Increased Capillary Filtration of Albumin in Diabetic Patients—Relation With Gender, Hypertension, Microangiopathy, and Neuropathy

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The aim of this study was to investigate the factors associated with an increase in capillary filtration of albumin (CFA) in a large series of diabetic patients and its relationship with gender, hypertension, microangiopathy, and neuropathy. One hundred sixty-three unselected diabetic patients, 74 type I and 89 type II, were included. An isotopic test of CFA was performed with 99m technetium–labeled albumin injected intravenously. Radioactivity was counted externally at the forearm with a gamma camera before, during, and after venous compression. After removal of venous compression, interstitial albumin retention (AR) was calculated and the radioactivity disappearance curve was analyzed by the Fast Fourier transform, which provides an index for lymphatic uptake of interstitial albumin (low-frequency to high-frequency amplitude peak ratio [LF/HF]). An increase in AR and LF/HF was found in 65 (39.9%) and 117 (71.7%) patients, respectively. Increased AR was significantly more frequent in women than in men ($P = .018$) and in patients without microangiopathic complications than in those with them ($P = .028$). In men, it was significantly more frequent in type I versus type II diabetic patients ($P = .004$), and AR was significantly higher in patients with peripheral neuropathy than in those without ($P = .004$). The LF/HF was also significantly higher in men with peripheral neuropathy ($P = .045$). In women, the AR level correlated negatively with postprandial glycemia ($P = .006$) and was significantly higher in patients without microangiopathic complications ($P = .003$). These data suggest the role of hormonal factors, both sex steroids and insulin, and the major role of peripheral neuropathy in the increase in CFA. The highly prevalent increase in CFA before the onset of microangiopathic complications is consistent with the presence of a functional microcirculatory disorder that might contribute to the occurrence of microangiopathic lesions.

AN INCREASE IN CAPILLARY permeability to large molecules has been reported in several series of diabetic patients. In most studies, the investigation consisted of measuring the transcapillary escape rate of radiolabeled albumin (TER-Alb). This method reflects indirectly the disappearance of albumin from the circulation. However, the accelerated disappearance of circulating albumin can be related not only to capillary hyperfiltration but also to an excessive sequestration of albumin in the interstitial space or the initial lymphatic vessels. For several years, we have been using a more direct noninvasive method our group developed to investigate capillary filtration of albumin (CFA). This method, derived from the Landis method, uses venous compression,[1] which can increase capillary pressure and transcapillary albumin leakage. This method also allows investigations of lymphatic washout of interstitial albumin.[1] It is thus possible to identify an increase in CFA and lymphatic pump failure. In a previous study using this method, we found a highly prevalent abnormal CFA in an unselected diabetic population, and our first results suggested the independent roles of hypertension, microangiopathy, and duration of diabetes. In a small series of diabetic patients without microangiopathy, we also found a significant association between an increase in CFA and neuropathy.[2]

Two pathogenetic mechanisms may be proposed to explain the increase in CFA: alterations either in the endothelial barrier or in hemodynamic factors.[3] The first hypothesis involves the thickening of the capillary basal membrane together with chemical changes in the membrane and the endothelium.[4-6] In the hemodynamic theory, blood pressure[7] and blood flow[8,9] play an important role. However, the results suggesting a link between an increase in TER-Alb and hypertension are controversial.[10,11] Recently, TER-Alb has been found to be higher in normotensive or moderately hypertensive type I diabetic patients with incipient nephropathy versus those with normal urinary albumin excretion,[11] and in normotensive type II diabetic patients with incipient nephropathy versus the normoalbuminuric patients.[12] This suggests that the increase in CFA might be a marker of general vascular dysfunction.[13] However, it is noteworthy that in none of these studies has the number of diabetic patients (either microalbuminuric or hypertensive) with an abnormal TER-Alb been clearly determined, and there has always been a considerable overlap of the values in the different patient groups and the control group. Moreover, to our knowledge, none of the studies that measured TER-Alb have looked for a link between diabetic neuropathy and the increase in CFA. Some experimental data also suggest the role of sex steroids in vascular permeability in diabetic animals and of insulin in the CFA increase via an elevation in blood flow in healthy subjects.[14-16] Therefore, the aim of the present study was to investigate the factors associated with an increase in CFA in a large series of diabetic patients and its relationship with gender, type of diabetes, hypertension, nephropathy, retinopathy, and neuropathy.

SUBJECTS AND METHODS

Patients

One hundred sixty-three unselected diabetic patients, 74 type I (insulin-dependent) and 89 type II (non–insulin-dependent), were investigated. They were hospitalized in our department for poor glycemic control. There were 67 women and 96 men of similar age (mean ± SEM, 51.7 ± 1.7 and 49.4 ± 1.4 years, respectively). The standard clinical and biological parameters are shown in Table 1. None of the patients had edema, cardiac failure, or liver dysfunction. All were free of cyclic edema,[17] hypothyroidism,[18] and acromegaly, ie, diseases associated with an increase in CFA. They had minimal glycosuria and no ketonuria at the time of the test. Sixty-five were hypertensive, with

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Table 1. Standard Clinical and Biological Parameters in the Diabetic Patients

Parameter	All Patients	Type I	Type II
Age (yr)	50.2 ± 1.1	46.0 ± 1.8	54.5 ± 1.2
Duration of diabetes (yr)	11.1 ± 0.6	13.8 ± 1.1	8.8 ± 0.6
Body mass index (kg/m^2)	25.9 ± 0.6	23.9 ± 0.7	28.0 ± 0.9
Fasting blood glucose (mmol/L)	8.8 ± 0.3	8.7 ± 0.5	8.9 ± 0.4
Postprandial blood glucose (mmol/L)	10.6 ± 0.4	11.2 ± 0.6	10.2 ± 0.5
Fructosamine (mmol/L)	2.57 ± 0.08	2.71 ± 0.10	2.46 ± 0.11
Hemoglobin A_{1c} (%)	8.34 ± 0.22	8.74 ± 0.30	8.02 ± 0.31
Cholesterol (mmol/L)	5.50 ± 0.10	5.27 ± 0.15	5.65 ± 0.13
Triglycerides (mmol/L)	1.67 ± 0.08	1.42 ± 0.11	1.87 ± 0.11
Creatininemia (μmol/L)	85.6 ± 2.1	91.1 ± 3.4	80.9 ± 2.4
Urinary albumin excretion rate (mg/24 h)*	18.5 ± 4.0	15.7 ± 4.7	19.6 ± 5.3

*n = 62.

resting blood pressure measured by mercury sphygmomanometer greater than 160/90 mm Hg. They were treated at the time of the investigation by β-blockers, diuretics, or antihypertensive agents. None of the patients were taking any medication that might affect microcirculation. Sixty-four had clinical signs of macroangiopathy (lower-limb arterial disease or coronary heart disease). The urinary albumin excretion rate was measured in 62 patients without macroproteinuria. Thus, 74 patients had signs of microangiopathy as defined by retinopathy (n = 47, assessed on fundus ophthalmoscopy and fluorescein angiography) and/or proteinuria greater than 0.15 g/24 h (n = 30) and/or a urinary albumin excretion rate greater than 30 mg/24 h (n = 15), and 35 patients were free of microangiopathic complications. The other 54 patients were free of retinopathy and proteinuria but were not classified according to the presence or absence of microangiopathy because the albumin excretion rate was not measured. Ninety-nine had peripheral neuropathy, the diagnosis of which was made when two or more of the following four evaluations were abnormal[19]: symptoms, conduction studies showing abnormalities in at least two different limb nerves, ankle tendon reflexes, and vibration perception threshold.

Isotopic Test of CFA

The isotopic CFA test was performed as previously described.[1,20,21] Briefly, it was performed with the subject at rest and seated with the arms kept horizontal. It consisted of injecting 1 mL human serum albumin labeled with 99m technetium (100 MBq/mL Kit TCK-2; Sorin Biomedica, Saluggia, Italy) into an antecubital vein and measuring the radioactivity externally at the forearm with a gamma camera (Elscint, Haifa, Israel). Ten minutes after the intravenous injection, venous compression (80 mm Hg) was exerted on one arm, inducing vascular stasis and a resulting increase in the radioactivity curve. Twelve minutes later, venous compression was removed and radioactivity decreased, generally reaching the basal level in 1 to 3 minutes in normal subjects. Labeled albumin retention (AR) was evaluated 10 minutes after removal of venous compression by calculating the percentage, [(residual radioactivity at 10 minutes − basal radioactivity)/(maximal radioactivity − basal radioactivity)] × 100. Among 80 healthy volunteers previously studied, AR was 0% in 76 subjects and less than 6% in the other four. AR was thus considered to be increased when it was at least 8%.

The last part of the radioactivity disappearance curve, recorded after removal of venous compression, was also analyzed by the Fast Fourier transform. The time-function curve A(t) was thus transformed into discrete series: a phase function and a frequency function B(f). Only B(f) was considered here,

$$B(f) = \int_{-\infty}^{+\infty} A(t) \times \exp(-j \times 2\pi \times ft) \times dt,$$

with ft being the Fourier transform. Four peaks of different frequencies with amplitudes higher than the other harmonics were thus identified. The ratio of the amplitude of the peaks of low frequency (LF) and high frequency (HF) was calculated (LF/HF). In 30 healthy volunteers, LF/HF was 0.42% ± 0.05% and never above 1%. A value of 1% or greater was thus considered abnormal. In the present series, this parameter was calculated in 125 cases.

The LF/HF is an index of lymphatic uptake of interstitial albumin and is not believed to reflect a phenomenon occurring in blood circulation. Indeed, the same test performed with indium 111–labeled albumin and 99m technetium–labeled red blood cells has shown that LF/HF is always normal with erythrocytes even when it is 1% or greater with albumin.[22]

The reproducibility of the method was tested by performing two measurements on 10 controls with an interval not exceeding 2 months between the tests. Both AR and LF/HF for the two tests correlated fairly ($P < .001$). Moreover, the stability of both indexes was verified at a 30- to 42-day interval in 10 diabetic patients involved in a randomized trial and taking a placebo treatment.[21] For AR, the mean coefficient of variation was 5.97% and the correlation coefficient was .872 ($P < .001$) between the two consecutive measurements. For LF/HF, the mean coefficient of variation was 6.57% and the correlation coefficient was .957 ($P < .0001$).

Biological Measurements

Metabolic control was assessed by blood glucose assays at 8 AM (fasting) and 2 PM (postprandial), hemoglobin A_{1c} measurement (on microcolumn chromatography: normal, 4% to 5.8%), and plasma fructosamine assay (Tetrazolium blue; Roche Diagnostic, Neuilly-sur-Seine, France). Serum total cholesterol, triglycerides, and uric acid and serum and urine creatinine levels were also measured. The urinary albumin excretion rate was determined from a 24-hour urine specimen using a laser immunonephelometric method as previously described.[23]

Statistical Analyses

Results are expressed as the mean ± SEM. The analyses included comparisons by the unpaired Student's *t* test, correlations according to a linear regression model, χ^2 test, and multivariate analysis according to a stepwise regression model.

RESULTS

AR was increased (≥8%) in 65 cases (39.9%). LF/HF was increased (≥1%) in 117 (71.7%).

An increase in AR was significantly more frequent in women (34 of 67) than in men (31 of 96, $\chi^2 = 5.60$, $P = .018$). The mean age was similar in women with (n = 34) and without (n = 33) increased AR (54.1 ± 2.3 *v* 49.2 ± 2.5 years). There was no significant correlation between the AR level and the age, duration of diabetes, blood pressure, body mass index, parameters of glycemic control, serum cholesterol and triglycerides, plasma creatinine, creatinine clearance, and urinary albumin excretion rate. The prevalence of an increase in AR was not significantly different in premenopausal and postmenopausal

women, type I and type II diabetic patients (32 of 74 *v* 33 of 89), and hypertensive and normotensive patients (30 of 65 *v* 35 of 98), nor was there any significant difference between patients with or without retinopathy or nephropathy. In patients with microangiopathy defined by the presence of retinopathy and/or proteinuria greater than 0.15 g/24 h and/or urinary albumin excretion greater than 30 mg/24 h, the prevalence of an increase in AR was significantly lower than in those without microangiopathy (32 of 74 *v* 23 of 35, $\chi^2 = 4.801$, $P = .028$). When gender and microangiopathy were entered into the model as independent variables, the multivariate analysis showed that increased AR was significantly associated with both factors ($P = .0002$).

Among the 96 men, AR was significantly more often increased in type I diabetic patients (23 of 51) than in type II diabetic patients (eight of 45, $\chi^2 = 8.161$, $P = .004$). As the mean value, AR was significantly higher in type I versus type II diabetic patients and in men with peripheral neuropathy versus those without (Table 2). When the type of diabetes and peripheral neuropathy were entered into the model as independent variables, the multivariate analysis showed that the AR level correlated significantly with both factors ($F = 6.319$, $P = .003$) with an adjusted R^2 of .101. The LF/HF was also significantly higher in men with peripheral neuropathy than in those without (1.85% ± 0.18% *v* 1.30% ± 0.17%, $P = .045$).

In women, the AR level correlated negatively with postprandial glycemia ($r = -.375$, $P = .006$) and was significantly higher in patients without microangiopathy than in those with it (n = 16, 15.31% ± 1.99% *v* n = 29, 7.62% ± 1.40%, $P = .003$). Both parameters were significantly associated with AR in the multivariate analysis ($F = 10.199$, $P = .00001$) with an adjusted R^2 of .453.

DISCUSSION

The present study aimed to investigate the determinants of CFA in a large series of unselected diabetic patients. It confirms our previous results showing the high prevalence of an alteration in CFA consisting of an increase in AR above a threshold strictly defined in a large series of healthy control subjects.

In the entire present series of diabetic patients, AR was only associated with gender, being significantly more frequently higher in women than in men. This difference does not seem to result from cyclic or orthostatic edema syndromes, since none of the women had such complaints. The mean age of the women was 51.7 years and was similar in patients with and without an increase in AR. These data are consistent with the influence of hormonal factors and may be compared with the higher frequency of retinopathy and nephropathy in diabetic patients after puberty. It is noteworthy that in male rats castration 10 days after streptozotocin-induced diabetes prevents the increase in CFA and also the increase in tissue sorbitol and decrease in tissue myoinositol content, which suggests a link between sex steroids and CFA and aldosereductase activity.[24]

Table 2. AR According to the Type of Diabetes and Peripheral Neuropathy in Men

Group	No. of Subjects	AR (%)	*P*
Type I diabetes	51	7.08 ± 1.26	.017
Type II diabetes	45	3.18 ± 1.00	
Peripheral neuropathy	57	7.05 ± 1.23	.004
No peripheral neuropathy	39	2.61 ± 0.85	

In normotensive diabetic patients, it has been shown that TER-Alb decreased significantly when glycemic control improved.[25] An in vitro demonstration of the effect of a high glucose concentration on transendothelial permeability to albumin has also been reported.[26] In this cross-sectional study, we did not find any correlation between the results of the CFA test and the parameters of glycemic control in the entire series, and even in women, AR correlated negatively with postprandial glycemia. However, in men, AR was significantly higher in type I diabetic patients. Likewise, an increase in microvascular fluid permeability, assessed by a plethysmographic system, has been found in young type I but not in type II diabetic patients.[27] The effect of insulin on CFA has been shown in healthy subjects during an acute euglycemic clamp test.[14] Insulin has also been shown to induce an increase in the formation of new capillary endothelial cells in rats.[28] The long-term effect of insulin on CFA remains to be demonstrated in diabetic patients.

Data regarding the relationship between CFA and hypertension are contradictory in the literature. In nondiabetic patients with essential hypertension, TER-Alb has been found to be increased and to correlate with blood pressure.[29] In insulin-dependent diabetic patients with nephropathy, the acute blood pressure decrease by intravenous clonidine can significantly reduce TER-Alb.[7] The independent influence of hypertension on transcapillary albumin leakage in diabetic patients has been suggested.[1,10] However, recently, TER-Alb has been found to be increased only in hypertensive type I diabetic patients with incipient nephropathy and not in hypertensive type I diabetic patients with a normal urinary albumin excretion rate.[11] In the present study, we did not find any influence of hypertension on CFA in the entire series or in patients with microangiopathic complications. However, a beneficial effect of antihypertensive medications on the CFA test may not be excluded. None of the patients were taking calcium-channel blockers, which have been shown to increase CFA.[30]

An increase in TER-Alb has also been reported in normotensive diabetic patients with microalbuminuria.[11] We have not found similar results in the present study. On the contrary, an increase in AR was found significantly more often in patients without microangiopathic complications than in those with them (66% *v* 43%). The difference was also significant in the women considered separately. An increase in microvascular fluid permeability has also been reported in type I diabetic patients with minimal evidence of microangiopathy.[27] These data are in agreement with a functional alteration of CFA that is more frequent before the onset of microangiopathic lesions and also with a potential pathophysiological role of this functional disorder in the occurrence of microvascular lesions. The higher value for AR in men with peripheral neuropathy than in those without is consistent with the aggravating role of neuropathy in microvascular functional disorders. We can hypothesize that neuropathy may increase capillary blood flow[31,32] and contribute to a loss of capillary blood flow autoregulation[33] via deficient sympathetic control of peripheral vasoconstriction, as we have recently shown in diabetic patients.[34]

The lymphatic system is responsible for the nearly complete

return of the plasma protein pool per day to the intravascular space, and physiologically, it has the capacity to strongly increase its own flow.[35] In pathological disorders with increased TER-Alb, a positive correlation has been found between the plasma albumin concentration and TER-Alb, which supports the important role of a secondary increase in lymphatic flow.[36] The wall of lymphatic vessels contains smooth muscle cells, the contraction of which is under neural control.[37] Neuropathy may induce a primary lymphatic pump failure and a resulting lymphatic defect of interstitial albumin uptake. Neuropathy may also contribute to saturating the lymphatic pump by increasing TER-Alb and thus increasing interstitial albumin stasis.[2] This phenomenon might be relevant, since an increase in LF/HF was a frequent abnormality (71.7%) and LF/HF was significantly higher in men with peripheral neuropathy than in those without.

In conclusion, this study on a large series of diabetic patients suggests the role of hormonal factors (sex steroids and insulin) for the first time in human diabetes and the major role of peripheral neuropathy in the increase of CFA. The highly prevalent increase of CFA in patients free of microangiopathic lesions and the possibility to reverse this disorder[21] suggest that the increase in CFA corresponds to a functional microcirculatory disorder. Peripheral neuropathy may have major consequences for CFA. The increase in CFA is likely to contribute and aggravate the development of severe microvascular complications. However, this point requires further investigation.

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