Serum Thrombomodulin as a Marker of Diabetic Macroangiopathy

Serum thrombomodulin (TM), as a marker of injury to endothelial cells, is reported to increase in diabetic individuals with retinopathy (1), yet it is curious that there have been no reports on the relation of its level to diabetic macroangiopathy. We have recently reported the usefulness of the average thickness of the intimal plus medial complex of carotid artery (IMT), detected by ultrasonography as an index of diabetic macroangiopathy even in diabetic children (2,3).

To clarify whether serum TM can be used as a marker of progression of diabetic macroangiopathy, we studied the relationship between serum TM level and annual change in IMT in diabetic patients (n = 79; 71 non-insulin-dependent and 8 insulin-dependent; 47 males and 32 females). TM was measured enzyme-immunologically using diagnostic kits (TM Panacela, Fuji REBIO, Japan). IMT was measured by ultrasonography as previously described (2,3) and was monitored at 6-month intervals for 2.4 ± 0.7 (mean ± SD) years. The annual change in IMT was mathematically calculated from the estimated slope by means of the least square of variance method.

TM level was significantly related to duration of diabetes (r = 0.34, P < 0.01). At the start of the monitoring, we measured TM level and divided diabetic patients into two groups: one with high (>4.5 ng/ml, mean + 2 SDs of normal controls) TM level (n = 22, 6.2 ± 2.7 ng/ml) and another with normal TM level (<4.5 ng/ml; n = 12, 3.1 ± 0.7 ng/ml). The diabetic patients with high TM levels showed a significantly greater annual change in IMT than did diabetic patients with normal TM levels (0.29 ± 0.28 vs. 0.09 ± 0.09 mm/year, P = 0.0029).

Table 1—*Patient characteristics*

	Normal TM group	High TM group	*P* value
Age (years)	60.6 ± 12.3	65.5 ± 9.5	—
Sex (M/F)	35/22	12/10	—
TM (ng/ml)	3.06 ± 0.68	6.19 ± 2.70	<0.005
IMT at initial examination (mm)	1.32 ± 0.43	1.61 ± 0.66	—
Diabetes duration (years)	12.8 ± 7.3	22.4 ± 9.2	<0.005
Body mass index (kg/m^2)	23.1 ± 3.1	22.0 ± 4.0	—
Smoking (cigarettes/day)	8.8 ± 18.9	4.9 ± 10.0	—
Systolic blood pressure (mmHg)	131.6 ± 14.5	144.9 ± 11.9	<0.005
Diastolic blood pressure (mmHg)	74.9 ± 8.1	72.6 ± 8.7	—
Serum creatine (mg/dl)	0.82 ± 0.17	0.98 ± 0.38	—
UN (mg/dl)	17.5 ± 4.0	20.2 ± 6.4	—
HbA_{1c} (%)	8.50 ± 1.44	8.71 ± 1.34	—
Total cholesterol (mg/dl)	209.0 ± 34.2	199.0 ± 23.8	—
Retinopathy	(39/14/4)	(2/7/13)	<0.001
Nephropathy (1/2/3)#	(47/5/5)	(11/8/3)	<0.05
Antiplatelet drug (off/on)	35/22	10/22	—

Data are means ± SD. Members of the normal TM group had TM levels ≤4.5 ng/ml, and members of the high TM group had TM levels >4.5 ng/ml. For retinopathy, the units are nondiabetic/simple diabetic/preproliferative and proliferative diabetic retinopathy.

Moreover, after the duration was matched between the two groups, we confirmed that annual change in IMT is still greater in those with high TM levels, as before. At the start of the monitoring, diabetic patients with high TM levels showed a slightly but not significantly thicker IMT than diabetic patients with normal TM levels (1.61 ± 0.66 vs. 1.32 ± 0.43 mm, P > 0.05). The diabetic patients with high TM levels showed significantly advanced diabetic retinopathy and nephropathy compared with patients with normal TM; however, their laboratory data, such as serum lipid level and HbA_{1c} level, showed no significant differences. No differences in smoking habits were found between the groups. Our results suggest that serum TM level can be a marker of progression of diabetic macroangiopathy as well as microangiopathy.

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