CLINICAL HEMORHEOLOGY, Vol. 9, pp. 351-359, 1989
0271-5198/89 $3.00 + .00 Printed in the USA.


FIFTH EUROPEAN CONFERENCE ON CLINICAL HEMORHEOLOGY

POSTER SESSION: DIABETES

# MICROALBUMINURIA IN DIABETICS : POSSIBLE INVOLVEMENT OF HEMORHEOLOGIC FACTORS IN BASELINE EXCRETION BUT NOT IN EXERCISE-INDUCED RISE

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(Accepted by Editor M.R. Boisseau)
(Received in final form by Executive Editorial Office 10.1.1989)

ABSTRACT

In diabetics, microalbuminuria reflects a multifactorial reversible glomerular dysfunction, announcing further development of overt nephropathy. This study aimes to determine whether microalbuminuria and its rise during a standardized exercise test are related to blood rheology. A cross-sectional study of 47 insulin dependent diabetics showed that impaired values of whole blood filterability (as found in 26 subjects) were associated with an increased resting microalbuminuria (21.755 $\pm$ 3.91 µg/min vs 8.125 $\pm$ 1.226, $p < 0.03$) whereas exercise induced rise in microalbuminuria did not differ between the two subgroups and showed no relationship with exercise-induced changes in filterability. Resting microabuminuria correlated with blood pressure only in the subgroup exhibiting reduced blood filterability ($r = 0.549$ ; $p < 0.01$). Preliminary results of an open study with pentoxifylline (800 mg/day during 3 months) suggest that this drug reduces resting microalbuminuria but not its exercise-induced increase. Those data might be consistent with the following working hypotheses : (a) hemorheologic disorders detectable with blood filterability measurement could impair glomerular microcirculation, increasing its sensitivity to blood pressure. Therefore, they could be an additional risk factor, as previously stated by Solerte. (b) microalbuminuria rise during exercise is not likely to be an artifact resulting from exercise-induced hemorheologic changes, but might be an improved index of abnormalities already existing at rest. (c) our findings seem to be consistent with previous reports suggesting a beneficial effect of pentoxifylline in this process. However, this latter concept requires further investigations.

Key words : Rheology, Erythrocyte deformability, Diabetes, Microalbuminuria, Pentoxifylline.

## INTRODUCTION

Microalbuminuria in diabetics is currently a subject of intensive research. The term «microalbuminuria» is used for qualifying an albumin excretion rate below values giving positive results with conventional test strips. In 1963, Keen and coworkers (1) described a radioimmunoassay technique for measuring microalbuminuria, and numerous investigators found that this parameter was frequently abnormal in diabetics. Viberti (2) suggested that the term «microalbuminuria» should qualify only the values of albumin excretion rates above the upper limit of normal individuals (whose albumin excretion rate was proposed to be called «normoalbuminuria»). The first results of longitudinal studies, in 1982 (3-5) indicated that microalbuminuria was a marker of increased risk of further nephropathy in diabetics. Mogensen (6) suggested that diabetic nephropathy was preceded by three stages of reversible functional disorders associated with a microalbuminuria : stage 1 (before onset of insulin treatment) ; stage 2 (in which albumin excretion rate was normal at rest but reached pathologic values during exercise or periods of poor diabetic equilibrium) ; stage 3 with a continuous microalbuminuria at rest.

The mechanism of these early stages of diabetic nephropathy remains uncompletely understood. Microalbuminuria has been shown to correlate with blood pressure and to be increased during periods of insufficient glycemic control. How does hyperglycemia «sensitize» the glomerulus of diabetics to the effects of blood pressure ? Among the various hypotheses which have been proposed , a hemorheologic theory of microalbuminuria has been developped. According to Simpson (7), impaired rheology of blood, in diabetics, could be responsible for raised intraglomerular pressure, resulting in exaggerated albumin urinary excretion.

Conflicting results have been published concerning this topic. A first study by Hill and coworkers (8) was unable to find any definite relationship between microalbuminuria and blood rheology in type I diabetic children. Those data, put together with the findings of Ditzel (9) concerning a lack of correlation between blood viscosity and glomerular hyperfiltration at the beginning of diabetic disease, suggested that blood rheology was not an important factor in the pathogenesis of early stages of diabetic nephropathy.

Nevertheless, recent papers by Solerte and coworkers are consistent with Simpson's theory: these investigators reported (a) that microalbuminuria was correlated to blood viscosity and negatively correlated to blood filterability (10-11) and (b) that pentoxifylline, a drug enhancing red cell deformability, reduced microalbuminuria (12-15). Therefore, the possible involvement of hemorheologic abnormalities in the pathophysiology of early renal dysfunction remains controversial.

On the other hand, if impaired blood fluidity increases microalbuminuria, it could be hypothesized that post exercise microalbuminuria, which is sometimes considered as an improved marker of early renal disease (16), results at least in part from exercise-induced hemorheologic distrurbances.

We investigated : (a) whether microalbuminuria is higher in patients with lowered blood fluidity ; (b) whether its rise after exercise is related to hemorheologic modifications resulting from muscular activity.

## MATERIALS AND METHODS

1. Cross-sectional study of 47 diabetics.

We have been studying 47 type 1 diabetic subjects by evaluating together microalbuminuria during an exercise test and filterability of whole blood and washed erythrocytes.

Patients (30 males, 17 females, age 18-62 yr, duration of disease 1 - 35 yr) were all routinely treated diabetics receiving 2 or 3 daily insulin injections. They had their normal breakfast and did not change their treatment on the day of the investigation. They underwent between 9 and 11 a.m. a 2 hr standardized test as previously described (17). Briefly, they remained recumbent during 60 min during which they drank 600 ml of water. At the onset of the following hour they performed a 20 min strenuous inframaximal exercise on cycloergometer. A triangular increase in workload (every 5 min) was used to rise heart rate up to 200/min minus the age. Heart rate was monitored on electrocardioscope. The final step was maintained 5 min. After exercise the patients remained recumbent until the end of the second hour. They urinated before starting the test and at the end of both the first and the second hour, so that two samples

of urine were collected, corresponding to resting and postexercise conditions.

2. Preliminary study of the effects of Pentoxifylline.

Patients (2 females, 9 males, age : 21-50 yr, duration of diabetes 9-29 yr) entered the study after informed consent. 3 had a nonproliferative background retinopathy with exsudates and microaneurysms. They received 800 mg of pentoxifylline every day during three months. An exercise test as described above was performed before this treatment and at the end of the third month. We carefully attempted to perform in each patient exercise tests as similar as possible, with the same workload steps.

3. Measurements.

Albumin excretion rate was determined by immunonephelometry on a Behring laser nephelometer (18). Glycated hemoglobins HbA1 were assayed with the kit «fast hemoglobins» (Eurobio). Blood and erythrocyte filterability were measured on 5 um Nuclepore sieves (kindly offered by Hoechst Pharmaceuticals). Sieve were reused after ultrasonic cleaning as previously described (18, 19). They were all from the batch No 54, P4 85.

Whole blood filterability was measured according to Reid (21) and expressed as a flow rate of red cells passing through the sieve under a negative pressure of 200 mm of water. Red cell filterability was determined under atmospheric pressure with the technique described by Weill and coworkers (22). Hematocrit (packed cell volume) was measured by microcentrifugation.

4. Statistics.

Values are given as mean ± SEM. Statistical comparisons were performed by nonparametric tests : Wilcoxon rank sum test for paired data and Mann-Whitney test for unpaired data. Correlations (linear regressions) were calculated by least square fitting. Statistical significance was defined as $p < 0.05$.

TABLE 1 — Comparison of diabetics with normal versus lowered blood filterability (BF). Values = mean ± SEM.

| | Group A Lowered BF (n = 26) | Group B normal BF (n = 24) | comparison |
|---|---|---|---|
| Age (yr) | 35.10 ± 2,30 | 32.24 ± 2.29 | n.s. |
| Duration of diabetes (yr) | 15.79 ± 1.39 | 12.32 ± 1.71 | n.s. |
| Blood pressure at rest (systolic) | 12.08 ± 0.32 | 11.70 ± 0.26 | n.s. |
| (mm Hg) (diastolic) | 7.16 ± 0.22 | 7.12 ± 0.17 | n.s. |
| HbA1 % | 9.46 ± 0.35 | 10.02 ± 0.37 | n.s. |
| Sex ratio (male/female) | 17/9 | 13/8 | n.s. |
| Resting microalbuminuria ( µg/min) | 21.76 ± 3.91 | 8.12 ± 1.23 | (*) |
| Exercise-induced microalbimuniria (µg/min) | 93.79 ± 25.25 | 39.09 ± 8.46 | n.s. |
| Blood pressure during exercice (systolic) | 6.83 ± 0.38 | 8.50 ± 0.68 | n.s. |
| (mm/Hg) (diastolic) | 17.06 ± 0.88 | 18.62 ± 0.97 | n.s. |

(*) $p < 0.03$ (Mann-Whitney test)

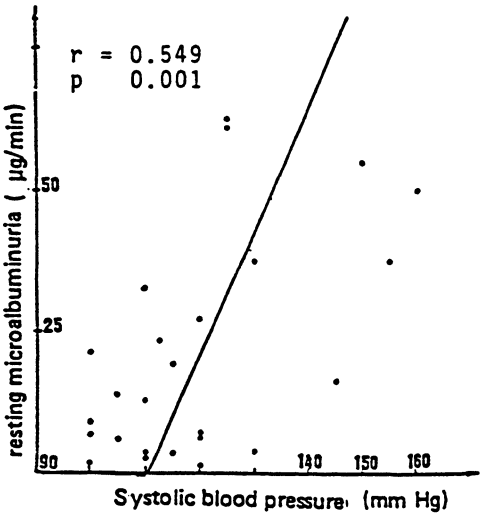


FIG. 1 – Correlation between resting microalbuminuria and blood pressure in group A ( $p < 0.01$).

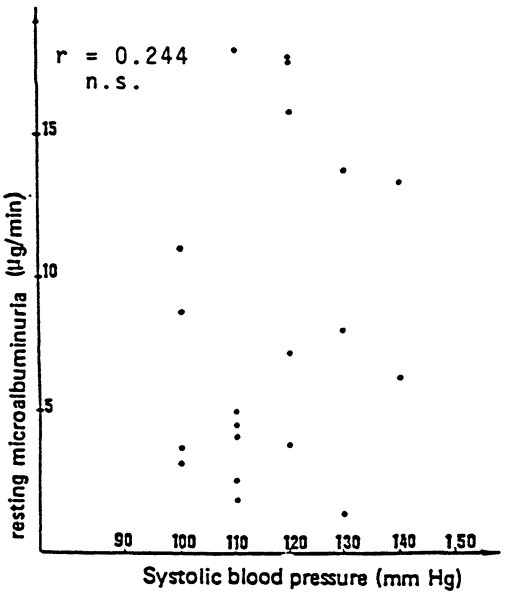


FIG. 2 – Correlation between resting microalbuminuria and blood pressure in group B (non significant)

## RESULTS

1. Cross-sectional study.

Control values of blood filterability for the same batch of sieves were measured in 20 nondiabetic healthy individuals. They were 1.334 ± 0.029 so that the lower limit of normality (mean ± 2 SD) was 1 ml/min. Blood filterability was lower than this value in 26 subjects. Albumin excretion rate was higher at rest ( $p < 0,03$ ) in this subgroup (table 1). There was no significant difference among the two groups with respect to exercise-induced rise in albumin excretion. Table 1 shows that the two groups were matched for blood pressure, diabetic equilibrium, duration of disease, sex ratio, and exercise-induced rise in blood pressure.

Linear regressions between blood pressure and resting microalbuminuria are plotted on fig. 1 and fig. 2 : a significant correlation can be detected only in the subgroup of patients with reduced blood filterability. In the other subgroup, there is only a nonsignificant tendency.

2. Effects of Pentoxifylline.

Preliminary results of our open trial with pentoxifylline (800 mg/day, during 3 months) are available for 11 subjects. As shown on fig. 4, resting microalbuminuria is reduced after treatment (14.98 ± 3.36 vs 28.35 ± 5.65 µg/min ; Wilcoxon rank sum test for paired data, $p < 0.025$) whereas postexercise values are not significantly modified after treatment (83.52 ± 20.83 vs 77.38 ± 12.05). Table 2 shows that pentoxifylline, during this trial, modifies neither HbA1 nor blood pressure. As expected, there is a (nonsignificant) tendency to increase blood filterability, which will probably reach significance when the number of patients will increase.

| | Before treatment | After treatment |
|---|---|---|
| HbA1 (%) | 10.03 ± 0.38 | 8.82 ± |
| Hematocrit (%) | 44.86 ± 0.90 | 40.54 ± 1.06 |
| Systolic blood pressure (mm Hg) | 13.18 ± 0.28 | 12.91 ± 0.50 |
| Diastolic blood pressure (mm Hg) | 7.54 ± 0.28 | 7.73 ± 0.34 |
| Blood filterability (ml/min) | 0.96 ± 0.08 | 1.24 ± 0.09 |
| Resting microalbuminuria ( µg/min) | 28.35 ± 5.65 | 14.98 ± 3.36 (*) |
| Exercise microalbuminuria (µg/min) | 77.38 ± 12.05 | 83.52 ± 20.83 |
| Delta valve ( µ g/min) | 62.14 ± 12.90 | 63.78 ± 22.88 |

(*) $p < 0.025$

TABLE 2 – Preliminary results of an open trial showing the effects of pentoxifylline (3 months, 800 mg daily) on resting and postexercise microalbuminuria (see text).

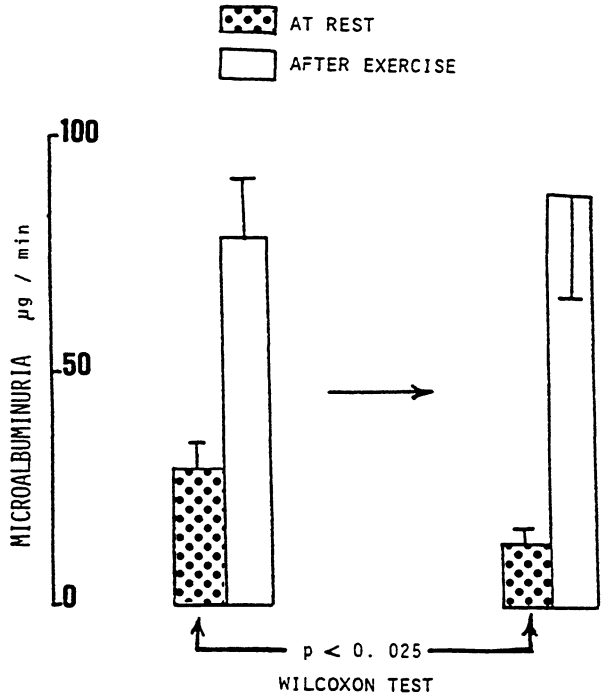


FIG. 3 – Modifications of microalbuminuria after treatment by pentoxifylline. Resting values are lowered whereas postexercise values remain unchanged (see text).

## DISCUSSION

1. A relationship between blood rheology and albumin excretion rate ?

In this study, we find that baseline microalbuminuria is higher in patients with reduced blood filterability, whereas no difference is to be found for postexercise increase in this parameter. Furthermore, our preliminary results with pentoxifylline seem to confirm Solerte's findings (12-15) that improving hemorheological status reduces resting microalbuminuria.

Those data suggest that abnormalities of blood fluidity (which can be detected by the whole blood filtration test and corrected by Pentoxifylline) might be involved in the pathogenesis of early renal dysfunction in diabetics, as previously hypothesized by Simpson (7).

It is interesting to notice that a relationship between albuminuria (in overt diabetic nephropathy) and blood viscosity at low shear rates has been recently reported by the team of Y. Isogai (24). Moreover, Pentoxifylline has been found to reduce macroalbuminuria in diabetics (25). Thus, our findings concerning the early (reversible) stages of diabetic nephropathy are also consistent with recent reports concerning irreversibly damaged diabetic kidneys.

Therefore, notwithstanding the first negative results reported by Hill (8), the hemorheologic theory of microalbuminuria cannot be rulled out. Further studies with more sophisticated hemorheologic and nephrologic measurements will be necessary to clarify this controversial question.

A theoretical model proposed by the team of J.C. Healy (26) suggests that increasing blood viscosity reduces the velocity of red cells and plasma circulating in the flocculus, resulting in a longer exchange time for a given quantum of blood. Therefore, heavy proteins which normally cross the membrane only in very reduced quantity will diffuse more widely to the Bowman's capsule. This model offers some similarities with the pathogenetic interpretations developped by both Simpson (7) and Solerte (15).

Our data concerning blood pressure in the two subgroups may suggest a complementary explanation for the relationship between blood rheology and microalbuminuria. We found that the correlation between blood pressure and microalbuminuria is significant only in the subgroup exhibiting abnormal blood filterability. It could be hypothesized that a reduction in blood fluidity is associated with a microcirculatory dysfunction with vasodilatation in the microvessels of the flocculus, resulting in a lower protection of this territory against the effects of systemic blood pressure. Therefore, variations in diabetic equilibrium could possibly modify microalbuminuria by influencing blood fluidity and thus glomerular sensitivity to blood pressure. Of course, such an explanation remains conjectural. Other possible mechanisms for the effects of hyperglycemia in this process have been reported (27). In this study, no clear relationship between HbA1 and blood filterability can be detected, but HbA1 is not likely to be the accurate marker for diabetic equilibrium in this case. HbA1 is mainly an index of long term integrated levels of blood glucose, whereas both microalbuminuria (28, 29) and red cell filterability (30) have been shown to be sensitive to short term modifications in glycemic control with an artificial pancreas.

2. Exercise-induced increase in microalbuminuria and rheologic parameters : no evidence for a relationship.

Previous results of a pilot study concerning blood filterability and exercise-induced microalbuminuria led us to the conclusion that the rise in albumin excretion rate which is observed after exercise was not likely to be related to exercise-induced changes in blood fluidity, as measured by the blood filtration test (31). The results we report here are consistent with these previous findings. The increase in albumin excretion during the exercise test does not show any relationship with modifications of blood filterability induced by muscular activity, and is not affected by Pentoxifylline. Therefore, it does not seem to be an artifact resulting from hemo - rheologic disturbances induced by strong workload. As previously stated by Feldt-Rasmussen (16), it is rather a sensitive marker of glomerular functionnal abnormalities already recognisable at rest.

The increase in microalbuminuria resulting from exercise has been found to be correlated with the rise in blood lactate (32) in athletes. In diabetics, it correlates mainly with : (a) the increase in blood pressure during muscular activity ; (b) resting levels of albumin excretion rate (33).

3. Possible therapeutical interest of pentoxifylline in incipient diabetic nephropathy.

In this work, we used pentoxifylline as a pharmacological tool for investigating the hemorheological aspects of early nephropathy. Therefore, no serious conclusions concerning its therapeutical usefulness in the management of diabetics at risk of nephropathy can be given. However, it is interesting to notice that our findings seem to be consistent with a larger study performed in Italy, which concluded that 1200 mg of pentoxifylline daily corrected microalbuminuria (12 - 15). These investigators found that pentoxifylline reduced both albumin excretion and blood pressure. Interestingly, with lower doses (800 mg), we observe a reduction of microalbuminuria without modifying blood pressure, suggesting that the correcting effect of the drug could be related to its hemorheologic effects rather than its effects on blood pressure. Further investigations will be necessary for clarifying this point.

4. Conclusion.

In summary, we report that, consistently with the hemorheologic theory of microalbuminuria, subjects with lowered blood filterability have a higher resting microalbuminuria, as well as a better correlation between microalbuminuria and blood pressure.

In contrast, exercise-induced microalbuminuria does not seem to be related to exercise-induced changes in blood rheology and appears to be insensitive to pentoxifylline. Which is the real importance of hemorheologic factors in the pathogenesis of incipient diabetic nephropathy requires further investigation.

## ACKNOWLEDGEMENTS

The collaboration of A.M. Puech-Cathala, B. Brunel, R. Ceaux, J.L. Jacquemin, M. Cayrol J. Bourrel, F. Poudevigne, D. Lauras and C. Sagnes is gratefully acknowledged ; as well as the material assistance of Hoechst-Behring Laboratories.

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