

## ORIGINAL ARTICLE

# Silent ischemia is more prevalent among hypertensive patients with microalbuminuria and salt sensitivity

S Bianchi<sup>1</sup>, R Bigazzi<sup>1</sup>, A Amoroso<sup>1</sup> and VM Campese<sup>2</sup>

<sup>1</sup>Unita' Operativa di Nefrologia, Spedali Riuniti, Livorno, Italy; <sup>2</sup>Division of Nephrology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Some patients with essential hypertension manifest greater than normal urinary albumin excretion (UAE). Salt-sensitive hypertensives also manifest greater UAE compared to salt-resistant individuals. Although the significance of these associations is not well established, several lines of evidence suggest that microalbuminuria and/or salt sensitivity may be associated with greater prevalence of cardiovascular risks and events. In this study, we have evaluated by ergometric exercise 42 subjects with microalbuminuria and 42 matched individuals with normal UAE. All these subjects also underwent a standardized protocol to determine blood pressure sensitivity to a high salt intake. Patients with microalbuminuria displayed greater levels of ambulatory blood pressure and a greater rise in systolic

blood pressure during exercise compared to patients with normal UAE ( $33.1 \pm 1.56$  vs  $26.4 \pm 1.7$  mmHg,  $P < 0.001$ ). Seven hypertensive patients with microalbuminuria developed ST segment depression during exercise compared to only one subject with normal UAE. Salt-sensitive patients manifested greater UAE than salt-resistant subjects (58 and 14 mg, 24 h,  $P < 0.001$ ) and greater prevalence of silent ischemia (6 vs 2) than salt-resistant individuals. In conclusion, these studies have shown that hypertensive individuals with microalbuminuria and/or salt sensitivity manifest an increased prevalence of silent ischemia.

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## Introduction

Some patients with essential hypertension manifest an increase in urine albumin excretion (UAE) above normal, but below the levels that are normally detectable by the Albustix. This corresponds to a UAE of  $> 30$  and  $< 300$  mg/24 h, and has been called microalbuminuria. The prevalence of microalbuminuria among patients with essential hypertension varies enormously among different studies, with rates ranging between 5 and 37%.<sup>1–6</sup> Recently, in a study of 11 343 nondiabetic hypertensive patients with a mean age of 57 years, microalbuminuria was present in 32% of men and 28% of women ( $P < 0.05$ ), and increased with age, severity and duration of hypertension.<sup>7</sup> A wide variability of UAE has also been shown among normotensive healthy subjects.<sup>8–10</sup>

The increasing interest in the significance of microalbuminuria derives, in large part, from the recognition that a rise in UAE is associated with

an increased incidence of cardiovascular complications<sup>11</sup> and morbid events, such as left ventricular hypertrophy,<sup>12–14</sup> myocardial ischemia,<sup>15,16</sup> hypertensive retinopathy, and increased thickness of the carotid artery.<sup>17</sup> The predictive value of microalbuminuria persists even when data are corrected for age, sex, obesity and levels of blood pressure.

We have previously shown that salt-sensitive patients with essential hypertension manifest greater UAE and other markers of cardiovascular risk when compared with salt-resistant individuals.<sup>18–20</sup> Thus, a close relation may exist between salt sensitivity, microalbuminuria and cardiovascular events.

The presence of ST segment depression without angina pectoris during electrocardiographic testing (silent ischemia) has been frequently described in patients with essential hypertension with no history of angina pectoris or myocardial infarction, and is associated with higher cardiovascular morbidity and mortality.<sup>21</sup>

The purpose of this study was to evaluate the prevalence of silent ischemia in a group of hypertensive patients characterized according to their UAE and/or according to their blood pressure sensitivity to

Correspondence: Dr VM Campese, LAC/USC Medical Center, 1200 North State Street, Los Angeles, CA 90033, USA.  
E-mail: campese@hsc.usc.edu

salt intake, and to determine whether microalbuminuria or salt sensitivity may be predictors of silent coronary heart ischemia.

## Patients and methods

### Patient population

A total of 84 patients with stage 1 or 2 essential hypertension<sup>22</sup> were included in the study. These subjects were selected from a larger group of patients attending our clinic. We enrolled 42 patients with essential hypertension and urinary albumin excretion greater than 30 mg/day, and 42 patients without microalbuminuria but with similar clinical characteristics (gender, age, BMI, smoking habits, and known duration of hypertension). In all, 55 individuals (29 with normal UAE and 26 with microalbuminuria) had never been treated with antihypertensive drugs prior to this study. In the remaining 29 patients, antihypertensive medications were withheld at least 4 weeks prior to the study. Patients were included if their blood pressure was consistently greater than 140/90 mmHg in three subsequent clinic visits, and their creatinine clearance was greater than 80 ml/min/1.73 m<sup>2</sup>. Exclusion criteria included age greater than 65 years, a family history of diabetes mellitus, an abnormal glucose tolerance test, women of child-bearing potential, a positive dip-stick test for proteinuria, nocturia or other reasons for arising from bed during the night, body mass index greater than 30, use of sedatives or stimulating agents, postural hypotension, abnormal electrocardiogram, heart failure, history of angina pectoris, myocardial infarction or cerebrovascular disease, central nervous system dysfunction or depression, difficulty with sleep, etc. A diagnosis of secondary hypertension was ruled out by the presence of normal routine blood chemistry, urinalysis and chest-X-ray. When clinically indicated, we measured urinary metanephrines to rule out a diagnosis of pheochromocytoma, plasma aldosterone to rule out primary aldosteronism, and performed renal angiogram to exclude renovascular hypertension. Patients with secondary hypertension were excluded. The study was approved by the Institutional Ethics Committee. Each subject gave consent after the nature, purpose and potential risks of the procedures were fully explained. All subjects were instructed to collect 24-h urine at three different occasions, 1 week apart, for the determination of UAE, urinary sodium and creatinine clearance. To ensure completeness of the 24 h urine collections, urinary creatinine was measured and only values greater than 20 mg/kg in males and greater than 15 mg/kg in females were considered to be consistent with good urine collections. Those urine samples that did not fulfill those criteria were discarded. Patients were defined to have microalbuminuria if the average UAE of the

three 24-h urine collections exceeded 30 mg day, in the absence of urinary infection.

All subjects came to the outpatient clinic after fasting overnight for 12–14 h. After the subjects had rested 30 min in the supine position and after venous catheters had been placed in an antecubital vein, blood pressure and heart rate were measured at least three times and blood samples drawn.

### Cycloergometric exercise test

All patients underwent a cycloergometric exercise (Ergoline 800 S, Mortara Instruments, Inc., Milwaukee, WI, USA), and ST segment changes were monitored by a cardiologist (AA) who was unaware of the amount of UAE in the patients tested. The work load was increased by 25 W every 2 min; blood pressure was monitored every 2 min by a mercury sphygmomanometer, and interrupted when maximal heart rate was achieved or when fatigue supervened. No patient interrupted the test due to angina pectoris or significant arrhythmias.

A diagnosis of ischemia was undertaken when ST segment depression of 2 mm occurred, following standard criteria.<sup>23–25</sup>

### Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring was performed by a Takeda A and D model TM-2420. The TM-2420 uses the Korotkoff method, the first and the fifth phase representing systolic and diastolic pressure, respectively. Two microphones within the pneumatic cuff can differentiate between Korotkoff sounds and noise. The TM-2420 was calibrated against a mercury sphygmomanometer before each recording. Left arm readings were taken with a standard-sized cuff beginning at 9 am. Measurements were made every 20 min from 7 am to 11 pm (daytime period) and every 30 min from 11 pm to 7 am (nighttime period). All patients underwent ambulatory blood pressure monitoring as outpatients, during a working day without any changes in their habits or diet. All subjects kept a diary to report the time of going to bed as well as every significant episode that could have happened during the recordings (such as physical and emotional stress and nocturnal awakenings and their causes). All patients awoke at 7 am with an alarm.

### Determination of salt sensitivity

After baseline determination of UAE and ABPM, patients were instructed by a dietitian to adhere, for the following 2 weeks, to an isocaloric diet containing 1.3 g of protein/kg, 126 kJ/kg of calories, 800 mg/day of calcium, and 80 meq/day of potassium, while their sodium intake varied. During the first week, they received a diet containing 20 meq/day of Na<sup>+</sup>, and during the remaining 7 days they received a

dietary Na<sup>+</sup> intake of 250 meq/day. Compliance to the prescribed diet was determined by measurements of 24 h urinary Na<sup>+</sup> excretion during the last 2 days of each diet. On the sixth and seventh days of each diet, all subjects returned to our clinic between 8 and 9 am for evaluation. Office blood pressure and body weight were measured after patients had voided and before eating breakfast. Hypertensive patients were defined to be salt-sensitive if their mean arterial pressure increased by at least 10 mmHg during a high compared with a low dietary Na<sup>+</sup> intake.

### Analytical procedures

Serum and urine creatinine were measured by an autoanalyzer.<sup>26</sup> Total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol were measured within 15 days after blood drawing. Total serum cholesterol, HDL-cholesterol and triglycerides were assayed by enzymatic methods. The concentration of low-density lipoprotein (LDL) was calculated by the formulae of Friedewald *et al.*<sup>27</sup> The albumin concentration in the urine was measured by the immunoturbidometric method.<sup>28,29</sup> Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

### Data analysis

From the 24-h blood pressure profile, the following values were calculated: 24-h average systolic values,

24-h average diastolic values, and daytime and nighttime average systolic and diastolic values. The recorder automatically discarded artifactual readings; computerized analysis excluded isolated diastolic readings less than 40 mmHg, systolic values greater than 240 mmHg, and differential pressure less than 20 mmHg.

The program StatView 4.01 was used for the statistical analysis of the data. Because population studies have shown a skewed distribution of microalbuminuria, we used nonparametric statistical techniques. The Kruskal–Wallis rank-sum test was performed to determine differences among normotensive and hypertensive subjects with or without microalbuminuria.<sup>30</sup> The Spearman's rank correlation technique was used to estimate correlations between microalbuminuria and other variables.<sup>31</sup> For parametric analysis, one-way analysis of variance (ANOVA) and the Shaffe test were used to estimate differences among groups and the least-squares analysis to estimate correlations between different parameters. *P* values less than 0.05 were considered significant.

### Results

The clinical characteristics of all 84 subjects included in the study are outlined in Table 1. The mean age was 47.8 ± 0.8 years, the mean systolic blood pressure was 157.6 ± 1.1 mmHg, and the mean diastolic blood pressure was 106 ± 0.8 mmHg. In total, 42 patients had normal UAE and 42 had microalbuminuria. The clinical characteristics of these

**Table 1** Clinical characteristics of hypertensive patients classified on the basis of the presence (Microalbuminuria) or absence (normal UAE) of microalbuminuria

	All n=88	Normal UAE n=42	Microalbuminuria n=42	P
Age (years)	47.8 ± 0.8	47.2 ± 1.2	48.5 ± 1	ns
Gender (M/F)	47/37	20/22	27/15	
BMI	26.4 ± 0.21	26 ± 0.2	26.6 ± 0.3	ns
Duration hypertension (years)	6.1 ± 0.3	6.4 ± 0.4	5.9 ± 0.4	ns
UAE (mg/24 h)	29 (5–129)	12 (5–28)	64 (30–129)	0.0001
Systolic BP basal (mmHg)	157.6 ± 1.1	156.6 ± 1.5	158.5 ± 1.5	ns
Diastolic BP basal (mmHg)	106 ± 0.8	105.4 ± 1.1	106.7 ± 1	ns
SBP maximum exercise (mmHg)	190.7 ± 1.7	183.1 ± 2.0	198.2 ± 2.2	0.0001
DBP maximum exercise (mmHg)	112 ± 0.7	110.5 ± 0.9	113.4 ± 1.0	0.05
ΔSBP with exercise (mmHg)	33.1 ± 1.56	26.4 ± 1.7	39.7 ± 2.2	0.0001
ΔDBP with exercise (mmHg)	5.9 ± 0.69	5.1 ± 0.8	6.7 ± 1.1	ns
SBP 24 h (mmHg)	145.3 ± 1.6	141.0 ± 2.0	149.5 ± 2.4	0.008
DBP 24 h (mmHg)	92.8 ± 1.1	89.9 ± 1.4	95.7 ± 1.5	0.01
SBP daytime (mmHg)	149.6 ± 1.6	146.4 ± 2.2	153.0 ± 2.3	0.05
DBP daytime (mmHg)	96.0 ± 1.0	94.1 ± 1.4	97.9 ± 1.4	0.06
SBP nighttime (mmHg)	135.6 ± 2.0	129.4 ± 2.4	141.8 ± 2.9	0.001
DBP nighttime (mmHg)	86.9 ± 1.4	81.9 ± 1.7	100.0 ± 2.0	0.001
Heart rate basal (bpm)	72.3 ± 0.7	72 ± 1.1	72 ± 0.9	ns
Heart rate maximum exercise (bpm)	110 ± 1.4	104.7 ± 1.4	114.6 ± 2.2	0.003
Δ Heart rate maximum exercise (bpm)	52.4 ± 2.0	45.6 ± 2.3	59.1 ± 3.1	0.0008
Triglycerides (mg/dl)	145 ± 4.8	138.5 ± 6.6	151.2 ± 6.8	ns
Total cholesterol (mg/dl)	213 ± 4.4	201.7 ± 5.5	224.2 ± 6.3	0.01
HDL cholesterol (mg/dl)	56 ± 1.8	61.8 ± 2.7	50.1 ± 2.1	0.001

BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; UAE: urine albumin excretion.

two groups are detailed in Table 1. There was no difference in age, BMI, baseline levels of systolic or diastolic BP, and duration of hypertension between the two groups. However, serum cholesterol was greater and HDL-cholesterol lower in patients with microalbuminuria than in those with normal UAE.

Following cycloergometric exercise, systolic and diastolic BP increased more in patients with microalbuminuria than in those with normal UAE ( $198.2 \pm 2.2/113 \pm 1.0$  vs  $183 \pm 2.0/110.5 \pm 0.9$  mmHg,  $P < 0.001$ ;  $\Delta$  systolic blood pressure  $39.7 \pm 2.2$  and  $26.4 \pm 1.7$  mmHg, respectively,  $P < 0.001$ ). Similarly, heart rate increased more in patients with microalbuminuria than in those with normal UAE ( $114.6 \pm 2.2$  vs  $104.7 \pm 1.4$  bpm,  $P < 0.003$ ;  $\Delta$  heart rate  $59.1 \pm 3.1$  vs  $45.6 \pm 2.3$  bpm,  $P < 0.0008$ ).

During exercise, eight patients developed electrocardiographic abnormalities consistent with ischemia and 76 did not. The clinical characteristics of these two groups are outlined in Table 2. The only significant differences between these two groups were a greater amount of UAE (65 (range 11–92) vs 22 (range 5–130) mg/24 h) and greater levels of systolic BP during maximum exercise ( $208.7 \pm 4.7$  vs  $190.4 \pm 1.8$  mmHg,  $P < 0.004$ ) in patients with evidence of ischemia than in those who did not manifest any significant electrocardiographic change during maximum exercise. Of the eight subjects who developed electrocardiographic abnormalities during exercise, seven had microalbuminuria and only one had normal UAE. HDL-cholesterol was also significantly lower in patients with evidence of ischemia than in those without such evidence. After a follow-up of 3 years, one patient with microalbuminuria developed a myocardial infarction and one developed angina pectoris. None of the patients with normal UAE developed clinical manifestations of coronary heart disease after the same period of observation.

When patients were evaluated for their blood pressure response to varied salt intakes, 43 were classified as salt-sensitive and 41 as salt-resistant (Table 3). Baseline systolic and diastolic blood pressure measured in the office were not different between salt-sensitive and salt-resistant individuals. However, ambulatory blood pressure recording showed greater daytime and nighttime systolic and diastolic blood pressure levels among salt-sensitive than among salt-resistant hypertensive subjects. In addition, salt-sensitive subjects displayed a greater rise in systolic blood pressure during exercise than salt-resistant patients ( $36.9 \pm 2.1$  vs  $29.0 \pm 2.2$  mmHg,  $P < 0.001$ ). Urine albumin excretion was also significantly greater among salt-sensitive than salt-resistant subjects (58 vs 14 mg/24 h,  $P < 0.0001$ ). Six salt-sensitive and only two salt-resistant subjects manifested ischemic changes during ergometric exercise.

## Discussion

This study has shown that the frequency of silent myocardial ischemia detected by stress electrocardiography is significantly greater among hypertensive patients with microalbuminuria than among those with normal UAE. The study has confirmed that while blood pressure measured in the office may not be different between patients with and without microalbuminuria, 24 h ambulatory blood pressure monitoring reveals substantial differences among these two groups.<sup>32</sup> More specifically, daytime blood pressure, but even more so nighttime blood pressure, was significantly greater among patients with microalbuminuria than among those with normal UAE. The study has also shown that patients with microalbuminuria manifest a greater rise in blood pressure during exercise compared to

**Table 2** Clinical characteristics of patients with or without silent ischemia

	Ischemia + n=8	Ischemia – n=76	P
Age (years)	48.5 ± 2.3	147.8 ± 0.8	ns
Gender (M/F)	7/1	40/36	
BMI	26.7 ± 0.6	26.3 ± 0.2	ns
Duration of hypertension (years)	7.6 ± 0.8	6 ± 0.3	ns
UAE (mg/24 h)	65 (11–92)	22(5–130)	0.003
Systolic BP (mmHg)	158.1 ± 4	157.5 ± 1.1	ns
Diastolic BP (mmHg)	104.3 ± 2.5	106.2 ± 0.8	ns
SBP maximum exercise (mmHg)	208.7 ± 4.7	190.4 ± 1.8	0.004
DBP maximum exercise (mmHg)	110.9 ± 2.1	112.1 ± 0.8	ns
HR maximum exercise (bpm)	114 ± 5.0	109 ± 1.4	ns
$\Delta$ HR with exercise (bpm)	54 ± 5.1	52 ± 2.2	ns
$\Delta$ SBP (mmHg) with exercise	50.6 ± 4.6	31.2 ± 1.5	0.002
$\Delta$ DBP (mmHg) with exercise	6.5 ± 1.4	5.8 ± 0.8	ns
Triglycerides (mg/dl)	148.6 ± 17	144.5 ± 5	ns
Total cholesterol (mg/dl)	229.7 ± 14	211.2 ± 4.6	ns
HDL cholesterol	45.2 ± 5.6	57.2 ± 2	0.006

BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; UAE: urine albumin excretion is expressed as median and range; heart rate: HR.

**Table 3** Clinical characteristics of hypertensive patients classified as salt-sensitive (SS) or salt-resistant (SR) individuals on the basis of their blood pressure response to salt

	SS n=43	SR n=41	P
Age (years)	48.5 ± 1.1	47.2 ± 1.2	ns
Gender (M/F)	26/17	21/20	
BMI	26.6 ± 0.32	26.1 ± 0.27	ns
Duration hypertension (years)	6.3 ± 0.5	6.0 ± 0.41	ns
UAE (mg/24 h)	58 (6–129)	14 (5–66)	0.0001
Systolic BP basal (mmHg)	158.5 ± 1.6	156.6 ± 1.4	ns
Diastolic BP basal (mmHg)	106.5 ± 1.0	105.6 ± 1.2	ns
SBP maximum exercise (mmHg)	195.5 ± 2.4	185.6 ± 2.2	0.003
DBP maximum exercise (mmHg)	112.7 ± 1.0	111.2 ± 1.0	ns
Δ SBP with exercise (mmHg)	36.9 ± 2.1	29.0 ± 2.2	0.001
Δ DBP with exercise (mmHg)	6.2 ± 0.9	5.6 ± 1.0	ns
SBP 24 h (mmHg)	147.9 ± 2.3	142.4 ± 2.2	ns
DBP 24 h (mmHg)	95.8 ± 1.5	89.8 ± 1.4	0.01
SBP daytime (mmHg)	152.9 ± 2.4	146.3 ± 2.0	0.04
DBP daytime (mmHg)	98.2 ± 1.4	93.7 ± 1.4	0.02
SBP nighttime (mmHg)	140.9 ± 2.7	130.1 ± 2.7	0.005
DBP nighttime (mmHg)	91.7 ± 2.1	81.9 ± 1.7	0.001
HR basal (bpm)	73.2 ± 0.85	71.3 ± 1.1	ns
HR maximum exercise (bpm)	113.2 ± 2.2	105.9 ± 1.6	0.01
Δ HR maximum exercise (bpm)	55.2 ± 3.2	49.4 ± 2.5	ns
Triglycerides (mg/dl)	152 ± 7.2	137 ± 6.2	ns
Total cholesterol (mg/dl)	226 ± 6.0	199 ± 5.8	0.001
HDL cholesterol (mg/dl)	52.1 ± 2.4	60.1 ± 2.8	0.03

BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; UAE: urine albumin excretion; HR: heart rate.

patients without microalbuminuria. In all, these findings support the notion that microalbuminuria may be, at least in part, the result of a greater pressure load on the microvascular circulation.

These studies have also confirmed that salt-sensitive hypertensive individuals manifest greater urine albumin excretion rate than salt-resistant patients.<sup>18</sup> Moreover, while office blood pressure was not different among these two groups, daytime and nighttime ambulatory blood pressure levels were significantly greater among salt-sensitive than among salt-resistant individuals. Finally, salt-sensitive individuals manifested a greater rise in blood pressure during exercise than salt-resistant individuals and a greater frequency of silent myocardial ischemia than salt-resistant individuals.

In all, these studies indicate that patients with microalbuminuria and those with salt sensitivity manifest a greater prevalence of myocardial ischemia, which may predispose them to more cardiovascular events. Although the mechanisms underscoring the association between microalbuminuria and silent ischemia are not clear, it is plausible that increased sympathetic nervous system activity during exercise, or greater microvascular damage of the myocardium, may play a role.

Previous investigators have shown a greater frequency of silent myocardial ischemia detected by stress echocardiography and electrocardiography among IDDM patients with microalbuminuria compared to normoalbuminuric IDDM patients.<sup>33</sup> In a cross-sectional, case-control study of 86

asymptomatic NIDDM patients, 43 of whom had micro-albuminuria, Rutter *et al*<sup>34</sup> observed a higher prevalence of ischemia response (65 vs 40%,  $P=0.016$ ), reduced total exercise time (5 vs 7 min,  $P<0.001$ ), reduced work and reduced age-predicted maximum heart rate among NIDDM patients with microalbuminuria compared to those with normal UAE. In a study of 203 diabetic patients (83 with IDDM), Janand-Delenne *et al*<sup>35</sup> found a frequency of 20.9% of silent myocardial ischemia among male patients and recommended a routine screening for these subjects. This study shows that a similar association is present among patients with essential hypertension.

It is of interest that blood pressure during exercise was greater in patients with microalbuminuria than in those with normal UAE. Previous studies have shown greater ambulatory blood pressure load among patients with ST segment depression than among those without these electrocardiographic changes, suggesting that blood pressure elevation may trigger ST-segment depression.<sup>36</sup> Some studies also indicate that acute elevations in blood pressure during exercise are related to painless ischemia, and this has been attributed to decreased pain perception caused by baroreceptor stimulation.<sup>37–40</sup>

Studies have shown that patients with microalbuminuria manifest greater evidence of cardiovascular risks and events when compared to patients with normal UAE. In a group of patients with essential hypertension, we previously observed that those patients who displayed an increase in UAE also

manifested an increased thickness of the carotid artery, a recognized marker of atherosclerosis.<sup>41</sup>

Yudkin *et al*<sup>42</sup> observed a greater incidence of coronary heart disease (74%) and peripheral vascular disease (44%) in patients with microalbuminuria than in patients without microalbuminuria (32.9 and 9%, respectively). After a follow-up of 3.6 years, there were nine deaths; three (2%) among the 149 subjects without microalbuminuria and six (33%) among the 18 microalbuminuric subjects. In a mixed group of normotensive and hypertensive individuals, Haffner *et al*<sup>43</sup> observed a greater prevalence of myocardial infarction among patients with microalbuminuria than among those without microalbuminuria (7.1 and 1.7%, respectively). The difference in cardiovascular events among patients with microalbuminuria persisted even when patients with hypertension were excluded. Similar results have been observed by Winocour *et al*.<sup>44</sup>

After a follow-up of 62–83 months, Damsgaard *et al*<sup>45–46</sup> reported a greater incidence of strokes and other cardiovascular events in elderly nondiabetic subjects with increased UAE than in those with normal UAE.

In a study of 11 343 nondiabetic hypertensive subjects, among patients with microalbuminuria, 31% had coronary artery disease, 24% had left ventricular hypertrophy, 6% had had a stroke, and 7% had peripheral vascular disease. In patients without microalbuminuria, these rates were 22, 14, 4, and 5%, respectively ( $P < 0.001$ ).<sup>7</sup>

In a retrospective cohort analysis of 141 hypertensive individuals followed-up for an average of 7 years, we observed a significantly greater number of cardiovascular events among 54 patients with microalbuminuria than among 87 hypertensive patients with normal UAE. Univariate regression analysis showed that UAE, cholesterol and diastolic blood pressure were independent predictors for the cardiovascular outcome. Stepwise logistic regression analyses showed that UAE was the most important independent predictor for cardiovascular complications, followed by diastolic blood pressure and serum cholesterol. This suggests that, although risk factors such as hypertension and hypercholesterolemia are causative for cardiovascular diseases, the presence of microalbuminuria may be a better expression of already established microvascular damage and predict cardiovascular events better than potentially causative factors.<sup>47</sup>

However, not all evidence is fully supportive of generalized vascular damage in patients with microalbuminuria.<sup>48</sup> In a prospective follow-up study of 345 nondiabetic hypertensive patients with several risk factors, it was observed that there was an increased risk of cardiovascular events in patients with UAE greater than 200 mg/24 h, but not in those with microalbuminuria.<sup>49</sup> A study of 870 young hypertensives (up to 45 years old) reported that no significant correlation existed between UAE and left ventricular mass, suggesting that in the early phases

of hypertension cardiovascular and renal damage may not occur in a parallel fashion.<sup>50</sup> Taddei *et al*<sup>51</sup> found no difference in vascular response to acetylcholine between micro- and normoalbuminuria hypertensive subjects. Gosling<sup>52</sup> has recently pointed out that microalbuminuria is a very sensitive index of inflammation, reflecting vascular permeability, and that vascular disease is only one of a large number of inflammatory processes that can lead to microalbuminuria.

Kuusisto *et al*<sup>53</sup> studied the impact of hyperinsulinemia and microalbuminuria, alone or in combination, on the incidence of cardiovascular events in 1069 elderly subjects followed for an average of 3.5 years. In all, 48% males and 60.8% females had hypertension. The incidence of fatal and nonfatal cardiovascular events was significantly greater in patients with than in those without microalbuminuria. By contrast, the incidence of cardiovascular events was only slightly, but not significantly, increased in patients with higher serum insulin levels. The combined presence of microalbuminuria and hyperinsulinemia increased the probability of fatal and nonfatal cardiovascular events, even after adjusting for other risk factors, such as male sex, cigarette smoking, hypertension and serum cholesterol levels.

The association between microalbuminuria, hyperinsulinemia and salt sensitivity is particularly intriguing. Recent evidence indicates that several patients with essential hypertension manifest insulin resistance and/or hyperinsulinemia.<sup>54</sup> Acute and chronic infusion of insulin may cause sodium retention,<sup>55</sup> may stimulate the sympathetic nervous system,<sup>56</sup> may alter cation transport and stimulate hypertrophy of smooth muscle cells in the absence of changes in serum glucose. These cellular effects of insulin, if present in smooth muscle cells, could underlie the increase in total body sodium and in blood pressure in salt-sensitive hypertensives.

The blood pressure of obese adolescents is salt-sensitive, as attested by a shallow slope of the renal-function relationship, and this sensitivity may be due to the combined effects of hyperinsulinemia and increased activity of the sympathetic nervous system.<sup>57</sup> Few studies have demonstrated an association between salt sensitivity and insulin resistance in both normotensive<sup>58</sup> and hypertensive individuals.<sup>59</sup> Galletti *et al*<sup>60</sup> observed that during a euglycemic insulin clamp, salt-sensitive hypertensives manifested markedly lower utilization of glucose than did salt-resistant individuals. We have shown that hypertensive patients with microalbuminuria manifest higher serum levels of insulin<sup>61</sup> and more insulin resistance than subjects with normal UAE.<sup>62</sup> In addition, we have observed that salt-sensitive subjects with essential hypertension manifest greater UAE than normotensive individuals.<sup>63</sup>

Because hyperinsulinemia and insulin-resistance have been associated with a greater incidence of

vascular disease,<sup>64–68</sup> and particularly coronary heart disease,<sup>69–71</sup> these associations could explain the greater incidence of ischemic events in patients with microalbuminuria and with salt sensitivity compared with those with normal UAE and salt-resistance. Insulin levels and insulin sensitivity were not measured in this study.

In conclusion, the presence of microalbuminuria and/or salt sensitivity in patients with essential hypertension carries an increased risk of silent ischemia and cardiovascular events. While long-term longitudinal studies are necessary to fully establish that microalbuminuria identifies patients at risk of developing cardiovascular events, we suggest that patients with microalbuminuria should be screened for the possibility of silent ischemia.

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