

## Original Article

# Utility of plasma fibrinogen in the differential diagnosis of thyrotoxicosis

Jie Ma\*, Rui Liu\*, Di Wu, Wei Miao, Qian Chen, Yushu Li, Haixia Guan

Department of Endocrinology and Metabolism, The Endocrine Institute and The Liaoning Provincial Key Laboratory of Endocrine Diseases, The First Hospital of China Medical University, Shenyang 110001, Liaoning, P. R. China.  
\*Equal contributors.

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**Abstract:** Background: A study had reported that a low TSH level is associated with elevated plasma fibrinogen (FIB) levels. Our purpose was to investigate the role of FIB in the differential diagnosis of thyrotoxicosis. Methods: The data of 104 patients with primary thyrotoxicosis at the First Hospital of China Medical University from July 2010 to March 2011 were analyzed and divided into three groups: 45 cases of subacute thyroiditis, 50 cases of Graves' disease, and 9 cases of toxic multinodular goiter. The patients with subacute thyroiditis were followed up before and after the treatment. FIB levels of the three groups were compared. Results: There was no significant difference in serum TSH, FT3 and FT4 between the patients with three different causes of thyrotoxicosis ( $P > 0.05$ ). The proportion of hyperfibrinogenemia in patients with subacute thyroiditis was 98%. The FIB levels of patients with subacute thyroiditis were significantly higher than those with Graves' disease and toxic multinodular goiter ( $P < 0.05$ ). Levels of ESR show a similar tendency. The FIB levels returned to normal with the remission of subacute thyroiditis. Conclusions: Elevated plasma fibrinogen is a common manifestation of the active phase of subacute thyroiditis. A FIB test can be used for the differential diagnosis of thyrotoxicosis. We can anticipate the outcome of subacute thyroiditis through the dynamic changes of FIB.

**Keywords:** Fibrinogen, thyrotoxicosis, subacute thyroiditis, diagnosis

## Introduction

Thyrotoxicosis is defined as a set of symptoms and signs related to elevated serum thyroid hormone concentration. Hyperthyroidism may be divided into a number of nosological subtypes with different aetiology, clinical presentation, prognosis and outcome of therapy. Subacute thyroiditis (thyrotoxicosis period), Graves' disease (hyperthyroidism period) and toxic multinodular goiter are three common subtypes of thyrotoxicosis [1]. The three kinds of thyrotoxicosis are quite different in treatment and prognosis, thus the differential diagnosis is particularly important. Dorr M et al. have reported that a low TSH level is associated with elevated plasma fibrinogen (FIB) levels compared with euthyroid subjects, but the exact cause and clinical significance of this phenomenon are unknown [2]. We wanted to investigate whether this is a direct effect of thyroid hormones on plasma protein regulation or a chronic inflammatory state induced by inflammatory diseases of the thyroid. Subacute thy-

roiditis is also known as granulomatous thyroiditis or giant cell thyroiditis [3]. It is often misdiagnosed because of its diverse clinical manifestations and their similarity to other thyroid diseases in atypical cases [1, 4-6]. Because it is considered a viral-related disease, we speculated that some inflammatory cytokine indicators would show specific changes in its progression and outcome, such as the erythrocyte sedimentation rate (ESR), which can be easily measured in clinic [7-10]. Therefore, we observed the changes of FIB, an inflammatory cytokine indicator which is simple to detect, in subacute thyroiditis and discussed the utility of FIB in the differential diagnosis and monitoring of subacute thyroiditis.

## Subjects and methods

### General information

The study included 104 unrelated patients diagnosed with primary thyrotoxicosis in an outpatient setting at the First Affiliated Hospital of

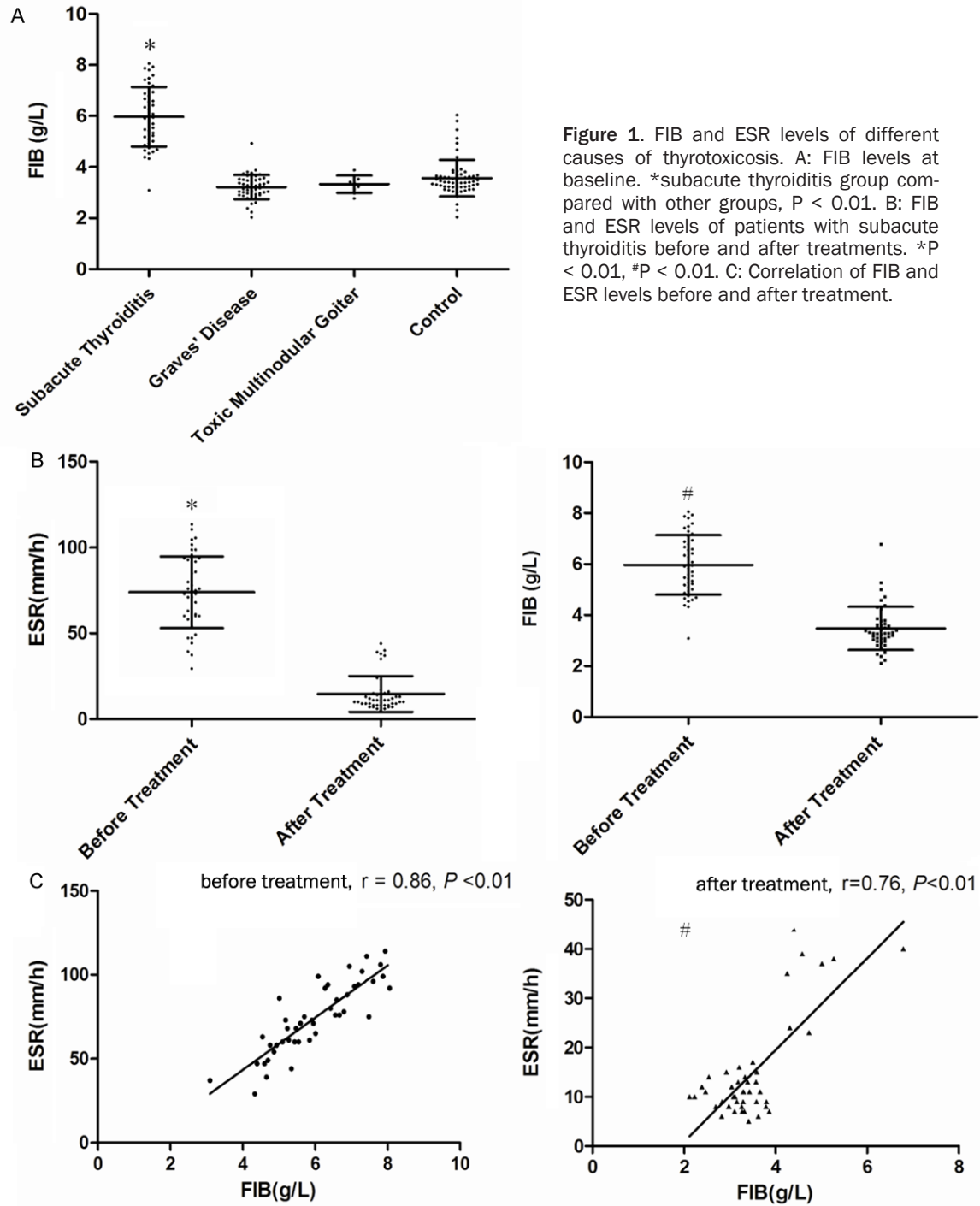
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**Table 1.** Clinical features of subjects at baseline

| Groups                              | n  | M:F    | Ages (yr)  | TSH* (mIU/L)  | FT3 (pmol/L) | FT4 (pmol/L)  | ESR (mm/h)    | FIB (g/L)   |
|-------------------------------------|----|--------|------------|---------------|--------------|---------------|---------------|-------------|
| Subacute thyroiditis                | 45 | 10:35  | 42.7 ± 5.6 | 0.004 ± 0.007 | 12.63 ± 5.92 | 37.14 ± 11.75 | 78.02 ± 26.97 | 5.97 ± 1.23 |
| Graves' diseases                    | 50 | 13:37  | 40.6 ± 9.3 | 0.001 ± 0.004 | 17.47 ± 4.58 | 41.28 ± 13.56 | 11.43 ± 2.55  | 3.21 ± 0.64 |
| Nodular goiter with hyperthyroidism | 9  | 1:8    | 43.9 ± 8.7 | 0.005 ± 0.013 | 11.31 ± 7.72 | 35.77 ± 16.81 | 14.21 ± 5.09  | 3.33 ± 0.59 |
| Euthyroid controls                  | 60 | 15:45  | 41.5 ± 4.4 | 1.9 ± 1.3     | 4.75 ± 0.32  | 15.69 ± 2.18  | 12.48 ± 4.32  | 3.56 ± 0.41 |
| <i>P</i> -value                     | —  | > 0.05 | > 0.05     | < 0.01        | < 0.01       | < 0.01        | < 0.01        | < 0.01      |

Data were given as mean ± standard deviation. \*The data for TSH do not adhere to a Gaussian distribution. A log-transformation was made before analysis.

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**Figure 1.** FIB and ESR levels of different causes of thyrotoxicosis. A: FIB levels at baseline. \*subacute thyroiditis group compared with other groups,  $P < 0.01$ . B: FIB and ESR levels of patients with subacute thyroiditis before and after treatments. \* $P < 0.01$ , # $P < 0.01$ . C: Correlation of FIB and ESR levels before and after treatment.

China Medical University from July 2010 to March 2011. They were divided into three groups: 45 cases of subacute thyroiditis (10 males, 35 females, aged 30-50 yr), 50 cases of Graves' disease (13 males, 37 females, aged 20-55 yr), and 9 cases of toxic multinodular goiter (1 male, 8 female, aged 25-57 yr). Sixty euthyroid subjects who were healthy and

denied a history of past or present illness, were selected for the control group (15 males, 45 females, 30-50 yr).

### Diagnostic criteria

Thyrotoxicosis was defined by an elevated serum FT3 and FT4, with a decreased serum

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TSH. Subacute thyroiditis was diagnosed by goiter, local neck pain or discomfort, with or without fever, increased ESR, negative thyroid autoantibody and an uptake dysfunction in technetium-99m pertechnetate ( $^{99m}\text{Tc}$ ) thyroid scan on the basis of thyrotoxicosis. Graves' disease was diagnosed by a diffuse enlargement of the thyroid, normal or elevated thyroid peroxidase antibody (TPOAb) and/or thyroglobulin antibody (TgAb), and/or positive TSH receptor antibody (TRAb) and an uptake enhancement in  $^{99m}\text{Tc}$  thyroid scan. Toxic multinodular goiter was diagnosed by nodular goiters confirmed with physical examination and ultrasound, negative TPOAb, TgAb and TRAb and an uptake enhancement in  $^{99m}\text{Tc}$  thyroid scan [1, 8-13].

### Assays

The fasting blood samples were drawn from all patients before treatment. For patients with subacute thyroiditis, non-steroidal drugs or glucocorticoids were administered according to the severity of neck pain, fever or other symptoms. Four to eight weeks after the treatment (median 6.7 weeks), these patients were drawn the blood samples again.

ESR was measured using the Westergren assay. FIB was analyzed by French STAGO Magnetic Beads Coagulation detection. Serum TSH, FT3, FT4, TPOAb and TgAb were analyzed by immuno-chemiluminescent assays (Abbott Labs, Abbott Park, IL US), and TRAb was detected by immuno-chemiluminescent assay (Roche Cobas, Roche, Germany).

The fasting blood samples of the normal control group were collected and serum TSH, FT3, FT4, FIB and ESR were assayed using the same methods.

The intraassay coefficients of variation (CV) of these laboratory assays were less than 7%, and the interassay CVs were less than 8%.

### Reference ranges

TSH levels from 0.35 to 4.94 mIU/L were considered euthyroid. The reference ranges for serum FT3 and FT4 were 2.63-5.70 pmol/L and 9.01-19.05 pmol/L, respectively. Serum TPOAb exceeding a level of 4.11 IU/mL, serum TgAb exceeding a level of 5.61 IU/mL, serum TRAb exceeding a level of 1.75 IU/L were considered as high serum autoantibody values. The refer-

ence ranges for ESR were 0-20 mm/h for females and 0-15 mm/h for males. The reference range for FIB was 2.00-4.00 g/L.

### Statistical analysis

The data for TSH do not adhere to a Gaussian distribution. A log-transformation was made before analysis and descriptive statistics were therefore reported as mean  $\pm$  standard deviation (SD). Intergroup comparison was performed by linear ANOVA or paired *t*-test. The relationship between variables was assessed using Spearman's correlation coefficients. The adjusted odds ratio (OR) and the 95% confidence interval (CI) were calculated. The level of significance was set at 5%. Statistical analysis was done using SPSS software (version 13, Chicago, IL, USA).

### Ethical aspects

Research protocols were approved by the Medical Ethics Committee of China Medical University. Research protocols were carefully explained to all participants, and an informed consent for voluntary participation was obtained from them.

### Results

There were no significant differences in terms of age and sex between the groups. Patients with subacute thyroiditis, Graves' disease or toxic multinodular goiter had lower serum TSH levels and higher FT3 and FT4 levels compared with euthyroid controls ( $P < 0.001$ ). There was no significant difference in serum TSH, FT3 and FT4 between the patients with different causes of thyrotoxicosis ( $P > 0.05$ ).

The FIB and ESR levels of patients with different causes of thyrotoxicosis are shown in **Table 1** and **Figure 1**. Before the treatment, the proportion of subacute thyroiditis patients with elevated serum FIB was 98% (44/45), which was significantly higher than the Graves' disease group (2%), the toxic multinodular goiter group (0%) and the normal control group (12%) ( $P < 0.05$ ). The mean FIB level of subacute thyroiditis patients was significantly higher than the Graves' disease group, the toxic multinodular goiter group and the control group ( $P < 0.05$ ). Levels of ESR show a similar tendency. There is a correlation between the plasma FIB and the ESR level ( $r = 0.86$ ,  $P < 0.01$ ).

The plasma FIB levels in patients with subacute thyroiditis before and after treatment were  $5.97 \text{ g/L} \pm 1.17 \text{ g/L}$  and  $3.48 \text{ g/L} \pm 0.85 \text{ g/L}$  ( $P < 0.001$ ), the same trend was seen with the ESR ( $74.16 \text{ mm/h} \pm 21.06 \text{ mm/h}$  before treatment,  $14.64 \text{ mm/h} \pm 10.40 \text{ mm/h}$  after treatment,  $P < 0.001$ ). In the 44 patients with elevated plasma FIB before treatment, two patients remained a higher plasma FIB levels than the normal range when they were followed up. One of them were still suffering from the symptoms of subacute thyroiditis, the other had repeated exacerbations. The remaining 42 patients' plasma FIB levels were back to normal after a relief in their symptoms. There was no correlation between a change in FIB levels and the patients' thyroid function in the follow-up period (4 cases of subclinical hyperthyroidism, 26 cases of normal thyroid function, 11 cases of subclinical hypothyroidism and 3 cases of clinical hypothyroidism).

### Discussion

Subacute thyroiditis is the most common thyroid pain disorder. Currently, it is believed to be caused by a viral infection. Its characteristic presentation is destructive damage to thyroid tissue with short-term pain and multi-systemic inflammatory responses [8]. After the onset of subacute thyroiditis, typical cases will experience a thyrotoxicosis phase (about 50% to 75% of patients, lasting for 3 to 8 weeks), a hypothyroidism phase (about 25% of patients) and a thyroid function recovery phase. The majority of patients' thyroid function will be back to normal in a few weeks to months, and the incidence of sustained hypothyroidism is generally reported in less than 10% of cases. The whole course of symptoms is about 6-12 months. Repeated exacerbations may happen in some cases, which can last for several months to 2 years; approximately 2-4% of patients may get a recurrence but these repeated episodes are rare [3]. The mechanism of subacute thyroiditis is the destruction of thyroid follicular cells and a rapid leakage of thyroid hormone into the blood circulation, which results in elevated levels of thyroid hormone in the blood. This is different from thyroid cells synthesizing redundant hormones as is normally caused by hyperthyroidism. Thus, subacute thyroiditis is often self-limiting and anti-thyroid drugs are not necessary. Its prognosis is relatively good [1].

In the present study, we observed the change of FIB in patients with different causes of thyrotoxicosis, including subacute thyroiditis, Graves' disease and nodular goiter with hyperthyroidism, to identify whether FIB could be used as an indicator for differential diagnosis of thyrotoxicosis. Our results gave us three novel ideas for clinical practice.

First, hyperfibrinogenemia is a common manifestation of the active phase of subacute thyroiditis. Plasma FIB is a glycoprotein which is abundant in the blood. It is synthesized by liver cells and plays an important role in the process of coagulation and hemostasis [14, 15]. An elevated FIB can be usually seen in conditions such as being elderly, during late pregnancy, taking estrogen preparations, ischemic infarction of cardiovascular and cerebrovascular diseases, diabetes, nephrotic syndrome, or the case of long-term or large-scale importation of blood products containing fibrinogen. Therefore, these conditions need to be monitored for hypercoagulability and the use of anticoagulant therapy should be implemented if necessary [16-19]. Fibrinogen is also an acute phase protein, which elevates in the short term during some stress conditions such as infection and severe trauma. It is also a reaction product of the acute phase of inflammation [20, 21]. As mentioned earlier, subacute thyroiditis is associated with viral infection. In our study, we found that an elevated FIB was seen in the active inflammatory phase of subacute thyroiditis, and that it returned to normal levels in the recovery stage. The elevated FIB in subacute thyroiditis reflects its change as an acute phase protein and does not have a significant impact on the coagulation system, therefore there is no need for anticoagulant medication.

Second, the detection of FIB contributes to the differential diagnosis of thyrotoxicosis. Dorr M et al. have reported that a low TSH level is associated with elevated FIB levels, but the exact cause and clinical significance of this are unknown [2]. Our study further analyzed whether the different causes of low TSH would lead to elevated FIB. We found that the main cause of hyperfibrinogenemia is subacute thyroiditis rather than Graves' disease or nodular goiter. Subacute thyroiditis is not rare, so we need to screen out patients with subacute thyroiditis for whom medication is not necessary in clinic. It is not difficult to identify typical subacute thy-

roiditis patients according to the characteristics of neck pain, systemic inflammatory symptoms and elevated serum thyroid hormone with reduced thyroid iodine uptake function [1]. However, some patients atypically manifest thyroid mass or a diffusely enlarged thyroid with slight or even no thyroid pain and no systemic symptoms. It is easy to be confused with nodular goiter or mild to moderate Graves' disease. If a patient visits a hospital that does not have thyroid iodine uptake function tests or TRAb determination, the differential diagnosis could be even more difficult. Determining FIB levels can be of help to identify the cause of thyrotoxicosis. It is easy to perform and has few restrictions, such as no fasting requirements. An abnormal hyperfibrinogenemia possibly suggests subacute thyroiditis rather than Graves' disease or nodular goiter.

Third, monitoring the dynamic changes of FIB can help to assess the disease outcome of subacute thyroiditis. As we saw in our study, plasma FIB increases in the active phase of subacute thyroiditis, and returns to a normal range when the symptoms ease after treatment. Therefore, the restoration of fibrinogen to normal values would predict that subacute thyroiditis should enter a remission, or recovery period. FIB changes almost simultaneously with ESR, another classic indicator of subacute thyroiditis, and their changes are closely associated. Thus, the two indicators potentially have the same role in monitoring the condition of subacute thyroiditis.

In summary, hyperfibrinogenemia is an acute inflammatory response of subacute thyroiditis which does not need special care. We believe that plasma FIB can be successfully used as a differential diagnosis and as a condition monitoring indicator of subacute thyroiditis.

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### Disclosure of conflict of interest

None.

**Address correspondence to:** Haixia Guan or Yushu Li, Department of Endocrinology and Metabolism,

The Endocrine Institute and The Liaoning Provincial Key Laboratory of Endocrine Diseases, The First Hospital of China Medical University, Shenyang 110001, Liaoning, P. R. China. E-mail: hxguan@vip.126.com (HXG); liyushu@hotmail.com (YSL)

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