VTF Yeung 楊鐸輝
KF Lee 李家輝
SH Chan 陳石開
LF Ho 何樂勳
SK Leung 梁兆基
HY Wong 黃顯約
MAPS Investigators

MicroAlbuminuria Prevalence Study (MAPS) in hypertensive type 2 diabetic patients in Hong Kong

香港高血壓乙型糖尿病人出現微白蛋白尿的情況

Objectives. To assess the prevalence of macroalbuminuria and microalbuminuria, and the level of blood pressure control in patients with type 2 diabetes and hypertension in Hong Kong.
Design. Cross-sectional clinic-based epidemiological study.
Setting. Six medical centres (including two public hospital diabetes centres) in Hong Kong.
Patients. Recruited from the medical centres from April to November 2002, after excluding those with bacteriuria and haematuria.
Main outcome measures. Body mass index; blood pressure; levels of blood glucose, macroalbuminuria, and microalbuminuria; treatments for hypertension and diabetes.
Results. The as per-protocol recruited population of 437 hypertensive type 2 diabetic patients had a mean age of 61.7 (standard error, 0.5) years. Overall, the prevalence of diabetic nephropathy in this population was high; 18.3% had macroalbuminuria (95% confidence interval, 16.5-20.2%) and 24.9% had microalbuminuria (95% confidence interval, 22.9- 27.0%). Predictive factors were advanced age, male sex, poor blood pressure control, and existing cardiovascular complications. Whilst almost all patients (96.1%) were receiving treatment for hypertension, only 25.6% had systolic/diastolic blood pressures below the 130/85 mm Hg target.
Conclusions. In Hong Kong, the prevalence of microalbuminuria and macroalbuminuria is high in type 2 diabetic patients with hypertension, particularly in males and those with poorly controlled systolic blood pressure. Tight glycaemic control, antihypertensive therapy, and use of renin-angiotensin system inhibitors/blockers are necessary to retard the progression of nephropathy to advanced renal disease.

目的：評估香港患有乙型糖尿病和高血壓的病人，出現巨白蛋白尿和微白蛋白尿的比率，以及血壓控制的情況。
設計：以診所為基礎的跨界別流行病學研究。
安排：香港六所醫療中心（包括兩間設在公立醫院的糖尿病中心）。
患者：2002 年 4 月至 11 月期間在醫療中心的病人（出現尿菌症和血尿的患者不在此列）。
主要結果測量：體重指數；血壓；血糖、巨白蛋白尿和微白蛋白尿的水平；高血壓和糖尿病的治療方法。
結果：是次研究共有 437 名患高血壓及乙型糖尿病病人參與，平均年齡為 61.7 歲（標準誤差0.5歲）。整體來說，糖尿病腎炎的現患率很高，當中因巨白蛋白尿引致的佔 18.3%（95% 置信區間，16.5-20.2%），因微白蛋白尿引致的佔 24.9%（95% 置信區間，22.9-27.0%）。可預測因素為年長、男性、血壓控制不善和已有心臟血管併發症。雖然幾乎所有病人（96.1%）都接受高血壓治療，只有 25.6% 病人能將其收縮 / 舒張血壓控制在 130/85 mm Hg 水平之下。
結論：香港的高血壓乙型糖尿病患者的巨白蛋白尿和微白蛋白尿的現患率很高，男性和控制收縮血壓不善的人情況尤甚。嚴格的血糖控制、防高血壓治療和使用腎素—血管緊張素系統抑制劑，對防止腎炎發展至嚴重腎病十分重要。

Key words:
Albuminuria;
Diabetes mellitus, type 2;
Diabetic nephropathies;
Hypertension;
Renin-angiotensin system

關鍵詞：
微白蛋白尿；
糖尿病，乙型；
糖尿病腎炎；
高血壓；
腎素—血管緊張素系統

Hong Kong Med J 2006;12:185-90

Department of Medicine and Geriatrics, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Hong Kong
VTF Yeung, MD, FRCP
Department of Medicine, Kwong Wah Hospital, Yau Ma Tei, Hong Kong
KF Lee, MB, ChB, MRCP
Private practice
SH Chan, LMCHK
LF Ho, MB, BS
SK Leung, MB, BS
HY Wong, MB, BS, MRCP

Correspondence to: Dr VTF Yeung (e-mail: yeungtf@ha.org.hk)

Introduction

Patients with type 2 diabetes are almost twice as likely to be hypertensive as

non-diabetics.[1] The prevalence of hypertension is even greater in patients with type 2 diabetes and elevated urinary albumin excretion (UAE). Higher levels of systolic blood pressure (SBP) are associated with a proportionally greater absolute excess in cardiovascular (CV) risk. This indicates a correspondingly greater potential for prevention of CV death among diabetic patients by controlling elevated blood pressure.[2] Because of the ageing population and an increase in obesity and sedentary lifestyle, the prevalence of diabetes is growing, particularly in Asia. Currently, Hong Kong has the highest rate of diabetes in Asia,[3] and renal failure is a leading cause of death among such patients. In part, this may be due to the high prevalence of hypertension and albuminuria in this population.[4]

Diabetic nephropathy is a common cause of end-stage renal disease (ESRD); the percentage of new patients requiring renal replacement therapy due to diabetic nephropathy increased from 25.3% in 1996 to 38% in 2004.[5] One of the initial markers of this condition is microalbuminuria, which indicates an increased risk of deteriorating renal function and mortality.[6] Because microalbuminuria and proteinuria in these patients are associated with adverse consequences including impaired survival,[7,8] screening and intervention programmes should be implemented early. Annual screening for microalbuminuria is recommended by the American Diabetes Association,[9] and a semi-quantitative dipstick test is an easy tool that can provide immediate and accurate results for this purpose.[10]

A few studies reporting the prevalence of microalbuminuria in Asian populations[11,12] only explored the percentage having microalbuminuria among patients with diabetes or hypertension. A recent study of diabetic patients showed a prevalence of 13.4% in a primary care setting in Hong Kong.[13] The MicroAlbuminuria Prevalence Study (MAPS) was the first to evaluate the prevalence of these two findings in patients with type 2 diabetes and hypertension.[14] Its primary objective was to assess the prevalence of these two findings. Secondary objectives were to assess levels of glycaemic and blood pressure control. Herein we report the results of a subanalysis of findings from patients in Hong Kong.

Methods

The design of MAPS has already been described[14] and is therefore outlined only briefly here. Out-patients, aged 18 years or above, with confirmed type 2 diabetes (treated or untreated) and hypertension (treated or untreated) were consecutively screened at each participating centre. Previously diagnosed hypertension and diabetes were historically defined as per patient's medical record and verified during monitoring visits. Patients with known (previously diagnosed) macroalbuminuria were excluded. Patient data included demographic information, medical history, dates of hypertension and diabetes were recognised, current diabetes status (complications such as retinopathy, peripheral neuropathy, as well as CV disease, glycaemic control, current therapy), current hypertensive status (mean of two consecutive measurements of supine office SBP and diastolic blood pressure [DBP], current treatment), and dyslipidaemic status (known or previously diagnosed dyslipidaemia, receipt of treatment with lipid-lowering agents or documented hypercholesterolaemia, hypertriglyceridaemia, elevated low-density lipoprotein–cholesterol, and/or low high-density lipoprotein–cholesterol by the physician/practitioner concerned). A single morning urine specimen was collected in a disposable plastic vessel on the day of screening. The detection of macroalbuminuria was carried out on the fresh urine (first morning void or random morning specimen) using a visual colorimetric semi-quantitative urine test strip (Nephur-7 Test; Roche Diagnostics GmbH, Mannheim, Germany) with a lower detection limit of 0.3 g/L and upper detection limit of 5 g/L. If negative for albumin, detection of microalbuminuria would be performed on the same urine with a second specific semi-quantitative urine test strip (Micral-Test; Roche Diagnostics GmbH, Mannheim, Germany). The intensity of the colour produced was visually compared with the reference chart on the Micral-Test bottle (0, 20, 50, 100, >100 mg/L). A measurement of 20 mg/L or above was considered positive. Specificity, sensitivity, and positive and negative predictive values of the Micral-Test were determined according to the manufacturer's evaluation report with a cut-off point of 20 mg/L: sensitivity of 90.1%, specificity of 87.2%, positive predictive value of 0.82, and negative predictive value of 0.93.

A total of 103 centres throughout 10 Asian countries and regions participated in the study. For the current analysis, data were restricted to patients recruited from the study centres in Hong Kong (primary care, specialist general medical and diabetes out-patient clinics in or affiliated to two public hospitals and the practices of four private physicians/practitioners). All patients with confirmed onset dates of diabetes and hypertension constituted the analysed population. Patients with positive leukocytes and nitrites, indicative of significant bacteriuria, and patients with erythrocytes or haemoglobin of 25/μL or above, indicative of significant haematuria, were excluded as per the agreed protocol.

Quantitative variables were described by their mean, standard error (SE) of mean, counts, and number of missing values. Qualitative variables were described by the counts and percentages of each response choice. Missing data were included in the calculation of percentages. Comparison of blood pressure among the normoalbuminuric and albuminuric subgroups was performed with analysis of variance followed by multiple comparisons. Prevalence rates were calculated with a two-sided 95% confidence interval (CI). For the multivariate analysis, links between two qualitative criteria were assessed by a Chi squared test

Table 1. Patient demographics of the per-protocol population (n=437)

Demographic information	Mean	Standard error of the mean
Age (years)	61.7	0.5
Body mass index (kg/m^2)		
Male	25.78	0.25
Female	25.83	0.19
Waist/hip ratio*		
Male	0.93	0.01
Female	0.89	0.01
Systolic/diastolic blood pressure (mm Hg)	145.7/80.0	0.9/0.5
Blood glucose (mmol/L)	8.0	0.1
Duration of hypertension (years)	7.4	0.3
Age at diagnosis of hypertension (years)	54.6	0.6
Duration of diabetes (years)	8.2	0.3

* Significant difference was found in waist/hip ratio between male and female subjects

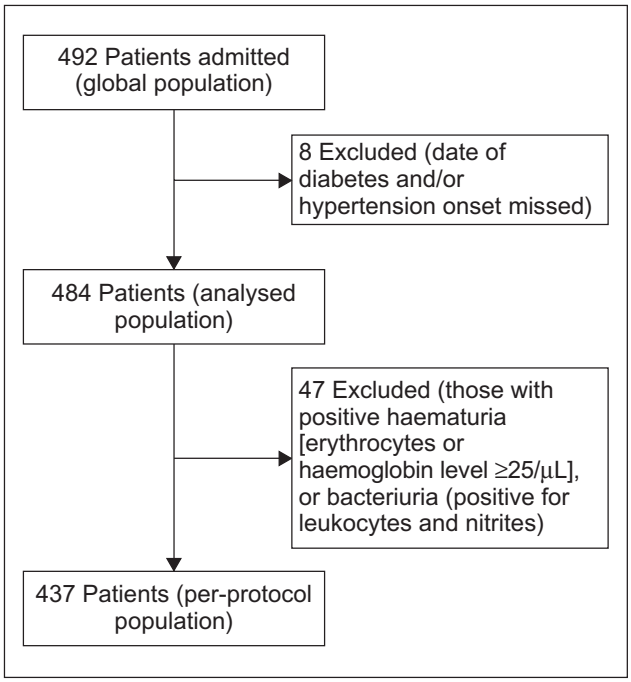

Fig. Patient classification

Table 2. Detection of macroalbuminuria and microalbuminuria of the per-protocol population (n=437)

	No.	%	95% CI
Macroalbuminuria	80	18.3	16.5-20.2
Microalbuminuria	109	24.9	22.9-27.0
Normoalbuminuria	248	56.8	54.4-59.1

or Fisher's exact test if the assumptions of the Chi squared test were not met. The best global model of prediction was assessed by a stepwise logistical regression. The significance level was set at $P<0.05$. All analyses were performed using Statistical Analysis System version 8.02.

Results

Hong Kong constituted 7.2% of the overall enrolment in MAPS. A total of 492 patients were recruited from six medical centres (including two diabetes centres in government hospitals) in Hong Kong from April to November 2002, with 81.3% from the public sector and 18.7% from the private sector. Reasons for excluding patients from the final per-protocol analysis are shown in the Figure. Patient demographics of the per-protocol population (n=437) are shown in Table 1. The majority (98.6%) were Chinese, 58.4% were female, 9.6% were current smokers and 14.7% were ex-smokers. A family history of hypertension was reported by 29.8% of patients, and diabetes by 31.1%.

Measures of glycaemic control revealed a mean glycosylated haemoglobin (HbA_{1c}) level of 7.2% (SE, 0.1%) and a mean creatinine level of 85.8 (SE, 1.2) μmol/L. Current methods of diabetes management included dietary control in 97.7% of patients, regular physical exercise in 81.5%, oral hypoglycaemic agents in 84.7%, and insulin therapy in 9.2%. Diabetic retinopathy and neuropathy were present in 14.9% and 2.8% of patients, respectively. Overall, 16.9% of patients had known CV complications including previous transient ischaemic attack (1.4%), stroke (6.0%), angina pectoris (8.5%), myocardial infarction (0.2%), heart failure (0.2%), and peripheral vascular disease (0.7%).

The proportion of patients receiving antihypertensive treatment was high (96.1%); 56.4% and 43.6% of them were prescribed monotherapy and combination therapy, respectively. Drugs used for this purpose were: angiotensin-converting enzyme (ACE) inhibitors (45.7%), calcium channel blockers (50.2%), angiotensin receptor blockers (ARB) [3.3%], beta-blockers (31.7%), diuretics (15.2%), and alpha-blockers (10.0%). Nonetheless, only 112 (25.6%) of per-protocol patients had SBP/DBP below the 130/85 mm Hg target,[15] with approximately one third (32.3%) of normoalbuminuric patients having normal blood pressure, compared with 15% of macro-albuminuric and 13.8% of microalbuminuric subjects. The SBP among macroalbuminuric, microalbuminuric, and normoalbuminuric groups of patients differed significantly (SBP±SE: 152.4±2.2, 149.8±1.7, and 141.7±1.2 mm Hg, respectively), but there was no significant difference in DBP (DBP±SE: 81.3±1.0, 81.4±1.1, and 79±0.6 mm Hg,

Table 3. Predictive factors for the presence of macroalbuminuria*

Variables	Levels	P value	Odds ratio (95% CI)
Age (vs [30-49] years)	<30	>0.05	<0.001 (0.000-1)
	>70	<0.05	7.308 (1.947-27.427)
	(>49-59)	<0.05	4.113 (1.128-15.005)
	(>59-70)	>0.05	2.934 (0.797-10.801)
Known cardiovascular complications (Yes vs No)	Yes	<0.05	2.756 (1.350-5.627)
Systolic blood pressure (vs normal: 130 mm Hg)	130-139 mm Hg	>0.05	0.846 (0.215-3.327)
	140-159 mm Hg	<0.05	3.133 (1.447-6.781)
	160-179 mm Hg	<0.05	3.888 (1.636-9.240)
	180-209 mm Hg	>0.05	3.320 (0.807-13.655)
Sex (vs female)	Male	<0.05	2.508 (1.425-4.414)

* Covariates for analysis: sex, age, duration of diabetes mellitus and hypertension, systolic and diastolic blood pressures, macrovascular complication, diabetes microvascular complication, smoker, diuretic, alpha-blocker, beta-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, angiotensin II antagonist, body mass index

Table 4. Predictive factors for the presence of microalbuminuria*

Variables	Levels	P value	Odds ratio (95% CI)
Systolic blood pressure (vs normal: 130 mm Hg)	130-139 mm Hg	<0.05	2.599 (1.121-6.026)
	140-159 mm Hg	<0.05	3.051 (1.565-5.947)
	160-179 mm Hg	<0.05	4.447 (2.088-9.470)
	180-209 mm Hg	<0.05	7.784 (2.610-23.211)
Sex (vs female)	Male	<0.05	1.687 (1.043-2.729)

* Covariates for analysis: sex, age, duration of diabetes mellitus and hypertension, systolic and diastolic blood pressures, macrovascular complication, diabetes microvascular complication, smoker, diuretic, alpha-blocker, beta-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, angiotensin II antagonist, body mass index

respectively), or the number and types of antihypertensive medication among these patients.

Dyslipidaemia was present in 181 (41.4%) patients: 63.0% were prescribed lipid-lowering drugs. The majority (79.0%) were taking statins and 21.9% were taking fibrates. One patient was prescribed both medications.

For the primary endpoint, the overall prevalence of albuminuria in the per-protocol population was 43.2%. The prevalence of macroalbuminuria, microalbuminuria, and normoalbuminuria are shown in Table 2. In the multivariate analysis, predictive factors for the presence of macroalbuminuria were male sex, mild or moderate SBP elevation, known CV complications, and old age (Table 3). The statistically significant predictive factors for the presence of microalbuminuria were male sex, and high normal, mild, moderate, and severe SBP elevation (Table 4).

Discussion

The MAPS is the first large multicentre epidemiological study conducted in Asia to determine the prevalence of microalbuminuria and macroalbuminuria in patients with type 2 diabetes and hypertension. This subanalysis of data from Hong Kong indicates that 24.9% of the 437 analysed patients had microalbuminuria and 18.3% had macroalbuminuria. The prevalence of microalbuminuria was slightly higher than the rates of 17% to 21% reported from western population–based studies in patients with diabetes.[16] The rate of abnormal albuminuria is consistent with a previously reported local prevalence of 47% as measured in a specialist diabetes clinic population.[17]

The prevalence of both macroalbuminuria and microalbuminuria were higher in male patients and those with poorly controlled blood pressure. Statistically significant predictive factors for macroalbuminuria included: older than 70 years, male sex, known CV complications, and mild-to-moderate systolic hypertension (140-179 mm Hg). Predictive factors for microalbuminuria included male sex and high normal, mild, moderate, and severe systolic hypertension. In a study of Hong Kong Chinese patients, the prevalence of hypertension in men with diabetes was 23.9% compared with 5% in those with normal glucose tolerance.[17] In women, the prevalence of hypertension was 8.7% in those with diabetes compared with 3.4% in women with normal glucose tolerance.[17] As hypertension is common in patients with diabetes, these findings highlight the need for adequate blood pressure control. Nevertheless, in our MAPS subgroup analysis, although almost all patients (96.1%) were receiving antihypertensive therapy, less than 26% of patients actually achieved adequate blood pressure control (<130/85 mm Hg). These low control rates are not substantially different from those in many western countries.[15]

Hyperglycaemia is an important determinant for the development of proteinuria in patients with type 2 diabetes. Effective glycaemic control prevents the development of nephropathy and reverses established pathology. Nevertheless, as evidenced by the mean HbA_{1c} of 7.2%, the majority of patients in this study did not achieve optimal glycaemic control.

Patients with type 2 diabetes often have a clustering of risk factors, including: hypertension, dyslipidaemia, obesity,

hyperinsulinaemia, and microalbuminuria (referred to collectively as the metabolic syndrome).[18] Microalbuminuria is the first clinical sign of diabetic damage to the kidney and is a predictor of progressive renal damage, myocardial infarction, and CV death.[4,6] Once present and left untreated, microalbuminuria progresses over 5 to 10 years to macroalbuminuria (in 22% to 50% of patients).[6,19] The development of macroalbuminuria is usually followed by a progressive decline in glomerular filtration rate.[16,20] Annual screening for microalbuminuria for all type 2 diabetes patients is recommended.[9] Use of a dip test by a strip is a simple method for primary screening and continued monitoring. In patients tested positive for microalbuminuria by dip test, quantitative analysis should be carried out to confirm the diagnosis and assist in risk stratification and formulation of a treatment regimen.

It is important to develop strategies that increase the percentage of patients who achieve optimal blood pressure control, as Asian patients with type 2 diabetes have a higher risk for renal complications and stroke compared with their Caucasian counterparts.[21] In Hong Kong, diabetes mellitus is now the leading cause of ESRD and the number of diabetic patients requiring renal replacement therapy is increasing at an annual rate of 10%.[6]

The benefits of reducing blood pressure to the recommended goal of lower than 130/85 mm Hg in WHO/ISH 1999 study[15] and lower than 130/80 mm Hg in JNC-7 2003 study[22] in patients with diabetes are well established, and supported by data including those of the UKPDS (UK Prospective Diabetes Study[23]) and HOT (Hypertension Optimal Treatment[24]) study. Further, it is widely established that optimal blood pressure, tight glycaemic control, and pharmacological blockade of the renin-angiotensin system (RAS) with ACE inhibitors or ARBs can decrease UAE rates and, subsequently, slow the progression from incipient to overt nephropathy. For example, in the MICRO-HOPE study,[25] high-risk diabetic patients who received ramipril 10 mg versus placebo for 4.5 years reduced their risk of overt nephropathy by 24%. In the IRMA 2 (IRbesartan MicroAlbuminuria type 2 diabetes mellitus in hypertensive patients) study,[26] hypertensive type 2 diabetic patients with microalbuminuria who took irbesartan 300 mg daily had a significant (70%, P<0.001) relative risk reduction for the development of diabetic nephropathy as measured by the changes in UAE. Additionally, the RENAAL (Reduction of Endpoints in Non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan) and IDNT (Irbesartan in Diabetic Nephropathy) trials[27,28] have conclusively demonstrated the advantage of ARB therapy. When used as part of a multidrug strategy to lower blood pressure, losartan 100 mg or irbesartan 300 mg have been shown to prevent doubling of serum creatinine, ESRD, or death in hypertensive patients with type 2 diabetes and macroalbuminuria. Despite this compelling evidence, ACE inhibitors and ARB were used in only 46% and 3% of patients, respectively. Furthermore, less than 50% of patients were receiving two or more antihypertensive agents, even though a number of clinical trials have confirmed the need for multidrug therapy in diabetes to reach target blood pressure.[29]

In conclusion, this subanalysis of data from the Hong Kong cohort of MAPS has demonstrated a high prevalence of significant albuminuria in hypertensive type 2 diabetic patients, amounting to a total of 43.2% of patients screened (24.9% with microalbuminuria and 18.3% with macroalbuminuria). Measures that target tight metabolic and optimal blood pressure control are urgently needed to address this major public health issue and contain the epidemic of ESRD due to diabetic nephropathy. In light of clear evidence of the benefits of RAS blockade, ACE inhibitors and/or ARB drugs should constitute important components of the therapeutic armamentarium in the management of hypertension and nephropathy among type 2 diabetic patients.

Acknowledgements

We would like to thank our diabetes educators and nurses, and the Monitoring Team of the participating centres in Hong Kong for their contribution to the study. This work was supported by a grant from Sanofi-Synthelabo.

References

1. Epstein M, Sowers JR. Diabetes mellitus and hypertension. Hypertension 1992;19:403-18.
2. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993; 16:434-44.
3. Diabetes e-Atlas. International Diabetes Foundation website: http://www.idf.org/e-atlas/home/. Accessed 6 Jan 2004.
4. Chan JC, Cheung CK, Cheung MY, Swaminathan R, Critchley JA, Cockram CS. Abnormal albuminuria as a predictor of mortality and renal impairment in Chinese patients with NIDDM. Diabetes Care 1995;18:1013-6.
5. Ho YW, Chau KF, Leung CB, et al. Hong Kong Registry Report 2004. Hong Kong J Nephrol 2005;7:38-46.
6. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med 1984;310: 356-60.
7. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systematic overview of the literature. Arch Intern Med 1997;157:1413-8.
8. Miettinen H, Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Proteinuria predicts stroke and other atherosclerotic vascular disease events in nondiabetic and non-insulin-dependent diabetic subjects. Stroke 1996;27:2033-9.
9. American Diabetes Association. Diabetic nephropathy. Position statement. Diabetes Care 2002;25(Suppl 1):85S-89S.
10. Spooren PF, Lekkerkerker JF, Vermes I. Micral-Test: a qualitative dipstick test for micro-albuminuria. Diabetes Res Clin Pract 1992; 18:83-7.
11. Mather HM, Chaturvedi N, Kehely AM. Comparison of prevalence and risk factors for microalbuminuria in South Asians and Europeans with type 2 diabetes mellitus. Diabet Med 1998;15:672-7.
12. Tomura S, Kawada K, Saito K, et al. Prevalence of microalbuminuria and relationship to the risk of cardiovascular disease in the Japanese population. Am J Nephrol 1999;19:13-20.

13. Tam TK, Cheng LP, Lau DM, et al. The prevalence of microalbuminuria among patients with type II diabetes mellitus in a primary care setting: cross-sectional study. Hong Kong Med J 2004;10:307-11.
14. Wu AY, Kong NC, de Leon FA, et al. An alarmingly high prevalence of diabetic nephropathy in Asian type 2 diabetes patients: the MicroAlbuminuria Prevalence (MAP) Study. Diabetologia 2005;48: 17-26.
15. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. J Hypertens 1999;17:151-83.
16. Parving HH. Diabetic nephropathy: prevention and treatment. Kidney Int 2001;60:2041-55.
17. Chan JC, Cheung CK, Swaminathan R, Nicholls MG, Cockram CS. Obesity, albuminuria and hypertension among Hong Kong Chinese with non-insulin-dependent diabetes mellitus (NIDDM). Postgrad Med J 1993;69:204-10.
18. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539-53.
19. Cooper ME, Frauman A, O'Brien RC, Seeman E, Murray RM, Jerums G. Progression of proteinuria in type 1 and type 2 diabetes. Diabet Med 1988;5:361-8. Erratum in: Diabetic Med 1988;5:422.
20. Ritz E, Tarng DC. Renal disease in type 2 diabetes. Nephrol Dial Transplant 2001;16(Suppl 5):11S-18S.
21. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia 2001;44(Suppl 2):14S-21S.
22. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560-72. Erratum in: JAMA 2003;290:197.
23. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998;317:703-13. Erratum in: BMJ 1999;318:29.
24. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998;351:1755-62.
25. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000;355:253-9. Erratum in: Lancet 2000;356:860.
26. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-8.
27. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9.
28. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345: 851-60.
29. Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis 2000;36:646-61.