Albuminuria is a marker of increasing intra- and extracranial vascular involvement in Type 2 diabetic Chinese patients

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Abstract

Background: Albuminuria has been reported to be a marker of cardiovascular risk factors and disease morbidity and mortality, but the relationship with intracerebral atherosclerotic disease is less clear.

Objectives: To identify determinants associated with increasing albuminuria in Chinese Type 2 diabetic patients.

Methods: Anthropometric and fasting biochemical parameters were compared between 857 Type 2 diabetic patients with normo- (n=475), micro- (n=250) and macroalbuminuria (n=132) who were matched for age, gender, duration and age of onset of diabetes. The prevalence of concomitant micro- and macrovascular disease and middle cerebral artery (MCA) stenoses, measured by transcranial Doppler, were also compared between the groups.

Results: Albuminuria was closely associated with a range of adverse parameters, including high blood pressure, dyslipidaemia and adiposity (all $p<0.001$). The prevalence of the micro- (retinopathy, $p<0.001$) and macrovascular diseases (peripheral vascular disease, $p=0.012$, myocardial infarction, $p=0.010$, MCA stenosis, $p<0.001$) increased significantly with increasing levels of albuminuria. Albuminuria was also found to be an independent predictor of micro- and macrovascular diseases.

Conclusions: Albuminuria was closely related to increasing levels of cardiovascular risk factors and micro- and macrovascular disease in this group of Type 2 diabetic patients and should be considered as a marker of early vascular disease.

Keywords: blood pressure, retinopathy, peripheral vascular disease, cardiovascular disease, middle cerebral artery stenosis, metabolic syndrome

Introduction

Cardiovascular disease is the major cause of morbidity and mortality in many developed and developing countries, including Hong Kong. In Oriental populations, there is a higher prevalence of stroke than in Caucasian populations where coronary heart disease (CHD) generally predominates.[1,2] Furthermore, despite increasing cholesterol levels in Asian countries, CHD mortality rates remain 3-5 times lower than in most Western countries. For instance, in the early 1990s in China age-adjusted mortality rates of 56 and 129/100,000 for CHD and stroke have been reported which contrast with those from US/UK Caucasians of 124/284 and 28/51 per 100,000, respectively.[3] In addition to differences in prevalence rates, the distribution of arterial atherosclerotic lesions differs between Oriental and Caucasian populations.[4,5] Similarly, intracerebral haemorrhage has been reported to be 2-3 times more frequent in Chinese than in Caucasian populations, accounting for 20-30% of strokes.[5]

Even in Chinese populations, there is variability in CHD and stroke rates, which are higher in urban than in rural populations, and stroke rates are higher in the North of China, due to the high prevalence rates of hypertension.[6] These intra-ethnic differences highlight the importance of environmental and lifestyle factors in the pathogenesis of these conditions. Migration studies also support that changes in environmental challenges can have profound effects on the prevalence of vascular disease risk factors.[7,8]

Ethnic differences associated with cardiovascular disease are therefore likely to result from the interaction of external environmental factors on the different genetic backgrounds. Understanding the relative contribution of risk factors in different ethnic groups will help to clarify potential mechanisms involved in the pathogenesis of cardiovascular disease.

In Chinese Type 2 diabetic patients, the prevalence of certain conditions such as hypertension and nephropathy are more common than in Caucasian diabetic populations.[9,10] In Chinese diabetic patients, a random spot urine albumin-to-creatinine ratio (ACR) >5.6 mg/mmol predicts progression to renal failure and early death.[11] Furthermore, the albuminuria associated with renal deterioration has been reported to be an index of atherosclerotic vascular disease morbidity and mortality.[12,13] However, our understanding of the relationship between albuminuria and intracranial atherosclerotic disease is less clear.

In the current study, we report on the association between albuminuria, as determined using 24 hour urinary albumin excretion rate, cardiovascular risk factors and the presence of intra- and extracranial cardiovascular disease in Chinese patients with Type 2 diabetes.

Methods

The study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All the Type 2 diabetic patients (n=966), recruited from the diabetes and neurology clinics at the Prince of Wales Hospital, were unrelated and gave written, informed consent. They were of Han Chinese origin, without any known ancestors of other ethnic origin, and were living in the Hong Kong Special Administrative Region of China at the time of the study. Patients were considered diabetic if the fasting plasma glucose was ≥7.8 mmol/L or the two hour post 75g oral glucose tolerance test plasma glucose level was ≥11.1 mmol/L.[14] Type 1 diabetic patients were defined on the basis of acute symptoms with heavy ketonuria (>3+) or ketoacidosis at diagnosis or requirement for continuous insulin treatment within one year of diagnosis and were excluded from the study.[14] None of the type 2 diabetic patients screened had previously suffered from a stroke.

Measurement of seated blood pressure, anthropometric (waist circumference and body mass index) and plasma biochemical (lipid and glycaemic profiles) parameters taken after an overnight fast have been described in detail previously.[10,15] The patients' medications were suspended for the morning of the examination providing assessment of trough levels, therefore assessment of the haemodynamic parameters as continuous variables is not possible. Subjects were defined as hypertensive, if, after 5 minutes rest, their seated systolic blood pressure (SBP) was ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg on at least two occasions or they were receiving blood pressure-lowering medication. Patients were assessed to rule out secondary causes of hypertension and renal disease. Urine was collected over 24 hours and the albumin excretion rate (AER) and albumin-to-creatinine ratio (ACR) determined. Urinary albumin concentration was measured by immunoturbidimetry.[16] The lowest detection limit was 2.5 mg/L and inter- and intra-assay CVs are less than 5%. A midstream urine was collected for culture and microscopy results used to rule out infection. Normoalbuminuria was classified as an AER <20 μg/min, microalbuminuria as an AER ≥20 to <200 μg/min and macroalbuminuria as an AER ≥200 μg/min.[13] In addition, we used an albumin-to-creatinine ratio >5.6 mg/mmol as a cut-off value as a predictor of end-stage renal disease.[11] The albuminuric status of the 966 patients with Type 2 diabetes was determined from a 24 hour urine collection, from whom 857 patients matched for age, gender, duration and age of onset of diabetes were identified and included 475 patients with normo-, 250 with micro-, and 132 with macroalbuminuria.

The patients were examined by transcranial Doppler (EME TC-2000). A single operator performed all the transcranial Doppler evaluations. We studied the middle cerebral artery (MCA) using a standardised protocol examining the artery with 4cm increments through the temporal window at 52-64 mm; anterior cerebral artery (temporal window, 68-72 mm), posterior cerebral artery (temporal window, 56-64 mm), siphon internal carotid artery (orbital window, 60-68 mm), and vertebrobasilar artery (occipital window, 56-106 mm).[17] Due to technical difficulty differentiating vascular lesions in the terminal internal carotid artery just before the bifurcation by transcranial Doppler we categorised the lesions as in the MCA. The criteria for occlusive arteries were defined by the peak systolic flow velocity as follows: ≥140 cm/s for the MCA.[17] Apart from the above velocity criteria, we took into account the age of patients, presence of turbulence or musical sound, and whether the abnormal velocity was segmental. Where it was not possible for insonation of the cerebral arteries through the temporal window, the patients (13.3% of the total group) were excluded from the analyses. The above diagnostic criteria in our neurovascular laboratory were based on our laboratory references, which had a quality assurance program with supplementary angiographic studies. [Gao S, Lam WWM, Chan YL, Liu JY, Wong KS. The optimal values of flow velocity on transcranial Doppler in grading middle cerebral artery stenosis in comparison with magnetic resonance angiography. J Neuroimaging 2002;12:213-218.] At our laboratory, we perform >1200 transcranial Doppler examinations each year.

Foot examination was performed with particular attention to the presence or absence of deformity (claws toes, callus, hammer toes), skin changes (atrophic changes such as dry skin and loss of hair, healed ulcers) and distal sensory neuropathy. The latter was considered to be present if the patient had typical symptoms of numbness or abnormal sensation in the distal limbs accompanied by at least 1 physical sign or 2 abnormal signs in the absence of symptoms. The physical signs included diminished ankle reflexes or sensation using monofilament (diminished sensation over foot dorsum or sole with normal skin) or graduated tuning fork where normality was defined as ≥6/8 or ≥4/8 in those <65 or ≥65 years subjects, respectively. The patient was considered to be at risk of developing diabetic foot syndrome if 2 of 3 of these risk factors (symmetrical sensory neuropathy, deformities or skin changes) were present. Foot pulses were examined in each patient and the ankle-brachial systolic arterial pressure ratio (ABR) was determined by Doppler examination in those with abnormal pulses. An ABR <0.9 in either leg was considered suggestive and <0.7 confirmatory of PVD.[18] Retinopathy was assessed by an ophthalmologist in all the patients. The fundi were examined through dilated pupils and retinopathy was considered to be present if there was one or more areas of haemorrhages, microaneurysms, cotton wool spots and/or laser coagulation scars related to diabetic retinopathy. Symptomatic peripheral vascular disease was diagnosed if claudication, gangrene or ischaemia-related amputation were present. Histories of coronary and cerebrovascular disease were recorded, as were the use of alcohol and tobacco products.

Data from normally distributed parameters are presented as mean±SD, whereas skewed data were logarithmically transformed and expressed as geometric mean with 95% confidence intervals. Differences in anthropometric and fasting plasma biochemical parameters between those patients with increasing levels of albuminuria were examined using analysis of variance. Dichotomous variables were compared using the χ^2-test. Gender was coded 0 and 1 for male and female, respectively.

For the regression analyses, all 966 diabetic patients were included. Stepwise multiple linear regression analysis was used to determine independent predictors of albuminuria (24 hour urinary albumin excretion rate). These variables included age, gender, body mass index, waist circumference, systolic blood pressure, pulse pressure, diagnosis of hypertension, glucose, triglycerides, HDL- and LDL-cholesterol levels and duration of diabetes.

MCA stenosis, and retinopathy were chosen as examples of macro- and microvascular disease, and were included in the forward conditional linear regression analyses to determine independent predictors of these conditions. These variables included were as described above for the stepwise multiple regression analysis. The variables included in the analyses were linearly related to the dependent variable. The Statistical Package for the Social Sciences was used in the analyses (SPSS. version 11.0.1, 2001, SPSS Inc, Chicago, Illinois, USA).

Results

The albuminuric status of the 966 patients with Type 2 diabetes was determined from a 24 hour urine collection, from whom 857 patients matched for age, gender, duration and age of onset of diabetes were identified and included 475 patients with normo-, 250 with micro-, and 132 with macroalbuminuria. In the matched groups, worsening albuminuria was associated with significantly increasing general (BMI) and central (waist circumference) adiposity (Table 1). Although increasing proportions of patients with micro- and macroalbuminuria received blood pressure and lipid-lowering therapies (Table 2), blood pressure and lipid (total, LDL-cholesterol and triglyceride) parameters increased significantly, whilst HDL-cholesterol levels were lower (Table 1). The changes in LDL-cholesterol levels were particularly evident in the group with macroalbuminuria. The proportion of current smokers was found to increase with albuminuria, with most of the current smokers being male (89.6%).

The prevalence of MCA stenoses, measured using transcranial Doppler, doubled between those with normoalbuminuria compared to those with macroalbuminuria (Table 2), whereas the proportion of those having stenoses in both arteries was nearly three times higher. Almost one quarter of the patients with macroalbuminuria had evidence of stenoses in the MCA. Concomitant increases in a number of other macrovascular conditions were also noted, with significant increases in the prevalence of patients with a history of myocardial infarction, and markers of peripheral vascular disease, including diabetic foot complications and impotency. Similarly, the microvascular complication, retinopathy, was also significantly higher in those with macroalbuminuria, being found in 50% of the subjects, which was 3.5 times more frequent than in the diabetic patients with normoalbuminuria.

A large number of the cardiovascular risk factors were independent predictors of 24 hour urinary albumin excretion rate. These included systolic blood pressure (β=0.21, p<0.001), duration of diabetes (β=0.19, p<0.001), triglycerides (β=0.10, p=0.008), male gender (β=-0.09, p=0.008), LDL-cholesterol (β=0.11, p<0.001), diagnosis of hypertension (β=0.13, p=0.001), body mass index (β=0.09, p=0.002), and smoking (β=0.07, p=0.033) and these accounted for 21% of the variance. The regression equation is as follows: 24 hour urinary albumin excretion rate = [0.007·systolic blood pressure] + [0.24·duration of diabetes] + [0.32·triglycerides] – [0.13·male gender] + [0.08·LDL-cholesterol] + [0.20·diagnosis of hypertension] + [0.02·body mass index] + [0.07·smoking] – 0.62; R^2=0.21, F=34.8, p<0.001.

The forward conditional linear regression analyses identified urinary albumin excretion rate as an independent predictor of both vascular conditions. The regression equations were as follows: MCA stenosis = [0.03·age] + [0.49·albumin excretion rate] – 3.90, Nagelkerke R^2=0.07, χ^2=32.5, p<0.001; and retinopathy = [-0.49·male gender] + [1.04·albumin excretion rate] + [1.63·duration of diabetes] + [1.91·glucose] + [0.02·pulse pressure] – 6.16, Nagelkerke R^2=0.41, χ^2=276.7, p<0.001.

Discussion

There is a clear relationship between ageing, gender and the duration and onset of diabetes and the development of cardiovascular and renal vascular complications.[9-13] We therefore matched the groups of diabetic patients with normo-, micro- and macroalbuminuria for these parameters to limit any potential confounding effect. However, despite this, increasing levels of albuminuria were closely associated with increases in a number of cardiovascular risk factors, including adiposity, blood pressure and lipid levels, with these parameters being independent predictors of 24 hour albumin excretion rate. This supports that the adverse metabolic milieu in patients with diabetes increases the risk of developing nephropathy and cardiovascular disease.[10] Albuminuria has been reported to be a marker of atherosclerotic disease, rather than directly promoting vascular disease. The presence of these concomitant risk factors is likely to promote endothelial dysfunction throughout the vasculature,[19] including in the glomeruli. High blood pressure, glucose and lipid levels have all been associated with alterations in the permeability of glomerular capillaries to protein that results in proteinuria.[20,21]

Smoking has been reported to be a major risk factor for atherogenesis and vascular disease mortality.[22,23] Reflecting the smoking habits in Hong Kong generally, 90% of the smokers were males, and a third of males with macroalbuminuria currently smoked whereas only 3% of females in that group smoked. In the current study, smoking was an independent predictor and the prevalence increased with increasing albuminuria supporting an involvement in damaging the vasculature. Tobacco smoke, which contains more than 4000 chemicals,[24] can damage the vascular endothelium directly.[25] Furthermore, smoking can increase oxidative stress and levels of acute phase proteins.[25,26] Even in the absence of smoking, other studies have reported that these parameters are increased suggesting an inflammatory component to the development of albuminuria.[27]

Type 2 diabetes is closely associated with micro and macrovascular disease, the major causes of morbidity and mortality in these patients.[28] In our study, the association of albuminuria and cardiovascular events as well as other vascular disease entities [29,30] were also observed. A key measure of cerebrovascular disease in our study was the transcranial Doppler measurement of intracranial stenoses. Intracerebral haemorrhage has been reported to be 2-3 times more frequent in Chinese than in Caucasian populations, accounting for 20-30% of strokes.[5] In Hong Kong, of 705 consecutively recruited stroke patients, occlusive arteries were found in 345 patients (49%), 37% of the total had only intracranial stenosis, 10% tandem (intracranial and extracranial) lesions and 2.3% only extracranial lesions.[17] Stenosis of the MCA was the most common lesion, found in 35.9% of the patients.[17] In the current study, we found a clear relationship between increasing levels of albuminuria and MCA stenoses, although age and albuminuria collectively only accounted for 7% of variance. This suggests additional unmeasured parameters further contribute to the development of intracranial atherosclerotic disease. Given the chronic nature of the development of stenotic arteries, it may be that different parameters contribute at different stages in the pathogenesis, which a cross-sectional study such as this would not be able to determine.

The conventional cardiovascular risk factors, including albuminuria, explained a greater proportion of the variance (41%) of the microvascular diabetic complication, retinopathy. Diabetic eye disease is the leading cause of new cases of blindness in many developed countries, for which macular oedema and proliferative retinopathy are major causes of loss of vision.[31] In the UK Prospective Diabetes Study, tight control of blood pressure and glycaemia effectively reduced the development of retinopathy.[32,33] These parameters were also independent predictors of retinopathy in the current study.

Given the close association between multiple vascular risk factors and albuminuria, it should be considered useful as an early indicator of both micro- and macrovascular atherosclerotic disease. Microalbuminuria is also a marker for the development of renal failure,[13] we have previously reported that an albumin-to-creatinine ratio >5.6 mg/mmol was a predictor of end-stage renal disease in Chinese type 2 diabetic patients.[11] It is therefore necessary to develop the most effective strategy to optimise all these risk factors, including albuminuria, to reduce the associated devastating cardiovascular complications. However, it is important to recognise the therapeutic challenges in the management of Type 2 diabetes. Despite intensive therapy,[34] treatment goals as defined by most international guidelines were only attained in 60-80% of type 2 diabetic patients. In another study, optimal glycaemic control (HbA_{1c} 6-7%) was only achieved in 10-30% of patients.[34]

In summary, albuminuria was closely related to increasing levels of cardiovascular risk factors and micro- and macrovascular disease in this group of Type 2 diabetic patients and should be considered as a marker of early vascular disease.

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Table 1 Demographic features in the 857 age, gender, duration and onset of diabetes-matched Chinese Type 2 diabetic patients categorised by albuminuric status

Parameters (%)	Albuminuria*			p value
	Normo-	Micro-	Macro-	
Numbers	475	250	132	-
Age (years)	53.5±10.4	53.0±11.4	55.3±11.3	NS
Gender (% Male)	43.4	44.4	53.8	NS
Duration of diabetes (years)	2.5 (2.2-2.8)	2.7 (2.3-3.2)	3.3 (2.6-4.1)	NS
Age of diabetes onset (years)	49.5±10.6	48.3±11.5	50.0±11.0	NS
24h albumin-to-creatinine ratio (ACR, mg/mmol)	1.0 (1.0-1.1)	6.0 (5.5-6.6)	85.5 (70.9-103.1)	<0.001
24h albumin excretion rate (AER, μg/min)	5.9 (5.7-6.2)	36.6 (33.9-39.5)	530 (445-631)	<0.001
Albumin-to-creatinine ratio >5.6 mg/mmol (%)	4.1	56.7	97.7	<0.001
Plasma creatinine (μmol/L)	72.1±18.7	73.6±23.3	112.4±88.8	<0.001
Body mass index (kg/m^2)	24.1±3.4	25.4±3.8	25.7±3.7	<0.001
Waist circumference (cm)	82.7±9.0	86.5±9.4	87.2±9.4	<0.001
Systolic blood pressure (mm Hg)	133±20	139±21	149±24	<0.001
Diastolic blood pressure (mm Hg)	80±11	83±10	85±13	<0.001
Mean arterial pressure (mm Hg)	98±13	102±12	107±15	<0.001
Pulse pressure (mm Hg)	53±15	56±17	64±19	<0.001
Glucose (mmol/L)	8.7 (8.4-9.0)	9.3 (9.0-9.7)	8.9 (8.7-9.5)	0.047
Glycosylated haemoglobin A_{1c}(%)	7.8±2.0	8.2±2.0	8.1±2.0	NS
Total cholesterol (mmol/L)	5.6±1.2	5.6±1.2	6.1±1.4	<0.001
HDL-cholesterol (mmol/L)	1.30±0.38	1.22±0.34	1.15±0.35	<0.001
LDL-cholesterol (mmol/L)	3.55±0.93	3.52±0.93	3.91±1.23	0.001
Triglyceride (mmol/L)	1.35 (1.28-1.43)	1.60 (1.48-1.73)	1.94 (1.72-2.18)	<0.001

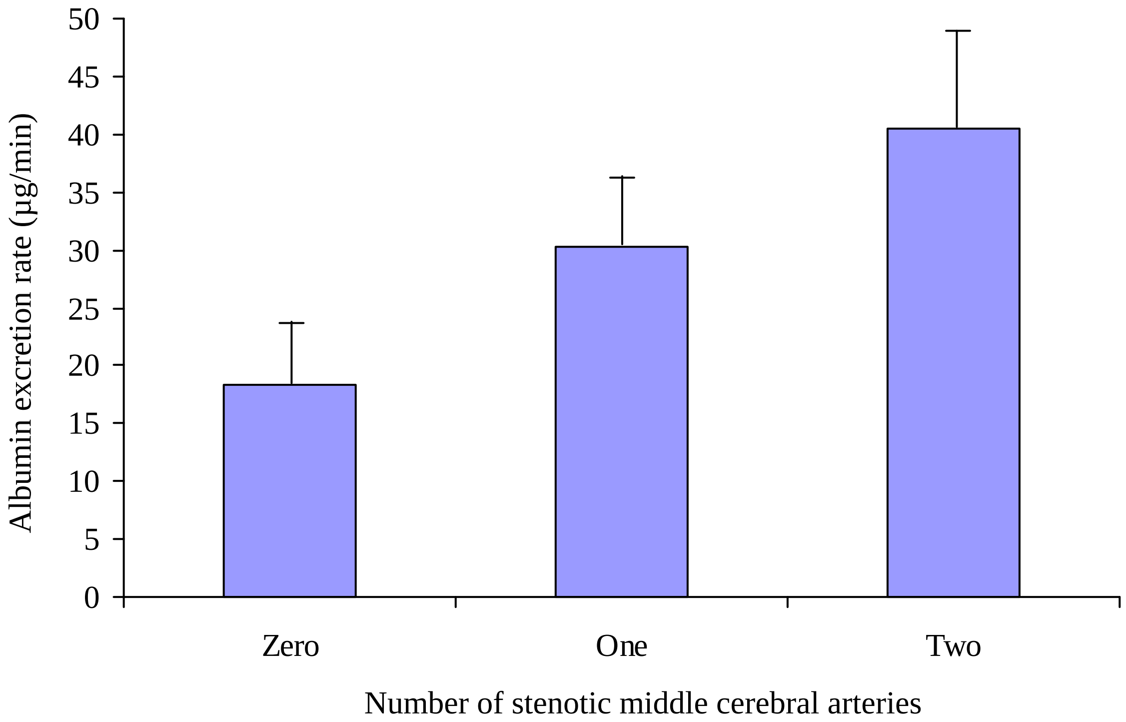
Mean±SD or geometric mean (95% confidence intervals); NS = non-significant, Rx=receiving therapy, * Normoalbuminuria was classified as an AER <20 μg/min, microalbuminuria as an AER ≥20 to <200 μg/min and macroalbuminuria as an AER ≥200 μg/min.[13]

Table 2 Prevalence rates of concomitant disorders and smoking and alcohol consumption in the 857 age, gender, duration and onset of diabetes-matched Chinese Type 2 diabetic patients categorised by albuminuric status

Concomitant disorders (%)	Albuminuria*			
	Normo-	Micro-	Macro-	p value
Numbers	475	250	132	-
MCA stenosis 1/2 vessel/combined	6.3 / 4.8 / 11.1	7.2 / 8.8 / 16.0	9.8 / 13.6 / 23.4	<0.001
Foot affected	2.7	4.4	9.1	0.002
Impotence (% of males)	19.4	20.5	32.4	0.044
Peripheral vascular disease	2.8	4.4	7.6	0.012
History of myocardial infarction	2.5	5.6	6.9	0.010
Retinopathy	14.4	30.4	50.8	<0.001
Prevalence of hypertension (Rx)	44.2 (21.7)	57.6 (31.2)	77.3 (51.2)	<0.001 (<0.001)
Prevalence of dyslipidaemia (Rx)	46.5 (4.0)	48.6 (4.3)	69.7 (9.9)	<0.001(0.025)
Treatment of diabetes	75.5	81.3	84.1	0.018
Smoking consumption (ex/current)	12.4 / 13.0	13.2 / 18.0	20.8 / 19.2	0.002
Alcohol consumption (ex/current)	9.5 / 7.8	14.0 / 7.6	19.4 / 7.8	NS

Mean±SD or geometric mean (95% confidence intervals); NS = non-significant, Rx=receiving therapy, *Normoalbuminuria was classified as an AER <20 µg/min, microalbuminuria as an AER ≥20 to <200 µg/min and macroalbuminuria as an AER ≥200 µg/min.[13]

Figure Increasing 24 hour urinary albumin excretion rate in 857 age, gender, duration and onset of diabetes-matched Chinese Type 2 diabetic patients with middle cerebral artery stenoses in 0, 1 or 2 vessels (ANOVA p value<0.001)


Albumin excretion rate (µg/min)
50
45
40
35
30
25
20
15
10
5
0
Zero
One
Two
Number of stenotic middle cerebral arteries