URINARY FIBRIN DEGRADATION PRODUCTS – A THREE YEAR COMPARATIVE STUDY

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Summary

Urinary fibrin degradation products (FDP) were determined by Merskey's passive haemagglutination test in 115 patients with biopsy proven chronic proliferative glomerulonephritis (GN), 94 with urinary tract infection (UTI), and 23 transplanted patients. The active GN values (12.3 μg/ml) are significantly higher than those for latent GN (0.3 μg/ml). Those for acute UTI (9.2 μg/ml) are significantly higher than for chronic UTI (1.3 μg/ml). In contrast to the reports published by others, the numerous 'false positive' and 'false negative' values make diagnosis of the activity unreliable.

Some prognostic value can be expected in GN with the nephrotic syndrome (NS): patients with steroid-sensitive NS excrete no FDP and patients with steroid-resistant NS excrete larger quantities of FDP.

We have confirmed that a rise in FDP level following kidney transplantation is indicative of an acute rejection crisis. However, since 10 of 27 rejections were FDP negative, the absence of FDP in the urine does not preclude rejection, so that the diagnostic value is restricted.

Introduction

It is the general opinion that the level of fibrin degradation products (FDP) in urine is indicative of intravascular (intraglomerular) coagulation which plays an important pathogenetic, although not immuno-aetiological role in glomerulonephritis (GN) and transplant rejection [1–3]. In the majority of publications it is stated that elevated urine FDP levels should be regarded as indicative of activity in GN, urinary tract infection (UTI) and transplant rejection [4–12]. Schmitt et al [13] have reviewed the status of FDP in nephrology.

These studies were initiated because of the still conflicting reports on the excretion of urinary FDP. Clarkson et al [7], Reichel et al [10], and Shah et al [11] described a diagnostically relevant relationship between the activity of chronic proliferative GN and elevated FDP levels in urine. Bendel et al attach no importance to FDP in this context [5].
Patients and Methods

During the past three years we studied 112 patients with GN, 94 patients with UTI (all of whom exhibited proteinuria), and 23 renal transplant patients. The FDP levels were determined in 1,050 urine samples with the tanned red cell haemagglutination inhibition immunoassay described by Merskey [14].

Glomerulonephritis

Chronic diffuse proliferative forms were observed in all patients with biopsy proven GN. Active or latent forms were distinguished by conventional clinical criteria such as urinary protein excretion in excess of 2 g/24 hr, and deterioration of kidney function.

GN patients with proteinuria exceeding 3.5 g/24 hr and a serum albumin content of less than 3.6 g% were regarded as exhibiting the nephrotic syndrome (NS). In all patients with NS treatment with prednisolone, 1–2 mg/kg/24 hr for at least two weeks was initiated. When this therapy reduced protein excretion to less than 2 g/24 hr, we considered the disorder to be steroid-sensitive.

Urinary Tract Infection

Chronic pyelonephritic (PN) patients had leucocyturia, proteinuria, intermittent symptomatic bacteriuria, and characteristic radiological changes. Fifty patients suffered from acute PN.

Kidney Transplantation

Renal transplant recipients were monitored daily while in hospital (average stay: 7 weeks). They received standard immunosuppression with prednisolone and azathioprine. Rejection was diagnosed using conventional clinical criteria without recourse to special examination or knowledge of FDP results.

A rise in the urine FDP level by at least two titre steps during the course of post-transplant monitoring was considered to be diagnostically relevant.

Results

Glomerulonephritis

The average value of 12.3 µg/ml obtained in active GN is significantly higher than the average for latent GN (0.3 µg/ml). It must be emphasised however that almost half of all patients with active GN are FDP-negative (Figure 1).

Among the NS patients there are clear differences in steroid sensitivity and in the urinary excretion of FDP. The average FDP value of 22.5 µg/ml for the NS group with no response to prednisolone treatment is distinctly higher than the average (0.9 µg/ml) for steroid-sensitive patients (Figure 2).
Figure 1. Urinary FDP in chronic proliferative glomerulonephritis. Triangles = active forms; Circles = inactive forms

Figure 2. Urinary FDP in GN patients with nephrotic syndrome and steroid therapy
Urinary Tract Infection

Findings comparable to those for GN were found in UTI. Although the significance can be calculated for the differences between the mean values (9.2 μg/ml for acute, and 1.3 μg/ml for chronic PN), it is apparent that one-third of each group exhibits ‘false positive’ or ‘false negative’ FDP values (Figure 3).

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UTI n=94
act. Δ ø 9.2 μg/ml
inact. ø 1.3 μg/ml

Figure 3. Urinary FDP in urinary tract infection. Triangles=acute pyelonephritis; Circles=chronic pyelonephritis

Kidney Transplants

Among the 23 patients there were six without rejection in whom no urinary FDP was excreted. Unexplained transient elevation of urinary FDP up to 16 μg/ml was observed in one of the 6 cases. In 17 patients there were 27 rejection episodes, but urinary FDP levels were characteristically elevated by an average of 4.7 titre steps in only 17 of the rejections. A ‘false positive’ result was obtained once, but this was probably due to a graft infection. Of the 8 patients in whom chronic rejection developed after an acute phase, the urinary FDP level was significantly elevated in only one. The remaining patients were FDP negative or exhibited urinary FDP levels up to 0.5 μg/ml (Figure 4).

Discussion

In these studies our objective was to assess personally the diagnostic value of urinary FDP excretion in estimating the activity of GN and UTI. Should the

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results of others [7,10,11] prove reproducible in providing specific criteria of activity especially in chronic GN, this would be an important clinical tool, particularly for long-term monitoring of GN patients.

The suggestion that high urinary FDP values in proliferative GN sometimes provide an indication of active disease has been confirmed. On the other hand, activity is not excluded by the absence of FDP excretion. In view of the large number of 'false positive' and 'false negative' results, practical application to individual GN patients is not recommended. As a result of our investigations we are unable to support the generally optimistic published reports regarding the use of this method for assessing the activity of GN.

From our observations we are also unable to substantiate the diagnostic relevance of this method in UTI. Here the significant deviations from average values are of no practical importance.

An observation of some prognostic importance was made regarding steroid sensitivity and FDP excretion in NS. Similar results have been published only in paediatric patients [4]. In contrast to the selective proteinuria accompanying steroid-sensitive NS, the proteinuria accompanying steroid-resistant NS is non-selective. The investigations undertaken by Hall et al [16] showed that high urinary FDP concentrations in NS correspond to non-selective protein excretion in contrast to the highly selective protein excretion found with low urinary FDP levels. It must be assumed that FDP excretion is not a function of GBM pore size alone. In NS, however, it would appear that the determination of urinary FDP levels provides a method which might replace the differential protein clearance test, so a relatively reliable prognosis could be made regarding the response to steroid therapy.
Publications on FDP in recent years have focused on renal transplantation, leading to the general opinion that elevated FDP levels can be regarded as a sign of transplant rejection. As a rule, reports state that urine FDP are found during the 14 days following transplantation and that this must be regarded as a consequence of ischaemia in perfusion and preservation. However, this phenomenon was observed in only 15 of our 23 patients, all of whom received cadaver kidneys.

If we consider the number of ‘false negative’ FDP findings in rejections, only Shah et al [11] report on one FDP negative rejection in the case of 10 acute rejection episodes. Bendel et al [5], Clarkson et al [6], Ekberg et al [17] and Zühlke et al [18] found a distinct rise in FDP levels in all rejections. In contrast to these, we found 10 FDP-negative cases among 27 rejections. We are unable to explain this discrepancy, but it substantially restricts the diagnostic value of the method.

We believe that a rise in the urine FDP titre indicates an acute rejection process, but the absence of FDP by no means indicates that no such process is taking place. Although the determination of urinary FDP levels is not a definitive method for identifying rejection, we nevertheless regard it as a suitable additional aid for reducing the uncertainty of rejection diagnosis.

The data presented here substantially reduce the diagnostic importance of FDP determination as a routine nephrological diagnostic method. Its use would appear advantageous only in certain particular cases, for example NS, where some benefits may be expected regarding prognosis and differential therapy.

References

11. Shah, BC, Ambrus, JL, Mink, JB, Albert, JD, Sampson, D and Murphy, GP (1972) Transplantation, 14, 705
Open Discussion

CZARNIECKI (Warsaw) Did you observe any correlation between your data and tests of blood coagulation, especially of those indicating a hypercoagulable state? Secondly, did you observe the presence of fibrinogen in your biopsy material?

KLINKMANN To the first point, I think the number of studies we have undertaken to compare these two sets of data are too small but as far as we can say we have not seen any correlation. Sorry I cannot answer your second question regarding fibrinogen deposits. We have not looked into this particularly.

RITZ (Heidelberg) I would concur with your conclusion that the practical value of FDP in urine is rather limited in the different types of nephrological diseases. However I would question your methodology. What is the evidence that you are measuring fibrin products with these techniques? I think this is important because of the interpretation of the data. You do not have any evidence that these products that you are measuring are fibrin rather than fibrinogen degradation products. This point is important, because the presence of fibrinogen degradation products in the urine may just be a reflection of the presence of non-selective glomerular proteinuria. Indeed, fibrinogen, once it has entered Bowman's space in a proteinuric patient, is susceptible to proteolytic cleavage, be it by leucocyte proteases or by urinary proteases (e.g. urokinase). This concept is supported by the demonstration by Dr Andrassay in our unit of an excellent correlation between non-selective glomerular proteinuria (Disc-electrophoresis) and FDP (Tanned red cell haemagglutination assay).

KLINKMANN I think you are well aware of the technique we have used. I pointed out at the beginning that it was fibrin as well as fibrinogen products involved in this, but unfortunately there is no other method for simple clinical use available. The aim of our study was just to find out what it tells us for our daily routine use. I did not conclude that this was the final statement. I am not going to have a funeral for FDP just yet, but at the present time I do not think we are justified in drawing any significant clinical conclusions using this method as routinely applied in our daily practice.

KENNEDY (Glasgow) With regard to the nephrotic syndrome in part of your study, did your fall in the FDP levels occur in advance of or parallel with the fall in the proteinuria?

KLINKMANN With, not in advance.