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Glomerular hyperfiltration predicts the development of microalbuminuria in stage 1 hypertension: The HARVEST

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Factors related to the development of microalbuminuria in hypertension are not well known. We did a prospective study to investigate whether glomerular hyperfiltration precedes the development of microalbuminuria in hypertension. We assessed 502 never-treated subjects screened for stage 1 hypertension without microalbuminuria at baseline and followed up for 7.8 years. Creatinine clearance was measured at entry. Urinary albumin and ambulatory blood pressure were measured at entry and during the follow-up until subjects developed sustained hypertension needing antihypertensive treatment. Subjects with hyperfiltration (creatinine clearance >150 ml/min/1.73 m^2, top quintile of the distribution) were younger and heavier than the rest of the group and had a greater follow-up increase in urinary albumin than subjects with normal filtration ($P<0.001$). In multivariable linear regression, creatinine clearance adjusted for confounders was a strong independent predictor of final urinary albumin ($P<0.001$). In multivariable Cox regression, patients with hyperfiltration had an adjusted hazard ratio for the development of microalbuminuria based on at least one positive measurement of 4.0 (95% confidence interval (CI), 2.1–7.4, $P<0.001$) and an adjusted hazard ratio for the development of microalbuminuria based on two consecutive positive measurements of 4.4 (95% CI, 2.1–9.2, $P<0.001$), as compared with patients with normal filtration. Age, female gender, and 24 h systolic blood pressure were other significant predictors of microalbuminuria. In conclusion, stage 1 hypertensive subjects with glomerular hyperfiltration are at increased risk of developing microalbuminuria. Early intervention with medical therapy may be beneficial in these subjects even if their blood pressure falls below normal limits during follow-up.

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According to the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7)[1] and the European Society of Hypertension/European Society of Cardiology,[2] guidelines for initiating antihypertensive treatment should be based on two main criteria: the level of systolic and diastolic blood pressure and the total level of cardiovascular risk. Microalbuminuria entails a higher incidence of fatal events in hypertension, and is thus considered an important adjunctive risk factor, which requires early antihypertensive treatment.[3–5] This is why assessment of albumin excretion rate (AER) is increasing in a risk stratification strategy for hypertensive patients.[6–8] According to early experimental studies, glomerular hypertension and hyperfiltration are key factors in mediating progressive renal damage.[9] A number of studies suggest that this model of renal injury may apply to the early diabetic kidney because hyperfiltration has been shown to predict the development of microalbuminuria and nephropathy in type I diabetes mellitus.[10–12] This finding has been attributed to poor glycemic control as hyperfiltration showed a correlation with hemoglobin A1c.[11] Little is known on the time course of AER in hypertensive subjects and on the factors that favor the development of microalbuminuria in the early stage of hypertension. In a group of young adults with mild to moderate hypertension and treated for the disease, Redon *et al*. found that the main factors influencing the occurrence of microalbuminuria during antihypertensive treatment were the values of AER at baseline and the slopes for systolic blood pressure and fasting glucose.[13] No data are available on evolution of AER in untreated hypertensive subjects. In particular, it is not known if glomerular hyperfiltration precedes the development of microalbuminuria in hypertension. The aim of this study was to investigate the time course of AER in a cohort of young subjects screened for stage 1 hypertension and to assess whether glomerular hyperfiltration influences the development of microalbuminuria in these individuals.

RESULTS

The clinical characteristics of the subjects divided into quintiles of creatinine clearance at the baseline are reported

in Table 1. Female gender was more prevalent in the 1st quintile than the other quintiles. Body mass index (BMI) and clinic systolic blood pressure increased with increasing levels of creatinine clearance, whereas age decreased across the quintiles. AER tended to increase across the quintiles, but the between-group differences were of borderline significance. No differences in family history for hypertension, hypertension duration, smoking, alcohol use, physical activity habits, plasma glucose, or lipids were found between the quintiles (data not shown). The length of follow-up and changes in 24-h systolic and diastolic blood pressure during the follow-up were similar in the five groups.

Follow-up data

In the whole group, mean follow-up was 7.8 ± 3.3 years. Among the entire cohort, 24-h blood pressure increased by $2.9 \pm 10.3/2.1 \pm 7.6$ mm Hg. Body weight increased by 1.7 ± 5.4 kg and AER rose from (geometric mean (interquartile range)) 4.6 (2.7–8.5) mg/24 h to 7.8 (4.7–12.2 mg/24 h). During the follow-up, 244 subjects developed sustained hypertension and were started on antihypertensive treatment. Their clinic blood pressure increased from $148.8 \pm 10.4/95.4 \pm 4.7$ mm Hg at baseline assessment to $155.6 \pm 10.9/101.8 \pm 7.2$ mm Hg at final visit. In the 258 subjects who remained untreated, clinic blood pressure fell from $145.0 \pm 10.4/92.7 \pm 5.0$ to $134.5 \pm 8.5/86.6 \pm 5.4$ mm Hg. Baseline creatinine clearance was similar in the two subgroups (124.6 ± 41.8 versus 123.1 ± 39.1 ml/min/1.73 m^2, P = NS).

In Figure 1, the log-AER values at baseline and after follow-up in the subjects divided into quintiles of creatinine clearance are shown. A significant relationship was found between creatinine clearance quintile and final AER level (unadjusted $P < 0.001$, and P adjusted for age, sex, BMI, baseline AER, and time to final assessment = 0.001). Log-AER was significantly higher in the subjects of the 5th quintile in comparison with the subjects of the first three quintiles. Similar trends were present in the subjects divided by sex. However, the relationship was significant in men (unadjusted $P = 0.001$, adjusted $P = 0.005$) and did not reach the level of statistical significance after adjustment for confounders in women (unadjusted $P = 0.01$, adjusted P = NS).

Predictors of final AER

A linear regression analysis was performed among the entire cohort of patients to identify factors that independently

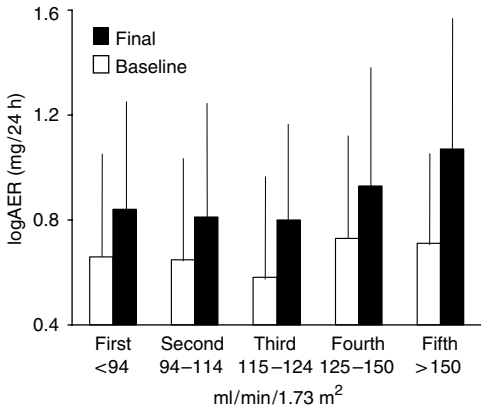

Figure 1 | Logarithm of AER at baseline and final assessments in the 502 subjects divided into quintiles of creatinine clearance at baseline. Adjusted P-values for final AER are: 5th quintile versus 1st quintile, $P = 0.006$; 5th quintile versus 2nd quintile, $P = 0.001$; 5th quintile versus 3rd quintile, $P = 0.002$; 5th quintile versus 4th quintile, P = NS.

Table 1 | Baseline characteristics, prevalence of final microalbuminuria, and changes in 24-h blood pressure during follow-up in the 502 subjects divided according to quintiles of creatinine clearance measured at baseline

Variable	1st Quintile	2nd Quintile	3rd Quintile	4th Quintile	5th Quintile	P-value
Creatinine clearance, range (ml/min/1.73 m^2)	<94	94–114	115–124	125–150	>150	—
Sex, M/F (*N*)	36/64	77/24	84/16	86/15	81/19	<0.001[a]
Age (years)	37.4±7.3	36.0±7.8	34.1±7.5	31.2±8.6	31.2±9.3	<0.001[a]
BMI (kg/m^2)	23.1±2.6	24.9±2.5	25.6±3.2	26.1±3.3	27.6±4.3	<0.001[a]
Duration of hypertension (months)	40.4±48.7	37.6±41.5	60.3±77.5	38.6±56.3	35.7±47.9	NS
Clinic systolic BP (mm Hg)	144.9±10.0	144.5±9.7	146.8±10.9	148.0±11.4	149.7±9.9	0.001
Clinic diastolic BP (mm Hg)	94.4±4.2	94.7±4.5	94.2±5.3	92.9±5.7	93.8±4.9	NS
Mean 24-h systolic BP (mm Hg)	127.6±12.3	131.1±11.7	129.2±10.1	131.0±9.7	131.7±10.9	NS
Mean 24-h diastolic BP (mm Hg)	82.3±8.4	82.0±7.8	81.1±7.5	79.7±8.0	81.2±8.0	NS
Albumin excretion rate (mg/24 h)[b]	4.6 (2.8–8.5)	4.7 (2.4–8.7)	3.7 (2.1–7.6)	5.3 (3.3–9.9)	5.2 (3.2–8.5)	0.058
Creatinine clearance (ml/min/1.73 m^2)	82.5±7.8	102.1±4.5	116.4±3.9	135.1±7.4	183.2±46.6	—
Length of follow-up (years)	7.5±3.5	7.3±3.5	7.6±3.4	8.5±2.8	8.3±3.1	NS
Total incidence of MA at follow-up (%)[c]	6.0	4.0	2.0	13.9	20.0	<0.001[a]
Incidence of persistent MA at follow-up (%)[d]	2.0	2.0	1.0	5.9	11.0	0.002[a]
Change in 24-h systolic BP (mm Hg)	2.8±10.9	2.7±10.2	3.2±9.4	1.8±8.8	3.7±12.0	NS
Change in 24-h diastolic BP (mm Hg)	1.3±7.5	2.9±7.3	2.9±6.9	2.0±6.6	1.3±9.3	NS

BMI, body mass index; BP, blood pressure; F, female; M, male; MA, microalbuminuria.
Data are mean±s.d., unless specified, and are adjusted for age, sex, and BMI.
[a]Unadjusted.
[b]Geometric mean (interquartile range) and P-value for log-transformed data.
[c]MA positive in at least one of two consecutive measurements.
[d]MA positive in two consecutive measurements.

influenced the level of AER at final assessment (Table 2). Independent predictors of final AER were baseline AER, baseline creatinine clearance, gender (female), age (borderline significance), and baseline mean 24-h systolic blood pressure. Time elapsed between baseline and final measurements and changes in 24-h systolic blood pressure during follow-up were other significant correlates of final AER. The mean 24-h diastolic blood pressure, clinic systolic blood pressure, clinic diastolic blood pressure, BMI, lifestyle factors, triglycerides, total cholesterol, and glucose at baseline, and changes in mean 24-h diastolic blood pressure, clinic systolic blood pressure, clinic diastolic blood pressure, body weight, triglycerides, total cholesterol, and glucose during the follow-up did not significantly influence the final level of AER.

Subjects with hyperfiltration

When subjects of the top creatinine clearance quintile (subjects with hyperfiltration, creatinine clearance >150 ml/min/1.73 m^2) were compared to the rest of the group (subjects with normal filtration), a higher follow-up increase in AER adjusted for age, gender, baseline AER, baseline 24-h blood pressure, change in 24-h blood pressure and follow-up length (21.5 ± 78.8 versus 8.0 ± 59.4 mg/24 h, $P<0.001$), and a higher adjusted final AER (geometric mean (interquartile range) = 11.6 (5.6–19.5) mg/24 h versus 7.0 (4.3–11.2) mg/24 h, $P<0.001$) were observed in the former than the latter. Microalbuminuria defined on the basis of at least one positive measurement ($n=46$) or two consecutive positive measurements ($n=22$) was developed more frequently by the subjects with hyperfiltration than those with normal filtration (Table 1 and Figure 2). Forty-seven per cent of the subjects with hyperfiltration versus 54% of the subjects with normal filtration (NS) did not require antihypertensive treatment according to current guidelines. To assess the proportional contribution of covariates to risk of developing microalbuminuria, a Cox model was fitted including hyperfiltration, age, gender, AER, and 24-h systolic blood pressure at baseline as independent variables (Table 3). Subjects with hyperfiltration had a 300% increase in risk of developing microalbuminuria in at least one of two consecutive measurements during the follow-up in comparison with the subjects with normal filtration. Twenty-four-hour systolic blood pressure at baseline was another significant modifiable predictor of final microalbuminuria, whereas change in 24-h systolic blood pressure over time did not attain the level of statistical significance ($P=0.06$). Of note, clinic blood pressure and change in clinic blood pressure over time did not predict final microalbuminuria in this model. When time to microalbuminuria positive in two consecutive measurements was considered as the outcome

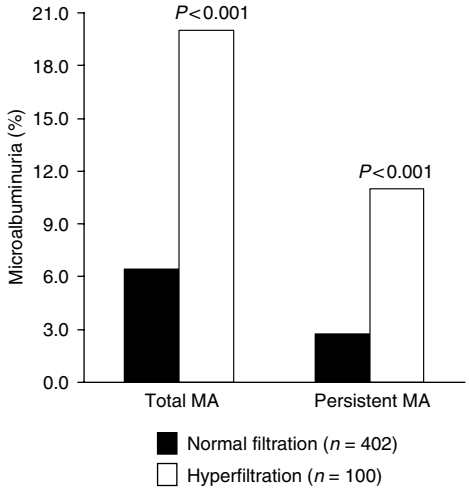

Figure 2 | Incidence of microalbuminuria during the follow-up in the subjects with hyperfiltration (creatinine clearance >150 ml/min/1.73 m^2, top quintile) and the subjects with normal filtration (creatinine clearance $\leqslant 150$ ml/min/1.73 m^2). Microalbuminuria was defined as an AER $\geqslant 30$ mg/24 h in at least one of two consecutive measurements (total microalbuminuria) or in two consecutive measurements (persistent microalbuminuria). MA indicates microalbuminuria.

Table 2 | Significant predictors of albumin excretion rate at final assessment: Summary of multiple regression analysis

Variable	Estimate[a]	s.e.	*t*-ratio	*P*-value
Log creatinine clearance	0.783	0.161	4.86	<0.001
Log AER, baseline	0.289	0.108	2.69	0.007
Sex (female)	0.328	0.100	3.28	0.001
Age	0.010	0.005	1.90	0.058
24-h SBP, baseline	0.014	0.004	3.19	0.002
24-h SBP change	0.011	0.004	2.43	0.015
Time to final assessment	0.000	0.000	4.52	<0.001

AER, albumin excretion rate; SBP, systolic blood pressure; s.e., standard error.
Multiple R=0.343. Squared multiple R=0.117.
Mean 24-h diastolic blood pressure, clinic systolic blood pressure, clinic diastolic blood pressure, BMI, lifestyle factors, and metabolic data at baseline, and changes in mean 24-h diastolic blood pressure, clinic systolic blood pressure, clinic diastolic blood pressure, body weight, fasting glucose, triglycerides, and total cholesterol during the follow-up were found to be nonsignificant by the model.
[a]Of the regression coefficient.

Table 3 | Results of the multivariable Cox regression analysis including factors predicting development of microalbuminuria (positive in at least one of two measurements) as categorical variables[a]

Factor	Adjusted hazard ratio	95% CI	*P*-value
Non-modifiable			
Age (<35 versus $\geqslant 35$ years)	2.7	1.4–5.5	0.004
Sex (female)	2.0	1.0–3.9	0.047
Modifiable			
Creatinine clearance			<0.001
>150 ml/min/1.73 m^2	4.0	2.1–7.4	—
$\leqslant 150$ ml/min/1.73 m^2	1.0[b]		
24-h Systolic blood pressure			0.005
$\geqslant 130$ mm Hg	2.5	1.3–4.9	
<130 mm Hg	1.0[b]	—	—

CI, confidence interval.
[a]The multivariate model was adjusted for albumin excretion rate at baseline.
[b]This served as the reference category. Modifiable factors were included as time-dependent variables.

variable, the association with hyperfiltration remained significant ($P<0.001$) with an adjusted hazard ratio of 4.4 (95% confidence interval (CI), 2.1–9.2).

DISCUSSION

Microalbuminuria is an independent risk factor for cardiovascular disease and has been recently proposed as a useful clinical marker for recognizing hypertensive patients who are at greater risk for progressive renal failure or cardiovascular events.[3–8,14] However, it is not known whether and to what extent AER increases in subjects whose blood pressure levels remain in the borderline hypertensive range and do not fulfill current criteria for treatment. This issue was explored in the normoalbuminuric participants of the Hypertension and Ambulatory Recording VEmetia Study (HARVEST) study, which enrolls young stage 1 hypertensive subjects never treated for hypertension. Data were censored subsequent to any intervention therapy, making this a true natural history study. The present results show that after a mean follow-up of about 8 years, in this cohort there was a substantial increase in AER. During the follow-up, 9.2% of the participants developed microalbuminuria in at least one of two consecutive measurements and 4.4% developed persistent microalbuminuria, and the risk of microalbuminuria was greater in the presence of hyperfiltration (Figure 2). As we have no information on creatinine clearance values before baseline and at the end of the study, we cannot know when glomerular filtration rate started to increase in our hyperfilterers and whether hyperfiltration was still present at the end of the study. However, most of these subjects come to medical attention when their blood pressure is elevated, and the present results indicate that detection of hyperfiltration in this clinical setting is strongly predictive of development of microalbuminuria.

Several longitudinal studies performed in diabetic subjects showed that glomerular hyperfiltration in patients with poor glycemic control precedes the development of microalbuminuria and that in the long run the increased intraglomerular flow may damage the renal structure.[11,15,16] Recently, Amin *et al.*[17] in a prospective cohort of children with type I diabetes demonstrated that glomerular hyperfiltration is predictive of microalbuminuria independent of hemoglobin A1c level. No longitudinal data are available in non-diabetic samples. In a cross-sectional analysis of a general population, borderline and overt microalbuminuria were independently associated with an elevated glomerular filtration.[18] In a cross-sectional analysis of the HARVEST participants, we showed that subjects with microalbuminuria have an increase in creatinine clearance in comparison with the normoalbuminuric subjects.[19] The above cross-sectional data suggested that the association between creatinine clearance and renal damage may follow a parabolic pattern also in non-diabetic subjects similar to the widely known parabolic or biphasic pattern in renal function as observed in diabetes.[15–17]

The present longitudinal results obtained in a cohort of young normoalbuminuric hypertensive subjects show that increased creatinine clearance at the baseline was associated with a higher final adjusted AER level and a more frequent development of microalbuminuria during the follow-up, indicating that there is a temporal relationship between hyperfiltration and microalbuminuria in stage 1 hypertension. At the baseline, subjects with hyperfiltration had a similar level of AER compared to the rest of the population. However, during the 8 years of follow-up microalbuminuria was developed three times more frequently by the subjects with hyperfiltration than by those with normal filtration.

The observed relationship between hyperfiltration and development of microalbuminuria might be explained by other factors, such as age, gender, obesity, metabolic abnormalities, and increased 24-h blood pressure load. Glomerular filtration rate tends to decline with age[20,21] and has been found to be positively related to BMI.[22] Indeed, our subjects in the top creatinine clearance quintile were younger and heavier than subjects in the other quintiles, and this may have introduced bias in the presented relation between baseline creatinine clearance and final albuminuria. However, even after adjusting for age, gender, BMI, glucose, lipids, 24-h blood pressure at baseline, and changes in body weight, metabolic variables, and blood pressure during the follow-up, the relationship between elevated filtration and development of microalbuminuria persisted. Longitudinal studies in treated non-diabetic hypertensive subjects showed that baseline clinic blood pressure[18] or clinic blood pressure changes over time[13] are significant predictors of microalbuminuria development. In the present study, blood pressure was measured with ambulatory monitoring, which is a more sensitive indicator of the 24-h blood pressure load than is clinic blood pressure. Our results show that both baseline 24-h blood pressure and ambulatory blood pressure changes during follow-up influence final AER.

In diabetic subjects, glomerular hyperfiltration is promoted by hyperglycemia.[23,24] However, in some studies the relationship between risk for the development of microalbuminuria and glomerular hyperfiltration was found to be independent of glycemic control.[15,17] In the present study of young hypertensive subjects at low cardiovascular risk, glomerular filtration rate was unrelated to glycemia and this may explain why we did not find a significant association between final AER and metabolic data in the longitudinal analysis. The stimuli provoking glomerular hyperfiltration and development of microalbuminuria in the early hypertensive kidney are unclear. An increase in glomerular capillary pressure and elevation in glomerular filtration rate might be the consequence of a functional decrease in nephron number, as shown in several animal and human models of renal injury.[9,25] Increased renal proximal tubule Na^+ reabsorption may occur in essential hypertensive patients, mostly in obese individuals,[26] and a significant role of increased Na^+ reabsorption in the pathophysiology of glomerular hyperfiltration in hypertension has recently been described.[27] Our subjects with hyperfiltration had increased BMI compared to the rest of the cohort and obesity has been

shown to cause glomerular hyperfiltration and preglomerular vasodilation, which likely exacerbate the effects of increased arterial pressure to cause renal injury.[28]

Limitations

Limitations of our study include first that to identify subjects with hyperfiltration creatinine clearance was used, which tends to overestimate the real glomerular filtration rate.[20] However, our results were obtained in a large homogeneous sample of subjects without kidney disease. Second, AER assessment at baseline was repeated only in the participants with AER >15 mg/24 h and, thus, we cannot exclude that some subjects with baseline AER below that level would develop microalbuminuria at repeat measurement. Third, our interval follow-up time of 8 years may have been inadequate for studying the temporal relationship between baseline glomerular filtration rate and final microalbuminuria. However, in most studies that found an association between baseline hyperfiltration and development of microalbuminuria in diabetic patients, length of follow-up ranged from 5 to 11 years.[12,15,17] Because we included white patients with mild hypertension younger than 45 years of age, our results may not be extrapolated to all hypertensive patients and may not be generalizable to other races or ethnicities. Finally, we cannot exclude that pathogenetic mechanisms other than hyperfiltration may lead to microalbuminuria in hypertension, as suggested by the tendency to a J-shaped relationship between glomerular filtration rate and AER in our patients. Indeed, subjects with hyperfiltration were more frequently male and were younger and heavier than subjects of the bottom creatinine clearance quintile, suggesting that the hyperfiltration-related mechanism of microalbuminuria is more common in men of young age and in obese individuals.

Clinical implications

According to the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7)[1] or the 2003 European Society of Hypertension/European Society of Cardiology[2] guidelines, in low-risk subjects screened for stage 1 hypertension, treatment should be deferred if their blood pressure levels decline to below 140/90 mm Hg. Those same guidelines acknowledge the importance of microalbuminuria as a cost-effective approach to the stratification of overall risk in hypertension. The present data indicate that subjects with stage 1 hypertension and glomerular hyperfiltration have a high risk of developing microalbuminuria irrespective of their blood pressure level and should thus be treated for hypertension even if their clinic blood pressure declines to within the normal range. Almost 50% of our subjects with hyperfiltration did not need antihypertensive treatment according to current guidelines. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, which are effective in reducing glomerular hypertension,[27] appear as drugs of choice for delaying the onset of microalbuminuria.[29] Aldosterone antagonists, at least at the level of conjecture, could also have a beneficial effect in these subjects as these drugs recently proved effective in reducing glomerular hyperfiltration.[30,31] Whether antihypertensive treatment is really beneficial for delaying renal damage in subjects with glomerular hyperfiltration should be tested in further studies.

MATERIALS AND METHODS

Study population

The study participants took part in the HARVEST, an observational study on the predictive value of 24-h ambulatory blood pressure for the development of sustained hypertension in young, 18–45 years old, never-treated patients with stage 1 hypertension.[32,33] The study is conducted in 17 Hypertension Units in Italy. In the HARVEST study, subjects with diastolic blood pressure between 90 and 99 mm Hg and/or systolic blood pressure between 140 and 159 mm Hg at baseline examination are enrolled. Baseline blood pressure was the mean of six readings obtained during two visits performed 2 weeks apart. Patients with diabetes mellitus, nephropathy, urinary tract infections, and other relevant cardiovascular risk factors are excluded.[32,33] Ten Hypertension Units opted to measure urinary albumin and 24-h blood pressure also during the follow-up, and thus the specific investigation on the time course of AER was carried out in 593 white subjects for whom AER and 24-h blood pressure measurements were available both at baseline and final assessments. Fifty-seven patients in whom creatinine clearance was unavailable and 34 patients with microalbuminuria at baseline were excluded leaving a final sample of 502 subjects for analysis. Mean ($\pm$s.d.) office blood pressure at entry in the 502 patients (364 men) considered in this report was $146.8 \pm 10.6/94.0 \pm 5.0$ mm Hg, their mean age was 34.0 ± 8.5 years, and their BMI was 25.5 ± 3.6 kg/m^2. In the present sample, blood pressure and age were slightly higher than in the rest of the cohort ($145.3 \pm 10.4/93.3 \pm 5.6$ and 33.1 ± 8.4 mm Hg, respectively; $P<0.001$ for all), whereas BMI and sex distribution were similar in the two subgroups. The study was approved by the HARVEST Ethics Committee, and written informed consent was given by the participants.

Procedures

The procedures followed were in accordance with institutional guidelines. The baseline data included a medical and family history and a questionnaire of current use of alcoholic beverages and tobacco and physical activity habits.[32] All subjects underwent physical examination, anthropometry, blood chemistry, urine analysis, office blood pressure and 24-h blood pressure measurements, electocardiogram, and 24-h urine collection for the measurement of AER. BMI was considered as an index of adiposity (weight divided by height squared). Creatinine clearance was computed from creatinine excretion in a 24-h urine collection and a single measurement of serum creatinine, and the data were normalized by body surface area. Twenty-four-hour blood pressure monitoring was performed with Takeda A&D TM2420 model 7 (A&D Co., Tokyo, Japan) or ICR Spacelabs 90207 monitor (Spacelabs Inc., Redmond, WA, USA). The arithmetic average of the edited pressure was used as the ambulatory measurement. At baseline, urine for AER measurement was collected during the 24-h recordings. AER measurement was repeated within 3 months in all subjects with AER >15 mg/24 h at first assessment, because an AER between 15 and 30 mg/24 h can be considered in the high-normal range.[34] Volumes were measured and urine specimens were frozen

(−20°C) and sent to the Coordinating Office at the University of Padova, where the AER level was measured by a commercially available radioimmunoassay kit (H ALB kit-double antibody, Sclavo SpA, Cinisello Balsamo, Italy). The lower limit of detection of this technique is an albumin concentration of 0.5 mg/l. The intra- and inter-assay variabilities of the method in our laboratory were 4.4 and 6%, respectively.[19] The values of AER in a healthy normotensive population of the same age range and gender ($n = 98$) was (geometric mean (interquartile range)) 5.7 (3.9–8.5) mg/24 h. Subjects were categorized as having normoalbuminuria (AER = 0–29 mg/24 h) or microalbuminuria (AER ⩾ 30 mg/24 h). All subjects with microalbuminuria at either first or repeat baseline assessment were excluded from the present analysis ($n = 34$). Other details on the methods used in the HARVEST study were reported elsewhere.[32,33,19]

Follow-up

After baseline examination, subjects were given general information about non-pharmacological measures by the HARVEST investigators. Follow-up visits were scheduled at 1, 2, 3, and 6 months and thereafter at 6-month intervals. After each visit, the clinical investigators transferred all relevant information to the coordinating center in Padova. Subjects were followed until they developed sustained hypertension requiring antihypertensive treatment according to the guidelines of the British Hypertension Society until 1999[35] and then of the 1999 World Health Organization/International Society of Hypertension[36] and 2003 European Society of Cardiology/European Society of Hypertension.[2] Ambulatory blood pressure monitoring and AER assessment were performed at the baseline, after 3, 5, 8, 10, 13, and 15 years, and/or just before starting antihypertensive treatment in the patients who developed sustained hypertension. The last available ambulatory blood pressure monitoring and AER data were used for the linear multivariable regression analysis and were defined as final ambulatory blood pressure and final AER, respectively. Other details on follow-up procedures were reported elsewhere.[32,33]

Data analysis

Data are presented as mean ± s.d., unless specified. AER was expressed as geometric mean (interquartile range) in mg/24 h. The distribution of clinical variables was compared across quintiles of creatinine clearance using the general linear model procedure and adjusting for age, sex, and BMI. The significance of differences in categorical variables was assessed with the χ^2 test. Differences in final AER and AER change over time were adjusted also for baseline AER and time to final assessment. The Tukey–Kramer multiple comparisons *post hoc* test was used for contrasts. Probability values for *post hoc* comparisons are provided in Figure 1. To explore the predictors of evolution of AER, multivariable linear regression analyses were performed with final AER as dependent variable and risk factors measured at baseline or their changes from baseline to study end as the independent variables. Multivariable time-dependent Cox proportional-hazards analyses were used to regress time until the development of microalbuminuria against hyperfiltration, including all variables found to be significant predictors of microalbuminuria at univariate analysis, using the previously published procedure.[19] Hyperfiltration, AER, and ambulatory systolic blood pressure were entered as time-dependent covariates. Both microalbuminuria detected in at least one of two consecutive measurements and microalbuminuria detected in two consecutive measurements were used as the outcome variable. The mean interval between the two measurements was 9.4 ± 5.7 months (range, 3–24 months). Dichotomous categories of risk factors were incorporated in Cox models, with the optimal category serving as the referent (Table 3). Age was divided into two categories above or below the median value in the group (35 years). Twenty-four-hour systolic blood pressure was categorized according to whether subjects had normal (< 130 mm Hg) or high (⩾ 130 mm Hg) ambulatory 24-h blood pressure.[37] A 5 mm Hg increase in blood pressure was arbitrarily used as a cutoff point for the follow-up change in 24-h systolic blood pressure. A two-tailed probability value < 0.05 was considered significant. For all statistical analyses, AER and creatinine clearance were logarithmically (base 10) transformed owing to their skewed distribution. All analyses were performed using Statistica version 6 (Stat Soft Inc., Tulsa, OK, USA). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

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Appendix

List of the HARVEST Centers that enrolled patients for this study: Cremona – Div. Medica: G Garavelli; Dolo – Div. Medica: F Pegoraro, S Laurini; Mirano – Cardiologia: D D'Este; Padova – Clinica Medica 4: F Dorigatti, V Zaetta, P Frezza, P Bratti, D Perkovic, C Guarnieri; Pordenone – Centro Cardioreumatologico: G Cignacco, G Zanata; Rovereto – Ala – Div. Medica: M Mattarei, T Biasion; Rovigo – Cardiologia: P Zonzin, A Bortolazzi; San Daniele del Friuli – Area di Emergenza: L Mos, S Martina, O Vriz; Trento – Div. Medica: G Devenuto, M Dal Follo; Vittorio Veneto – Div. Medica: M Santonastaso, E Cozzutti, R Garbelotto, A Mazzer. *Trial coordinator*: P Palatini.