Microalbuminuria reflects a generalized transvascular albumin leakiness in clinically healthy subjects

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1. In epidemiological studies microalbuminuria, i.e. slightly elevated urinary albumin excretion rate, predicts increased atherosclerotic vascular morbidity and mortality. This study aimed to test the hypothesis that microalbuminuria in clinically healthy subjects is associated with a systemic transvascular albumin leakiness. In animal experiments the outflux of albumin and lipids to the arterial wall are highly correlated, and both are elevated in atherosclerosis.
2. All participants were recruited at random from a population-based epidemiological study, where the upper decile of urinary albumin excretion rate was 6.6 μg/min. Twenty-seven patients with persistent microalbuminuria (urinary albumin excretion rate 6.6–150 μg/min), and 56 age- and sex-matched control subjects with persistent normoalbuminuria (UAER ⩽ 6.6 μg/min) were studied.
3. The systemic transvascular albumin leakage was measured as the fractional disappearance rate of ^{125}I-labelled albumin from the total plasma compartment in 1 h after intravenous injection.
4. The fractional disappearance rate of albumin from the plasma compartment was higher in the microalbuminuric than in the normoalbuminuric group [5.8 (95% confidence interval 5.3–6.2; $n=27$) versus 5.0 (4.6–5.5; $n=56$)%/h, $P<0.05$]. The positive correlation between urinary albumin excretion rate on continuous scale (logarithmically transformed) and the fractional disappearance rate of albumin from the plasma compartment [slope 0.4 (95% confidence interval 0.1–0.7; $n=83$), $r=0.29$, $P<0.005$] was independent of age, sex, smoking status, blood pressure, body size, plasma volume, plasma albumin concentration and concentrations of blood glucose, serum insulin and serum lipids.
5. In conclusion, microalbuminuria is an independent marker of systemic transvascular albumin leakiness in clinically healthy subjects. This finding may partly explain the increased atherosclerotic vascular morbidity and mortality in microalbuminuric subjects. It is suggested that the observed transvascular leakiness, in addition, may cause increased lipid insudation to the arterial walls.

INTRODUCTION

A slightly elevated urinary albumin excretion rate (UAER), termed microalbuminuria, has been proposed as a risk factor for atherosclerotic vascular disease. Originally, Yudkin et al. [1] observed highly increased vascular morbidity and mortality among individuals with microalbuminuria. These findings were later partly confirmed by Damsgaard et al. [2, 3]. Subsequent cross-sectional studies revealed weak but significant associations between microalbuminuria and conventional atherogenic risk factors such as increased blood pressure [4–11], dyslipidaemia [4, 6, 7, 9–11] and hyperinsulinaemia [4, 7, 10]. However, a convincing explanation of the findings reported from the above-mentioned prospective studies is still missing.

One of the earliest events in atherogenesis is a universally increased transvascular leakage of different macromolecules [12]. These early alterations may also affect the glomerular vasculature, provoking an increased urinary albumin excretion. Such an association would offer an explanation for the link between microalbuminuria and atherosclerosis.

It is well established that microalbuminuria in patients with insulin-dependent diabetes mellitus is indicative of an increased generalized transvascular leakage of albumin [13, 14] along with a state of endothelial dysfunction [15, 16]. Administration of dietary cod-liver oil, which may prevent atherosclerosis, partially normalizes the transvascular leakage of albumin in these patients [17]. Furthermore, in insulin-dependent [18] as well as in non-insulin-dependent diabetic subjects [19, 20] microalbuminuria predicts atherosclerotic vascular disease. It is reasonable to deduce that this association is con-

Key words: atherosclerosis, microalbuminuria, systemic transvascular albumin leakage, urinary albumin excretion.
Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; J_{alb}, outflux of albumin from the plasma compartment; IVM_{alb}, intravascular mass of albumin; PV, plasma volume; TER_{alb}, fractional disappearance rate of albumin; UAER, urinary albumin excretion rate.
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ferred through a generalized transvascular leakiness of macromolecules. It seems obvious to put forward the same theory in healthy individuals.

The aim of the present study was to test the hypothesis that microalbuminuria is associated with a generalized increased transvascular leakage of albumin in clinically healthy subjects. Classification of the subjects as microalbuminuric or normoalbuminuric was based upon three urine collections. The transvascular leakage of albumin was measured as the fractional disappearance rate of albumin (TER_{alb}) from the total plasma compartment.

METHODS

Subjects

All participants were recruited from The Copenhagen City Heart Study, which is a population-based longitudinal study of atherosclerotic vascular disease and its known and potential risk factors [21, 22]. Eighty-eight subjects were enrolled, 28 with microalbuminuria (6.6 μg/min) and 60 age- and sex-matched controls with normoalbuminuria (UAER $\leq$ 6.6 μg/min) as measured in overnight-collected urine samples by an ELISA method [23]. All were clinically healthy Caucasians aged 40–65 years. The sampling procedure and the study design are described in detail elsewhere [11]. The participants gave informed consent, and the study was in accordance with the Helsinki II Declaration and was approved by the regional ethics committee.

Measurement of transvascular albumin leakage (TER_{alb})

The participants met at 08.00 hours after a 10-h fast and tobacco abstinence. All were placed in the recumbent position, and a 17G Teflon cannula was inserted in an antecubital vein in both arms – one for blood sampling and the other for injection. After 1 h at rest TER_{alb} was measured as previously described by Parving and Gyntelberg [24]: 74 kBq (2 μCi) of ^{125}I-labelled human serum albumin (Code IFE-IT23S, Kjeller, Oslo, Norway) containing less than 1% free ^{125}I was injected [specific radioactivity 740 kBq/10 ml (20 μCi/10 ml)]. Venous blood samples of 10 ml were drawn without stasis into heparinized tubes before and 10, 15, 20, 30, 40, 50, 55 and 60 min after injection. After centrifugation at 1500 *g* for 10 min, plasma radioactivity was counted in duplicate samples of 2 ml in a model 5005 Cobra Auto-Gamma Counting System (Packard Instruments, IL, U.S.A.), (minimal total c.p.m. above background 20000, background value 300 c.p.m.). The mean c.p.m. at each time point was corrected for total plasma protein concentration (Refractometer TS-B, American Optical Company, Keene, NH, U.S.A., coefficient of variation 0.5%), and plotted against time after logarithmic transformation. TER_{alb} was then calculated on the basis of the slope of the best line fitted by the least-squares method, assuming that the radioactivity declined monoexponentially with time. Only measurements with a linear correlation coefficient of at least 80% and a standard error of TER_{alb} not exceeding 1.5%/h were accepted. Otherwise, one outlier was allowed to be rejected in order to obtain the highest possible correlation coefficient above 80% and the lowest possible standard error of TER_{alb} under 1.5%/h. This rejection procedure was performed in 13 subjects – four in the microalbuminuric group and nine in the normoalbuminuric group. Five subjects, one in the microalbuminuric group and four in the normoalbuminuric group, were excluded from the study as rejection of one outlier did not enable the criteria (correlation coefficient $\geq$ 80% and standard error of $TER_{alb} \leq 1.5\%$) to be fulfilled. Plasma volume (PV) was calculated from the total amount of injected radioactivity divided by the plasma radioactivity at time zero as derived from the intercept of the fitted line. The obtained value was corrected for body surface area. Plasma albumin concentration was measured by ELISA [23]. Intravascular mass of albumin (IVM_{alb}) was calculated as PV times plasma albumin concentration. Outflux of albumin (J_{alb}) was calculated as TER_{alb} times IVM_{alb}.

Other measurements

Blood pressure was measured four times (twice in each arm) after at least 2 h at rest, and the average was recorded. Hawksley's random zero sphygmomanometer (West Sussex, U.K.) and an appropriate-sized cuff were used. Height and weight were measured without shoes and heavy clothing. Body mass index was calculated as weight/height^2 (kg/m^2), and body surface area by the formula $0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}$ (m^2). Serum total cholesterol, high-density lipoprotein (HDL)-cholesterol and triacylglycerol concentrations were measured by enzymatic colorimetric methods (CHOL CHOD-PAP, HDL-CHOLESTEROL PRECIPITANT containing phosphotungstic acid and magnesium chloride and Triglycerides GPO-PAP respectively; Peridochrom, Boehringer-Mannheim, Mannheim, Germany). Blood glucose concentration was also measured by an enzymatic colorimetric method (Granutest; Diagnostica, Merck), and serum insulin concentration was measured by an ELISA method. Furthermore, plasma sodium and potassium concentrations (flame photometry), plasma creatinine concentration (colorimetric method of Jaffé) and blood haemoglobin concentration, leucocyte count, haematocrit and erythrocyte sedimentation rate were measured. Smoking habits were recorded and categorized as never, previous or current smoking.

Statistics

Data on a continuous scale are given in means with 95% confidence intervals (CIs) when normally

Table 1. Basic clinical and biochemical characteristics of the microalbuminuric and the normoalbuminuric group. Values on a continuous scale are means (95% CI), except for serum triacylglycerol and serum insulin, which are geometric means (95% CI), and for UAER, which are medians (ranges). Values for smoking status are fractions (95% CI). UAER, urinary albumin excretion rate. *$P<0.05$.

	Normoalbuminuria	Microalbuminuria
Female/male (number)	25/31	9/18
Age (years)	55 (53–57)	55 (52–58)
Body mass index (kg/m²)	24.5 (23.6–25.3)	25.5 (24.0–26.9)
Body surface area (m²)	1.84 (1.79–1.88)	1.89 (1.81–1.97)
Systolic blood pressure (mmHg)	119 (116–123)	127 (122–132)*
Diastolic blood pressure (mmHg)	69 (67–71)	74 (71–78)*
Serum total cholesterol (mmol/l)	5.9 (5.7–6.1)	5.9 (5.5–6.4)
Serum HDL-cholesterol (mmol/l)	1.45 (1.34–1.57)	1.26 (1.08–1.43)
Serum triacylglycerol (mmol/l)	1.1 (1.0–1.2)	1.1 (0.9–1.4)
Blood glucose (mmol/l)	4.9 (4.7–5.0)	4.9 (4.7–5.1)
Serum insulin (pmol/l)	25 (22–28)	27 (23–33)
Smoking status (%)		
Never	20 (10–30)	19 (4–34)
Previous	20 (10–30)	19 (4–34)
Current	60 (47–73)	62 (44–80)
UAER (μg/min)	2.2 (0.7–6.3)	9.9 (6.7–107.3)

distributed, and in geometric means with 95% CI when non-normally distributed, except for UAER, which is shown in median and range. Categoric data are given in fractions with 95% CI. Tests for differences were performed by Student's unpaired *t*-test. Simple and multiple linear regression analyses with backward elimination were performed with TER_{alb} as the dependent variable. Slopes of regression lines, β, with 95% CI, and correlation coefficients, r, are given. Non-normally distributed variables were logarithmically transformed before the analyses in order to approach the normal distribution. *P*-values less than 0.05 (two-tailed) were considered of statistical significance. The analyses were run on the personal computer statistics package SPSS for Windows version 6.0.

RESULTS

The basic clinical and biochemical characteristics of the two groups studied are given in Table 1. Blood haemoglobin concentration, leucocyte count, haematocrit, erythrocyte sedimentation rate and serum concentrations of sodium, potassium and creatinine were all similar in the two groups (data not shown).

TER_{alb} was higher in the microalbuminuric group than in the normoalbuminuric group [5.8 (95% CI 5.3–6.2; $n=27$) versus 5.0 (4.6–5.5; $n=56$)%/h, $P<0.05$] (Table 2). PV, plasma albumin concentration and IVM_{alb} were all similar in the two groups, implying that J_{alb} was elevated in the microalbuminuric in comparison with the normoalbuminuric group [6.9 (95% CI 6.1–7.6; $n=27$) versus 5.9 (5.4–6.3; $n=56$) g/(h × 1.73 m²), $P<0.05$] (Table 2).

Table 2. Fractional disappearance rate of albumin (TER_{alb}), plasma volume (PV), plasma albumin concentration, intravascular mass of albumin (IVM_{alb}) and outflux of albumin (J_{alb}) in the microalbuminuric ($n=27$) and the normoalbuminuric ($n=56$) group. Values are means (95% CI). *$P<0.05$.

	Normoalbuminuria	Microalbuminuria
TER_{alb} (%/h)	5.0 (4.6–5.5)	5.8 (5.3–6.2)*
PV (l/1.73 m²)	2.78 (2.67–2.88)	2.82 (2.71–2.94)
Plasma albumin (g/l)	42.3 (41.3–43.2)	42.0 (40.8–43.2)
IVM_{alb} (g/1.73 m²)	118 (112–124)	118 (113–124)
J_{alb} [g/(h × 1.73 m²)]	5.9 (5.4–6.3)	6.9 (6.1–7.6)*

When considering UAER on a continuous scale, $\log_e$ UAER was significantly associated with TER_{alb} [$\beta=0.4$ (95% CI, 0.1–0.7; $n=83$), $r=0.25$, $P<0.01$]. The strength of this association was even greater when adjusted for the effects of age, sex, tobacco smoking, blood pressure, body mass index and surface area, plasma volume, plasma albumin concentration and concentrations of blood glucose, serum insulin and serum lipids [$\beta=0.4$ (0.1–0.7; $n=83$), $r=0.29$, $P<0.005$]. Moreover, current smoking [$\beta=0.8$ (0.2–1.5; $n=83$), $r=0.28$, $P<0.01$] and $\log_e$ serum triacylglycerol [$\beta=0.8$ (0.1–1.5; $n=83$), $r=0.24$, $P<0.05$] were both independently associated with TER_{alb}.

DISCUSSION

This study showed that in clinically healthy subjects the generalized transvascular albumin leakage (TER_{alb}) is positively correlated with the urinary albumin excretion rate (UAER). In a representative group of clinically healthy subjects with microalbuminuria, both TER_{alb} and J_{alb} were elevated by about 15% as compared with a similar group with normoalbuminuria. This significant difference in TER_{alb} could be demonstrated even though the difference in median UAER between the two groups was only 7.7 μg/min, and in spite of the considerable intra-individual variation in both UAER (36%) [25] and TER_{alb} (14%) [26]. Since an increased transvascular leakage of macromolecules is seen in the earliest stages of the atherogenesis [12], this finding may contribute to explain the increased vascular morbidity and mortality observed in microalbuminuric individuals [1–3].

The physiological mechanisms and assumptions upon which measurement of TER_{alb} is based, and the interpretation of the quantity, have been thoroughly reviewed by Parving [26]. Clearly, the mechanism of the elevated TER_{alb} in clinically healthy subjects with microalbuminuria cannot be deduced from the present results. However, in animal models the outflux of albumin and lipids in arteries are highly correlated [27], and both are elevated in atherosclerosis [28]. Moreover, in humans with severe clinical atherosclerosis, TER_{alb} is higher than in healthy subjects (J. S. Jensen,

unpublished data). Although the main part of the transvascular albumin leakage probably takes place in the capillaries, investigations in animals suggest a similar transfer process of plasma macromolecules across the endothelial layer of capillaries and arteries [29].

In the present study TER_{alb} was positively correlated with UAER independently of age, sex, smoking status, blood pressure, body size, plasma volume, plasma albumin concentration and concentrations of blood glucose, serum insulin and serum lipids. Current tobacco smoking and serum triacylglycerol concentration also correlated positively with TER_{alb} independently of other variables measured. Both elevated UAER [30] and TER_{alb} [31] are described among smokers. Nevertheless, adjustment for smoking status in the multiple regression analysis did not abolish the positive correlation between UAER and TER_{alb}. This observation is unique, and it is tempting to hypothesize that smokers – as well as non-smokers – at least in part are protected against atherosclerosis if their endothelial barrier is tight, i.e. if they are normoalbuminuric. Both systolic and diastolic blood pressure were slightly elevated in the microalbuminuric group. It is well established that TER_{alb} [24] and UAER [32] are elevated in subjects with pronounced but not moderate [14, 32] arterial hypertension. Since blood pressure did not contribute significantly to the increase in TER_{alb} in the present non-hypertensive study population, it seems rather unlikely that the slight blood pressure elevation could account for the enhancement of TER_{alb} in the microalbuminuric group. Nor is it likely that the elevated TER_{alb} could be ascribed to a higher total endothelial surface area since the plasma volume was similar in the two groups. Lastly, it should be mentioned that the urinary loss of albumin was negligible as compared with the overall outflux of albumin from the total plasma compartment. Thus, in the microalbuminuric group UAER constituted only about 0.01% of J_{alb}.

In this study microalbuminuria was defined as a UAER between the upper decile in the background population (6.6 μg/min) and 150 μg/min [11, 33]. The reason for this arbitrary division of the population is that a substantial proportion, e.g. 10%, must exhibit microalbuminuria if it is to be considered as a clinically relevant and sensitive atherosclerotic risk factor in the future.

From the present study it is concluded that the transvascular leakage of albumin is increased in clinically healthy individuals with microalbuminuria irrespective of blood pressure and smoking status. This finding provides circumstantial evidence for a causal relationship between microalbuminuria and atherosclerosis. It suggests, in connection with the increased vascular morbidity and mortality observed in microalbuminuric subjects [1–3] that microalbuminuria reflects a generalized transvascular leakiness. Further studies are required to clarify the nature of such leakiness, and to what extent it is reversible. Moreover, studies should be carried out in order to elucidate whether the abnormality is genetically determined or acquired secondarily to the presence of established atherogenic risk factors or other factors.

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