

## 证的研究

血栓相关分子标志物在糖尿病  
血瘀证中的临床意义

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**摘要** 以血浆 $\alpha$ -颗粒膜蛋白(GMP-140)、组织型纤溶酶原激活剂(tPA)、纤溶酶原激活物抑制剂(PAI-I)、凝血酶-抗凝血酶Ⅲ复合物(TAT)和血浆纤溶酶- $\alpha_2$ 抗纤溶酶抑制物(PAP)、内皮素(ET)等血栓前状态分子标志物,探讨与糖尿病血瘀证的相关性。结果显示,糖尿病血瘀证患者存在着血小板活化、内皮细胞受损、纤溶酶的改变,其血浆GMP-140、TAT、PAP、ET均高于非血瘀证和正常对照组。提示血小板活化、内皮细胞受损、凝血/纤溶平衡的改变有利于血瘀证的发生。糖尿病血瘀证的病理生理机制与血小板、内皮细胞、凝血、纤溶等改变皆有关。

**主题词** 糖尿病/诊断 血瘀/诊断 @血栓相关分子标志物

近10年来,对糖尿病血瘀证的研究已从单纯的舌下脉流行病调查发展至应用血液动力学、微循环、病理、生化及细胞、分子生物学等多方面的研究,尤其是近几年已认识到糖尿病血瘀证的形成与现代医学血栓与止血理论有关。认为其与糖尿病及糖尿病并发症患者血液呈高凝状态、常存在血栓前状态的病理过程极其相似。故本文从这一角度检测某些血栓相关分子标志物,旨在从血小板活化、内皮细胞功能、凝血纤溶平衡改变等几方面对糖尿病血瘀证的本质研究进行较为系统的探索。

### 1 临床资料

根据WHO糖尿病诊断标准<sup>[1]</sup>,在1993年9月~1994年12月及1996年9月~12月分二个阶段对我院门诊及住院就诊115例及50例Ⅱ型糖尿病(NIDDM)患者分别进行检测。165例中男97例,女68例,年龄40~83岁,中位数60岁。根据1987年中医血瘀证诊断标准,165例中符合血瘀证86例,非血瘀证79例。在分阶段观察时均设有健康组作对照,每阶段

20人,男、女各半,中位数分别为52和55岁。

### 2 方法与结果

2.1 血浆GMP-140测定:酶联免疫吸附法(1993年)及双抗夹心固相免疫法(1994年)皆证实NIDDM血瘀证患者其GMP-140值明显高于非血瘀证组( $P<0.05$ 或 $P<0.01$ )。两组与健康人组比较,差异亦有显著性( $P<0.05$ 或 $P<0.01$ )。1993、1994年分批进行ET测定(放免法),1993年血瘀证与非血瘀证组比较,差异有显著性( $P<0.05$ );1994年重复测定,并增加病例数,测得差异有非常显著性( $P<0.01$ ),两组与健康人组比较差异均有显著性( $P<0.05$ 或 $P<0.01$ ),见表1。

2.2 血浆tPA含量及PAI-I活性的测定:tPA含量(发色底物法)在血瘀证组与健康人组间差异有显著性( $P<0.05$ );血瘀证与非血瘀证组间比较无显著性差异。PAI-I活性(发色底物法)在血瘀证与健康人组间、非血瘀证与健康人组间差异皆有显著性( $P$ 均 $<0.01$ ),见表2。

2.3 血浆TAT、PAP浓度的测定:糖尿病血瘀证组与非血瘀证组间,TAT及PAP均差异显著( $P$ 均 $<0.01$ ),血瘀证与健康人组TAT、PAP亦差异显著( $P$ 均 $<0.01$ ),但非血瘀证组与健康人组间差异无显著性( $P$ 均 $>0.05$ )。

### 3 讨论

在我们以往的研究工作中发现糖尿病血瘀证与常见并发症有关,尤与血管并发症关系最为密切<sup>[2]</sup>。而血瘀的形成与血液成分、血流状况、血管壁等病理变化有关<sup>[3]</sup>,血瘀证的形成似乎与止血机制紊乱有相似之处,因此本文从止血机制相关的分子标志物着手进行糖尿病血瘀证的本质研究。

止血机制的紊乱常涉及到血管、血小板、凝血、纤溶等方面,糖尿病及其糖尿病并发症时常示有血管内皮细胞的损伤,血浆ET的增高;血小板易栓、易聚、易活化,以及血液抗凝、纤溶等改变。这些因素又交叉作用,表现为止血机制的紊乱,如活化的血小板能使毛细

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表 1 3 组血浆 GMP-140、ET 含量的比较( $\bar{X} \pm S$ )

| 组别    | GMP-140(ng/ml)    |                    | ET(pg/ml)         |                    |
|-------|-------------------|--------------------|-------------------|--------------------|
|       | 1993 年            | 1994 年             | 1993 年            | 1994 年             |
| 血瘀证组  | 43.80±17.10(17)*△ | 42.34±31.08(42)*△△ | 71.30±20.60(17)*△ | 74.29±30.67(42)*△△ |
| 非血瘀证组 | 31.50±17.30(24)*  | 26.10±9.88(32)**   | 59.00±11.80(24)*  | 40.09±22.87(32)**  |
| 健康人组  | 20.44±14.63(20)   | 16.14±4.55(20)     | 48.65±15.67(20)   | 27.77±11.35(20)    |

与健康人组比较, \*  $P < 0.05$ , \*\*  $P < 0.01$ ; 与非血瘀证比较, △  $P < 0.05$ , △△  $P < 0.01$

表 2 组血浆 tPA 含量、PAI-1 活性比较( $\bar{X} \pm S$ )

| 组别    | 例数 | tPA<br>( $\mu\text{g/L}$ ) | PAI-1<br>(AU/ml) |
|-------|----|----------------------------|------------------|
| 血瘀证组  | 17 | 4.37±0.69*                 | 3.00±1.13**      |
| 非血瘀证组 | 24 | 4.57±1.77                  | 3.33±1.53**      |
| 健康人组  | 20 | 3.97±0.42                  | 1.79±0.66        |

与健康人组比较, \*  $P < 0.05$ , \*\*  $P < 0.01$

血管的微血栓形成,通过分泌活性物质使局部原存的血管病变加速发展,血小板活化后尚可影响糖尿病原激活物抑制剂的释放,凝血系统的激活,抗凝作用的削弱,使血液易成血栓前状态。本文选择 GMP-140 为血小板活化指标,血浆 GMP-140 在正常全血中表达最少,其特异性与敏感性较其他标志蛋白为佳。ET 为反映血管内皮细胞损伤的特异性标志之一。tPA 及 PAI-1 是凝血和纤溶的常用检测指标,但通过 tPA 及 PAI 的测定来估价整个凝血-纤溶系统的活性状态,尚有一定的局限性。纤溶酶生存后在血浆中只存在数秒即被其抑制物灭活,其中  $\alpha_2$ -AP 约灭活 92% 纤溶酶,而血液循环中纤溶酶与其主要抑制物形成的纤溶酶- $\alpha_2$  抗纤溶酶抑制物(PAP)可反映机体纤溶酶的生存率和生存量,血液循环中的凝血酶与其主要抑制物形成的凝血酶-抗凝血酶 III 复合物(TAT)可反映机体凝血酶的生存率和生存量,因而再选择 TAT、PAP 为凝血和纤溶的指标。本文着重探讨这些反映血栓前状态的分子标志物<sup>[4]</sup>能否作为糖尿病血瘀证的检测指标。

近 10 多年来在糖尿病血瘀证的研究中发现,该病的血瘀证发生率很高,为 52%~61%<sup>[5]</sup>,血瘀证的易患因素与慢性并发症相关<sup>[6]</sup>。中医气血理论亦证实糖尿病气虚、阴虚均可导致血瘀,且临床确诊的糖尿病患者大多病程较长,多伴有舌质紫暗、或有瘀斑、舌下静脉曲张、脉涩沉迟等征象,亦符合中医“久病必有瘀”的理论。中医研究还发现,糖尿病及其慢性并发症常存在临床不明显的血瘀证<sup>[6]</sup>。因此运用先进的现代医学实验检查来探讨血瘀证的本质和尽早发现不明显的血瘀证已显得十分重要。本研究选择上述反映血栓前状态的分子标志物作为糖尿病血瘀证的检测指标是由于血栓前状

态即为血液有形成分和无形成分的生物化学和血液流变学发生某些变化,从而使血液处于即利于发生,但又不一定发生血栓形成或血栓栓塞疾病的状态,故又称血栓前期或血液高凝状态,这似乎与血瘀证相仿。本实验结果亦阐明了糖尿病血瘀证与这些指标改变皆有关,证实了血小板活化、内皮细胞的受损、凝血纤溶的改变等皆参与了血瘀证的形成,亦是血瘀证产生的病理生理基础。提示血浆 GMP-140、ET、TAT、PAP 等亦可作为反映糖尿病血瘀证客观而敏感的指标。

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### 本刊征稿

《中医杂志》自开辟“病例讨论”栏目以来,深受读者欢迎。现继续征稿如下:(1)近年在病房里曾经讨论过的有西医明确诊断的病例。(2)病历记录完整。(3)在会诊时突出中医辨证施治的讨论(可以有不同看法),对提高读者临床辨证水平有一定启迪。(4)讨论中决定所用的治疗方法结果如何。最好有治疗前后化验等检查指标对比。(5)附有单位证明。来稿请寄北京市东直门内北新仓 18 号中医杂志社 9 号编辑收,邮编:100700。

## ABSTRACTS FROM ORIGINAL ARTICLES

### **Observation on Rate of Remission in 68 Cases of Acute Promyelocytic Leukemia Treated with All-trans-retinoic Acid Concerted with TCM Therapy**

*Han Xingzhe, Dong Zhe, Guo Shaoquan*

TCM principle of cooling blood and supporting resistance as a concerted therapy with all-trans-retinoic acid were applied in our hospital from 1992-1997 for 68 cases of promyelocytic leukemia. The rate of remission was 94.1% (in 64 cases) with a duration of remission lasting 35-49 days. No obvious toxic and side effects and complications were observed. The duration of remission in the treatment group was obviously shorter and the remission rate was obviously higher than those of the group treated with alone. The side effect of increasing leukocytes of which can also be ameliorated by the treatment.

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**Key words:** Leukemia promyelocytic acute/TCM therapy

(Original article on page 535)

### **Clinical Observation on 30 Cases of Asthenic-yang Type Aplastic Anemia Treated Mainly with Bushen Compound**

*Qiu Zhongchuan, Chen Pei, Wang Yunlu, et al.*

Thirty cases were treated. Of them, 2 were basically cure, 8 remitted, 14 remarkably ameliorated, 6 cases ineffective, the total effective rate being 80%. Changes in signs and symptoms revealed that the rate of amelioration was over 75%. After the therapy, the values of CD<sub>3</sub>, CD<sub>4</sub>, and CD<sub>4</sub>/CD<sub>8</sub> were all markedly increased, CD<sub>8</sub> markedly lowered with significant statistic difference ( $P < 0.05$ ), indicating that this method is an effective therapy for aplastic anemia.

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**Key words:** anemia aplastic/TCM therapy

(Original article on page 537)

### **Influence of Compound Salvia Injection on Cerebral Vascular Dynamics in Cerebral Infarction**

*Li Xiaohong, Guan Yuqing, Bing Shuli*

50 cases of early cerebral infarction were treated with

compound salvia injection and their CVA were examined before and after the treatment and compared with the control group. Results showed the changes of CVA indices in patient with early cerebral infarction were significantly different as compared with the control group ( $P < 0.05$  or  $P < 0.01$ ). All indices but DR in the treatment group after the treatment were all significantly changed ( $P < 0.05$  or  $P < 0.01$ ). Comparison of the 2 groups after treatment showed that Vmin, W, CP showed significant difference ( $P < 0.05$  or  $P < 0.01$ ). Conclusion: Early exam of CVA in cerebral infarction provide a basis for its diagnosis. This treatment accelerate the cerebral vascular circulation, improve the elasticity of vascular wall, and lower the blood viscosity.

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**Key words:** cerebral infarction/TCM therapy brain/blood injection of salviae/therapeutic action

(Original article on page 543)

### **Clinical Significance of Thrombo Molecular Markers in Blood-stasis Syndrome in Diabetes Mellitus**

*Shi Zhiyun, Shi Saizhu, Chen Jianqiu, et al.*

By applying the thrombo pre molecular markers, including plasmal GMP-140, tPA, PAI-I, TAT, PAP, ET, their correlation with blood stasis type diabetes were explored. Results showed that, the diabetic with blood-stasis type revealed the activation of platelets, injury of endothelial cells, changes of fibrinolysin. Their plasmal GMP-140, TAT, PAP, ET were all higher than that of the control group, indicating that the activation of platelets, injury of endothelial cells, and changes in the balance of blood coagulation/fibrinolysis are likely to benefit the incidence of blood stasis. The pathophysiological mechanism in blood stasis type diabetes is related to the changes in platelet, endothelial cells, blood coagulation and fibrinolysis.

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**Key words:** Diabetes mellitus/diagnosis blood stasis/diagnosis@thrombo molecular markers

(Original article on page 554)