

# Plasma fibronectin and thyroid function

W GRANINGER, K PIRICH, K DERFLER, W WALDHÄUSL

*From the Department of Chemotherapy and the 1st Department of Medicine, Division of Clinical Endocrinology and Diabetes Mellitus, University of Vienna, Vienna, Austria*

**SUMMARY** Plasma fibronectin concentrations up to 85 mg/100 ml were found in hyperthyroid patients. There was a significant correlation between free thyroxine index and plasma fibronectin values. Hypothyroid patients had low to normal fibronectin concentrations. Parallel decreases of thyroid hormones and plasma fibronectin concentrations were noted during treatment with thiamazole. A direct effect of thyroid hormones on fibronectin synthesis seems probable.

Fibronectin, formerly known as cold insoluble globulin, is a glycoprotein with a molecular weight of about 450 000 daltons which consists of two subunits connected by disulphide bands. Plasma fibronectin has recently gained interest in host defence mechanisms with regard to reticuloendothelial system function.<sup>1-3</sup> Here, it serves as an opsonin, facilitating clearance of particulates such as fibrin microaggregates, injured cells, and bacterial and non-bacterial particulates. Low concentrations of plasma fibronectin in sepsis may indicate exhausted systemic host defence and increased fibronectin consumption via reticuloendothelial system clearance. Low concentrations of fibronectin have also been reported in patients with malnutrition.<sup>4</sup> In contrast, moderately raised plasma fibronectin values have been found in nephrosis, cholestasis, gestosis, and in patients with cancer.<sup>5-7</sup> Based on the accidental observation of a high fibronectin concentration in a patient with hyperthyroidism we have studied the relation of fibronectin and thyroid hormone concentrations.

## Material and methods

One hundred and one female patients (10 hypothyroid, 23 hyperthyroid, and 68 with thyroid disease but with normal thyroid function) attending the thyroid outpatient service were included in this study. Forty healthy women without a history of thyroid disease and normal thyroid function served as control subjects. All patients and controls were of comparable age with a mean age of 52 years (range 23-75) and none showed any signs of malnutrition. Because of sex differences in plasma fibronectin concentrations<sup>5</sup> only women were investigated.

Plasma concentration of fibronectin and prealbumin as well as serum concentration of total thyroxine were measured in all patients and control subjects. Free thyroxine index was calculated in patients with abnormal total thyroxine concentrations.

## ANALYTICAL METHODS

Total thyroxine (Bio-Rad, Richmond, CA) and free thyroxine index (Bio-Rad) were determined radioimmunologically. Plasma fibronectin concentration was measured according to the method of Saba *et al*<sup>8</sup> by an immunoturbidometric assay using edetic acid coated polypropylene tubes for blood samples. As a nutritional parameter, prealbumin was determined by agar immunodiffusion (Partigen, Behring Werke AG, Marburg, FRG). All tests were run in duplicate.

## STATISTICAL METHODS

Analysis of variance with a confidence of  $\alpha = 0.01$  was used. Multiple comparisons between different means were done using the method of Scheffé.<sup>7</sup> Data in the text and the table are given as mean  $\pm$  standard deviation (SD).

## Results

Values of plasma fibronectin, prealbumin, total thyroxine, and free thyroxine index are given in the Table. Patients with thyroid dysfunction as well as control subjects and euthyroid patients had comparable prealbumin concentrations. In contrast, the mean plasma fibronectin concentration in hyperthyroid patients was 58% above that of normal control subjects and euthyroid individuals suffering from non-thyroidal disease and was reduced by 27% in hypothyroid patients. Thus patients with hyperthyroidism had a mean plasma fibronectin con-

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|                             | Control subjects<br>(n = 40) | Patients                |                           |                          |
|-----------------------------|------------------------------|-------------------------|---------------------------|--------------------------|
|                             |                              | Hypothyroid<br>(n = 10) | NormEuthyroid<br>(n = 68) | Hyperthyroid<br>(n = 23) |
| Age (years)                 | 51.3 ± 11.2                  | 58.8 ± 19.6             | 52.6 ± 15.4               | 45.8 ± 16.5              |
| Total thyroxine (µg/100 ml) | 8.8 ± 1.3                    | 2.0 ± 1.5               | 7.6 ± 1.2                 | 15.1 ± 2.9               |
| Free thyroxine index        | 0.86 - 1.13                  | 0.8 ± 0.03              | —                         | 1.3 ± 0.2                |
| Prealbumin (mg/100 ml)      | 35.9 ± 7.5                   | 35.3 ± 9.5              | 36.1 ± 10.8               | 39.7 ± 11.8              |
| Fibronectin (mg/100 ml)     | 33.5 ± 4.3                   | 25.3 ± 5.3              | 34.4 ± 5.03               | 54.2 ± 13.7              |

Values given as mean ±SD.

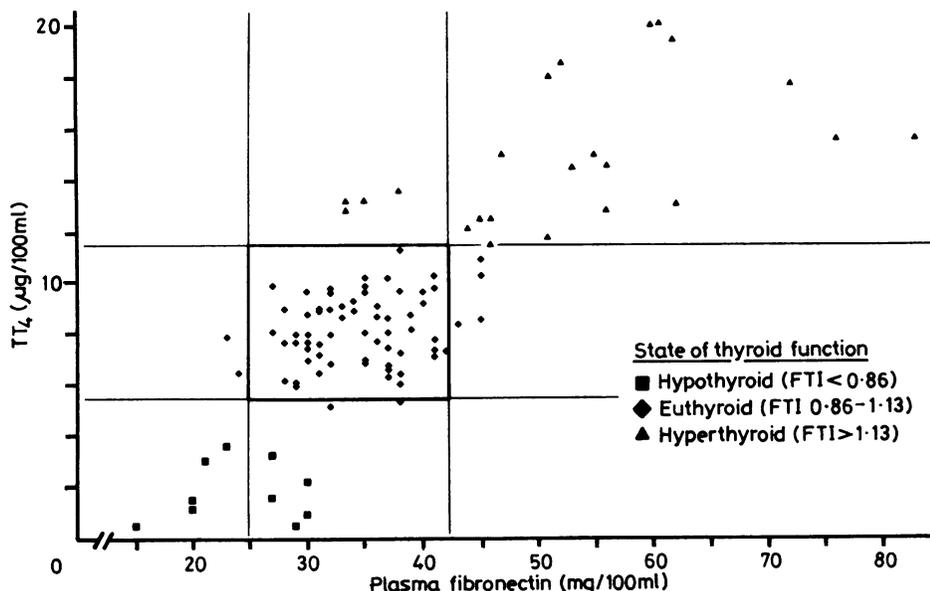


Fig.1 Relation between plasma concentrations of total thyroxine ( $T_4$ ) and fibronectin concentrations in female patients with euthyroid ( $n = 68$ ), hyperthyroid ( $n = 23$ ), or hypothyroid state ( $n = 10$ ). The normal range is given by the crossed area. FTI = free thyroxine index.

centration of 25.3 mg/100 ml, whereas this value was exceeded more than twofold by the 52.4 mg/100 ml in hyperthyroid patients. Relating plasma fibronectin to total thyroxine values (Fig. 1) showed that half of the hypothyroid patients had lower fibronectin values than euthyroid subjects and patients, while 82% of all hyperthyroid individuals had fibronectin concentrations above the normal range of 25.0–42.0 mg/100 ml. A significant correlation ( $r = 0.68$ ;  $n = 23$ ) was found between free thyroxine index and plasma fibronectin concentrations in hyperthyroid subjects. Changes in plasma fibronectin, total thyroxine, and free thyroxine index in a 55 year old hyperthyroid woman during treatment with thiamazole are shown in Fig. 2. It is apparent that daily thyreostatic treatment with thiamazole (days 1–6: 160 mg intravenously; days 7–10: 120 mg intravenously; and 20 mg three times daily orally thereafter) was accompanied by consistent and parallel falls in both plasma thyroid hor-

mone and fibronectin concentrations.

**Discussion**

Decreased concentrations of plasma fibronectin have been reported in patients with septicæmia, burns, after trauma,<sup>1-3</sup> in disseminated intravascular coagulation,<sup>7</sup> and during starvation.<sup>4</sup> While in septicæmia low concentrations of plasma fibronectin have been attributed to increased opsonisation of collagenous debris, injured platelets, immune complexes, and bacterial as well as non-bacterial aggregates after consumption by the reticuloendothelial system, low plasma fibronectin in starvation has been attributed to its impaired synthesis in the liver.

Increased plasma fibronectin concentrations as described in gestosis,<sup>6</sup> primary biliary cirrhosis, obstructive jaundice, and nephrotic syndrome<sup>5</sup> have been ascribed to its increased production, decreased metabolism, or reduced renal clearance. The

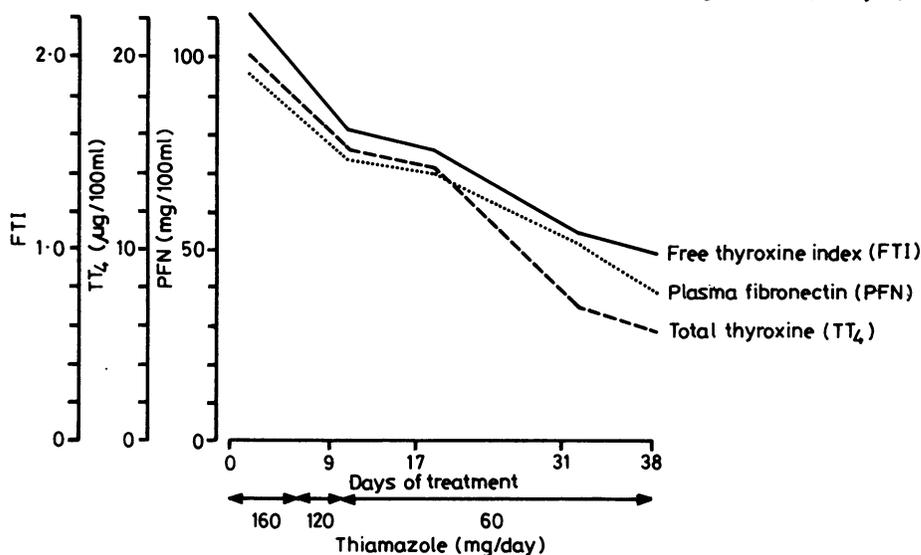


Fig. 2 Changes in plasma fibronectin, total thyroxine, and free thyroxine index in a hyperthyroid female patient during treatment with thiamazole.

significantly raised plasma fibronectin values found in hyperthyroid patients in this study and their reduction in hypothyroid individuals suggest that fibronectin metabolism is related to thyroid hormone availability. This hypothesis was also supported by the fall in plasma fibronectin concentration during successful thyrostatic treatment of a severely hyperthyroid patient (Fig. 2). As patients with non-thyroidal disease known to increase fibronectin concentrations<sup>5-7</sup> were excluded from this study, a direct effect of thyroid hormones on endothelial synthesis of plasma fibronectin has to be assumed in hyperthyroidism. In this context one has also to remember that thyroid hormones promote protein synthesis<sup>10</sup> and that hyperthyroidism is associated with increased concentrations of plasma angiotensin converting enzyme<sup>11</sup> and factor VIII,<sup>12</sup> which, like fibronectin, are both synthesised by endothelial cells.<sup>2</sup>

With regard to the low fibronectin concentrations in hypothyroid patients, it is of interest that low concentrations of thyroid hormones<sup>13-15</sup> and fibronectin<sup>2,3</sup> have also been described in severe illness such as trauma, burns, and sepsis. In cases of sepsis, but not in the other two conditions, increased consumption of fibronectin by the reticuloendothelial system may explain low fibronectin concentrations. Since plasma prealbumin was normal in our hypothyroid patients, thereby indicating a normal nutritional state,<sup>16</sup> the low fibronectin concentrations were not attributable to impaired hepatic protein synthesis. Thyroid hormone availability appears to explain at

least some of the observed variabilities in plasma fibronectin concentration as changes in total thyroxine concentrations were closely paralleled by those of fibronectin in both the hypothyroid ( $r = 0.53$ ;  $n = 10$ ) and hyperthyroid state ( $r = 0.57$ ;  $n = 23$ ). But again it remains open to discussion whether this relation reflects a specific interaction of thyroid hormones with fibronectin synthesis or just an epiphenomenon of an underlying thyroid disease.

Against this background we conclude that decreased as well as increased plasma fibronectin concentrations may be triggered by a variety of clinical events ranging from thyroid dysfunction to malnutrition and to changes in reticuloendothelial system clearance during septicaemia. No decision can be made as to the relative role played by any of these mechanisms in the variability of plasma fibronectin concentration. Since many factors affect plasma fibronectin concentration the diagnostic and prognostic value assigned to its determination in severe illness including sepsis<sup>1-3</sup> should be viewed with caution.

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Requests for reprints to: Dr W Graninger, Department of Chemotherapy, University of Vienna, Lazarettgasse 14, A-1090 Vienna, Austria.