not fulfill the generally accepted criterion for persistent MA, requiring that 2 out of 3 determinations are within the target range. However, this requirement has been shown to reduce the point prevalence by only one-fifth.[11] Secondly, this study was not population based and therefore selection bias in recruiting the centers and the diabetic patients cannot be ruled out. However, the prevalence of micro- and macroalbuminuric patients found in the Asian subset (55% of N = 9111) of the DEMAND Study was comparable with the prevalence (58.6%) observed in a cross-sectional study of 5549 type-2 diabetic patients from 10 Asian Countries using consecutive screening.[24] Third, a single recording of BP did not comply with the standard measurement of BP (2 or more times on each of 2 or more visits). Fourth, bias was documented in relation to the missing variables, for example HbA$_{1c}$ and eGFR. Fifth, dosing of the different drugs was not obtained. Finally, serum creatinine assays were not calibrated to national and preferable international reference standards.

A very high prevalence of micro- and macroalbuminuria and reduced kidney function, conditions associated with enhanced renal and CV events, was detected in type-2 diabetic Indonesian 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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