

THE RELEVANCE OF PROTEIN C AND ANTITHROMBIN III IN DIABETES MELLITUS

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Received for Publication : 1/3/1992

INTRODUCTION

signs.

In addition to the classical risk factors for both arterial and venous thrombosis, the concept of molecular markers of hemostasis activation is now well recognized. Under physiological conditions, activation of certain pathways occurs to arrest local clots. During this process, various products of activation are released. Similarly, when pathological conditions exist, high levels of these various components may be produced and other pathways can then become activated (Meyer, 1985).

Several investigators suggested that a hypercoagulable state may associate diabetes mellitus (Uno et al., 1989). However, its pathogenesis is multifactorial including platelet dysfunction, vascular anomalies, coagulation factors, fibrinolytic system, natural coagulation inhibitors including protein C, antithrombin III activity. The later has been proved to be strongly related to hyperglycemia in diabetic patients (Ceriello et al., 1987).

Since the specific components in the circulation indicate the nature of prethrombotic or thrombotic event, define clinical conditions giving warning

Protein C-a vitamin k dependent zymogen - is considered a component of a complex anticoagulant pathway as well as a fibrinolytic agent (Mannucci, 1988). Its activation

MANSOURA MEDICAL JOURNAL

involves thrombin, thrombomodulin, females.

Ca⁺⁺, factor Va and VIII (Esman et al., 1985 and Clouse, 1986). Acquired defects of protein C might cause a thrombophilic state (Kernoff, 1989). In diabetic patients, several studies reported a deficiency in protein C antigen while others stated that it is a decreased functional activity despite its normal plasma concentration (Ceriello et al., 1990). These controversial opinions initiated us to further evaluate the protein C activity in diabetic patients particularly its clinical relevance in this common systemic disease

MATERIAL AND METHODS

This study comprised 18 diabetic patients, 12 males and 6 females with a mean age 37 ± 2.3 years and the duration of diabetes was 6.42 ± 10.8 years. All patients were under oral antidiabetic therapy. Ten healthy non diabetic subjects were investigated as a control group. They were 7 males and 3 females, their mean age was 30 ± 3.1 years for males and 27 ± 4.6 for

All patients and controls were subjected to the following investigations :

- * Routine clinical, haematological and serum biochemical investigations including glucose tolerance test.
- * Coagulation profile including bleeding time (BT), coagulation time (CT), prothrombin time (PT), APTT and thrombin time using the standard methods (Daci & Lewis, 1991).
- * Antithrombin III (AT III) Assay : using single radial immunodiffusion technique, Hobb's modification of the Mancini technique (Cederholm-Williams et al., 1981).
- * Protein C (PC) Assay : Using a coagulometric method modified from an assay of Kisiel (1979) and Francis & Patch (1983).

RESULTS

		BT min.	CT min.	PT min.	APTT min.	TT min.	AT III min.	PC activity % of norm.
Control (n :10)	Mean	2.12	6.75	12.75	26.66	11.16	0.289	87.33
	±SD	0.71	2.26	1.13	2.27	0.83	0.047	12.46
Diabetics (n :18)	Mean	2.22	7.92	14.26	32.64	11.08	0.19	67.26
	±SD	0.78	2.14	1.41	2.62	1.23	0.05	9.82
P		>0.05	>0.05	>0.05	<0.01	>0.05	<0.001	<0.001

DISCUSSION

It is well proved that diabeted mellitus is strongly associated with a hypercoagulability state with its consequence thrombophilic complications elsewhere in the body (Uno et al., 1989). Reduced PC plasma levels have been recently found in clinical conditions with in vivo activation of blood coagulation system (Griffin et al., 1982 and Mannucci & Vigano, 1982).

In the present study a highly significant reduction in PC activity was ob-

served in the diabetic group when compared to the control group. Moreover, a highly significant reduction in AT III concentration was also noticed in diabetics. The diminished PC activity may be attributed to the fact that PC activated by thrombin during the in vivo activation of the coagulation system is rapidly cleared from the circulation. This has been found to be in agreement with Mannucci & Vigano (1982). In diabetes mellitus, it is possible that hypercoagulability induces an increased turnover of PC, compensated for by a faster rate of synthesis of the inhibitor (Mannucci, 1983). On the

otherhand, fibrinopeptide A level is considered a good index of thrombin formation (Nossel, 1976), and an increase of fibrinopeptide A, directly related to abnormal glucose levels, has been reported in diabetics (Jones, 1985 and Ceriello et al., 1989) suggesting an enhanced thrombin formation related to hyperglycemia. Vukovich et al. (1986) and Cerillo et al. (1990) suggested that the reduction of PC in the circulation, resulting in an enhanced clearance from the blood. Interestingly, formation of activated PC has been demonstrated to be conditioned by AT III, through AT III-thrombin inhibition (Delvos, 1987). The existence of hyperglycemia dependent reduction of AT III biological activity in diabetes reported by ceriello (1987) and Marongiu (1991) who suggested that may be operative in supporting the formentioned suggestion.

SUMMARY AND CONCLUSIONS

Protein C-a natural coagulation inhibitor - is activated by thrombin. It cleaves off an NH₂ terminal activation peptide. Many investigators reported that PC has been incriminated in the hypercoagulability state in diabetic patients. This induced us to study PC activity and AT III concentration in this disease. We investigated 18 diabetic patients - on oral hypoglycemic therapy - for PC activity and AT III concentration and compared their results to those of 10 selected healthy control subjects. A highly significant reduction was found in both studied parameters in the diabetic group. These findings stress the major role of hyperglycemia in determining PC reduction in diabetics, and suggest that PC reduction is probably associated to hyperglycemia - enhanced thrombin formation.

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مدلول نشاط البروتين "س" ومضاد الثرومبين ٣ فى مرضى السكر

الملخص والاستنتاجات:

البروتين "س" هو أحد المثبطات الطبيعية للتجلط وينشط عن طريق الثرومبين ويؤدى إلى انشطار مجموعة الأمينو المنشطة للبتيد. وقد سجل كثير من الباحثين أن البروتين "س" له دور كبير فى زيادة التجلط فى مرضى السكر مما دفعنا إلى دراسة نشاط البروتين "س" ومضاد الثرومبين ٣ فى هذا المرض. وقد تم فحص ١٨ مريضاً بالسكر يعالجون عن طريق الأقراص بالفم وأجرى لهم نشاط البروتين "س" ومضاد الثرومبين ٣ وقورنت نتائجهم ١٠ أشخاص من الأصحاء كمجموعة ضابطة. وقد وجد أن هناك انخفاضاً ملحوظاً فى هذين الاختبارين فى مجموعة مرضى السكر مما يؤكد أدور الكبير لارتفاع السكر فى الدم فى انخفاض البروتين "س". وقد يعزى ذلك إلى ارتفاع السكر المنشط للثرومبين.

