

## 폐경전 여성과 폐경후 여성에서 혈전 형성 및 용해인자의 차이

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= Abstract =

### The Difference of Thrombogenic and Fibrinolytic Factors in Premenopausal and Menopausal Women

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**Background** : Thrombotic and fibrinolytic factors which change in women following menopause, may be of pathogenetic importance in atherogenetic and thrombotic cardiovascular diseases by altering fibrinolysis on vascular surfaces. We investigated whether parameters of thrombosis and fibrinolysis were different before and after menopause.

**Methods** : Thrombotic factors such as plasma plasminogen activator inhibitor type 1(PAI-1), fibrinogen,  $\alpha_2$ -antiplasmin, lipoprotein(a) were measured. In addition, fibrinolytic factors such as plasma tissue-type plasminogen activator(t-PA), plasminogen, antithrombin-III were also assessed in 41 premenopausal women, 174 menopausal women and 201 men.

**Results** : PAI-1 and fibrinogen and t-PA were significantly higher in menopausal women than in premenopausal women( $13.1 \pm 6.6$  vs  $16.9 \pm 9.5$ ng/ml,  $p=0.046$ ,  $293.6 \pm 83.3$  vs  $347.5 \pm 256.9$ mg/dl,  $p=0.001$ ,  $10.1 \pm 4.4$  vs  $12.5 \pm 5.6$ ng/ml,  $p=0.003$ ). A positive significant correlation was found between PAI-1 and t-PA levels( $r=0.444$ ,  $p=0.003$ ), but there were no significant relationship between PAI-1 and any other thrombogenic and fibrinolytic factors.

**Conclusion** : PAI-1, fibrinogen, t-PA were higher in menopausal women than in premenopausal women. The findings suggest that increase of atherosclerotic and thrombotic cardiovascular diseases after menopause may be influenced by these changes.

**KEY WORDS** : PAI-1 · Fibrinogen · t-PA · Menopause.

서 론

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가



t-PA가 (12.1 ± 4.9 vs 13.3 ± 5.6ng/ml, p=0.018),  
 $\alpha$ 2-antiplasmin (337.4 ± 235.2 vs 303.2 ± 294.8ng/ml, p=0.011, 98.0 ± 10.1 vs 96.1 ± 13.4ug/ml, p=0.03), PAI-1, plasminogen, AT-III, Lp(a)  
 (Table 1, Fig. 1).

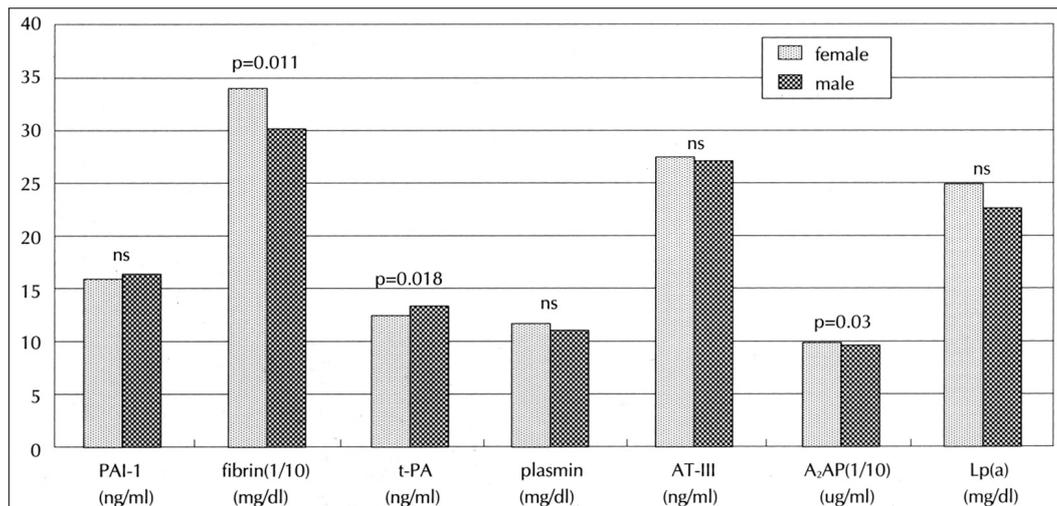
2. 여성에서 폐경에 따른 혈전형성 촉진인자 및 용해인자 변화

PAI-1, t-PA (13.1 ± 6.6 vs 16.9 ± 9.5ng/ml p value, 293.6 ± 83.3 vs 347.5 ± 256.9mg/dl p value)

**Table 1.** Thrombogenic and fibrinolytic parameter by SEX

	Female (n=215)	Male (n=215)	p-value (n=215)
PAI-1 (ng/ml)	16.2 ± 9.2	16.9 ± 9.9	0.569
t-PA (ng/ml)	12.1 ± 4.9	13.3 ± 5.6	0.018
Fibrinogen (mg/dl)	337.4 ± 235.2	303.2 ± 294.8	0.011
Plasminogen (mg/dl)	11.5 ± 2.3	11.1 ± 2.3	0.079
AT-III (ng/ml)	27.5 ± 5.7	27.3 ± 5.6	0.612
A <sub>2</sub> AP (ug/ml)	98 ± 10.1	96.1 ± 13.4	0.03
Lp(a) (mg/dl)	24.9 ± 23.4	22.7 ± 21.6	0.570

A<sub>2</sub>AP : alpha 2 antiplasmin



**Fig. 1.** Differences of thrombogenic and fibrinolytic parameters between female and male. Fibrin : fibrinogen, plasmin : plasminogen, AT-III : antithrombin III, A<sub>2</sub>AP : alpha 2 antiplasmin, Lp(a) : lipoprotein(a), ns : not significant

가 (10.1 ± 4.4 vs 12.5 ± 5.6ng/ml p value, Table 2, Fig. 2).

3. 같은 연령대 성별에 따른 혈전형성 촉진인자 및 용해인자 변화

49

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(Table 3),

50

t-PA가

(Table 4).

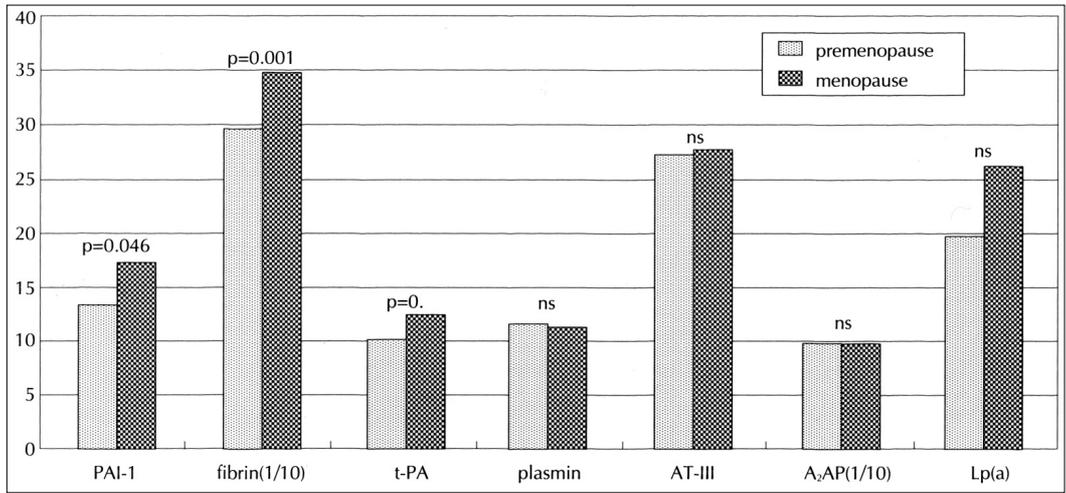
4. PAI-1과 다른 혈전형성 촉진인자 및 용해인자간의 상관관계

PAI-1 t-PA

,  $\alpha$ 2-antiplasmin, Lp(a), plasminogen, ant-

**Table 2.** Differences of thrombogenic and fibrinolytic parameters in premenopausal and menopausal women

	Premenopause (n=41)	Postmenopause (n=174)	p-value
PAI-1	13.1 ± 9.2	16.9 ± 9.5	0.046
t-PA	10.1 ± 4.4	12.5 ± 5.6	0.003
Fibrinogen	293.6 ± 83.3	347.5 ± 256.9	0.001
Plasminogen	11.6 ± 1.8	11.4 ± 2.4	0.704
AT-III	27.2 ± 3.8	27.6 ± 6	0.43
A <sub>2</sub> AP	97.9 ± 11.1	98.1 ± 9.9	0.372
Lp(a)	19.7 ± 19.4	26.1 ± 24.2	0.227



**Fig. 2.** Differences of thrombogenic and fibrinolytic parameters between premenopausal and menopausal women. Fibrin : fibrinogen, plasmin : plasminogen, AT-III : antithrombin IA<sub>2</sub>AP : alpha 2 antiplasmin, Lp(a) : lipoprotein(a), ns : not significant

**Table 3.** Sexual difference of fibrinolytic parameters before fifty-year old age

	Female (n=42)	Male (n=55)	p-value
PAI-1	13.1 ± 7	17.9 ± 12.1	0.501
t-PA	10.1 ± 4.4	12.2 ± 6.2	0.11
Fibrinogen	279.3 ± 103	275.8 ± 68.4	0.501
Plasminogen	11.5 ± 2.3	11.1 ± 2.3	0.079
AT-III	27.5 ± 5.7	27.3 ± 5.6	0.612
A <sub>2</sub> AP	97.9 ± 11.1	96.5 ± 14.8	0.177
Lp(a)	24.9 ± 23.4	22.7 ± 21.6	0.57

**Table 4.** Sexual difference of fibrinolytic parameters after fifty-year old age

	Female (n=173)	Male (n=146)	p-value
PAI-1	16.9 ± 9.5	16.5 ± 9.2	0.501
t-PA	12.5 ± 4.9	13.8 ± 5.2	0.033
Fibrinogen	347.5 ± 256.9	317.9 ± 92.9	0.155
Plasminogen	11.4 ± 2.4	11.1 ± 2.3	0.079
AT-III	27.6 ± 6	27.1 ± 5.8	0.612
A <sub>2</sub> AP	98.1 ± 9.9	96.6 ± 9.8	0.069
Lp(a)	26.1 ± 24.2	23.1 ± 22.5	0.341

**Table 5.** Correlation coefficient between PAI-1 and throm-bosis-lysis profiles

	r-value	p-value
t-PA	0.444	0.00316
Fibrinogen	0.035	0.488
Plasminogen	-0.0072	0.889
AT	-0.086	0.0934
A <sub>2</sub> -AP	-0.009	0.858
Lp(a)	-0.083	0.101

thrombin III

(Table 5).

고 안

가

(HDL)  
 가 2) (LDL) 3)  
 가 가  
 , , 14-16)  
 가 5,6)  
 (foam cell)  
 7,8,17)  
 nitric oxide(NO)  
 18),  
 (antioxidant) 가 19)

(thromboembolic diseases)  
<sup>20,21)</sup> .  
 가 . Gram 340 t - PA antigen 가 t -  
 PA 가 , t - PA 가 35)  
 t - PA PAI - 1 가  
 tPA - PAI complex 가 . Jan -  
 , plaminogen activator inhibi -  
 tor - type(PAI - 1), <sub>2</sub> - antiplasmin sson <sup>36)</sup> t - PA 가  
 ,  
 tissue - type plasminogen activator(t - PA) ,  
 plasminogen, antith - rombin - III, Lp(a) Study cohort Ridker <sup>37)</sup> Physians ' Health 가  
 ,  
 . Thompson <sup>38)</sup> Ridker  
 .  
<sup>22,23)</sup> PAI - 1 t - PA antigen  
 8 ~10 가 .  
 . PAI - 1가 t - PA  
 t - PA antigen 가  
 12 ,  
 9 -9 30 . PAI - 1 t - PA 가 가  
 t - 가 가  
 PA , PAI - 1 가 가 .  
 1 ~4 trisodium 10  
 citrate EDTA <sup>24,25)</sup> <sup>39,40)</sup>  
 pH  
 5.9 PAI - 1/t - PA <sup>41 - 43)</sup>  
 fibrinolytic system component  
 가 pH가 .  
 citrate - based co -  
 llection tube(pH 4.5)(Stabilyte tubes Biopool™,  
 Sweden) .  
 PAI - 1 data Caerphilly and Speedwell <sup>44)</sup>  
<sup>26)</sup> 가  
 PAI - 1 <sup>27,28)</sup> PAI - 1 <sup>45)</sup>  
<sup>29)</sup> megakaryocyte <sup>30)</sup> 가 .  
 - granule <sup>31)</sup> 가 가  
 PAI - 1 fibrin <sup>46,47)</sup> .  
 t - PA t - PA . 50  
<sup>32,33)</sup> t - PA .

가 , 2 - antiplasmin, lipoprotein(a)  
 t - PA, plasminogen, antithrombin  
 가  
 PAI - 1 , t - PA ,  
 가  
 가  
 Lp(a)  
 19.7mg/dl 26.1mg/dl  
 가  
 2 - antiplasmin  
 가

결 과 :  
 1) PAI - 1 t - PA 가 (13.1 ± 6.6 vs 16.9 ± 9.5ng/ml, 293.6 ± 83.3 vs 347.5 ± 256.9mg/dl, 10.1 ± 4.4 vs 12.5 ± 5.6ng/ml).  
 2) PAI - 1 t - PA parameter (r=0.444, p=0.0316) (r=0.0072 0.086).

결 론 :  
 PAI - 1  
 t - PA 가 ,  
 가

**References**

- 1) Tracey RP, Bovill EG : *Thrombosis and cardiovascular risk in the elderly. Arch Pathol Lab Med* 116 : 1307, 1992
- 2) Tikkanen MJ, Nikkila EA, Kuusi T, Sipinen SU : *High-density lipoprotein-2 and hepatic lipase : Reciprocal changes produced by oestrogen and norgestrel. J Clin Endocrinol Metab* 54 : 1113-1117, 1982
- 3) Godstrand IF, Wynn V, Crook D, Miller NE : *Sex, plasma lipoproteins, and atherosclerosis : Prevailing assumptions and outstanding questions. Am Heart J* 114 : 1468-1503, 1987
- 4) Bailey CJ, Ahmed-Sorour H : *Role of ovarian hormones in the long-term control of glucose homeostasis. Effects of insulin secretion. Diabetologia* 19 : 475-481, 1980
- 5) Goldman JA, Ovadia JL : *The effect of estrogen on intravenous glucose tolerance in women. Am J Obstet Gynecol* 103 : 172-178, 1969
- 6) uotola H, Pyorala T, Loikkanen M : *Effects of natural oestrogen/progestogen substitution therapy on carbohydrate and lipid metabolism in postmenopausal women. Maturitas* 8 : 245-253, 1986
- 7) Beldekas JC, Smith B, Gerstenfeld LC, Sonenshein GE, Franzblau C : *Effects of 17 betaoestradiol on the biosynthesis of collagen in cultured bovine aortic smooth muscle cells. Biochemistry* 20 : 2162-2167, 1981
- 8) Cheng LP, Kuwahara M, Jacobsson J, Foegh ML : *Inhibition of myointimal hyperplasia and macrophage infiltration by oestradiol in aorta allografts. Transplantation* 52 : 967-972, 1991
- 9) Folsom AR, Qamhieh HT, Flack JM, et al : *For the*

가  
 PAI - 1, t - PA 가  
 가  
 요 약

연구배경 :  
 tissue - type plasminogen activator(t - PA)  
 plasminogen activator inhibitor type 1(PAI - 1)

PAI - 1 가 t - PA urokinase type - PA

연구방법 :  
 416 [ : =201 : 215( 41 ,  
 174 ), 55.7 ± 12.1 , 57.4 ± 10.1  
 ] PAI - 1,

- investigators of the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Plasma 섬유소원 : levels and correlates in young adults. *Am J Epidemiol* 138 : 1023-1036, 1993
- 10) Gebara OCE, Mittleman MA, Sutherland P, et al : Association between increased estrogen status and increased fibrinolytic potential in the Framingham Offspring Study. *Circulation* 91 : 1952-1958, 1995
  - 11) Moon TE : Estrogen and disease prevention. *Editorial. Arch Intern Med* 151 : 17-18, 1991
  - 12) Folsom AR, Wu KK, Davis CE, Conlan MG, Sorlie PD, Szklo M : Population correlates of plasma fibrinogen and factor VII, putative cardiovascular risk factors. *Atherosclerosis* 91 : 191-205, 1991
  - 13) Lee AJ, Smith WCS, Lowe GDO, Tunstall-Pedoe H : Plasma 섬유소원 and coronary risk factors : the Scottish Heart Health Study. *J Clin Epidemiol* 43 : 913-919, 1990
  - 14) Slater EE : Insulin resistance and hypertension. *Hypertension* 18 (suppl 1) : I-108-I-114, 1991
  - 15) Porte D Jr : Beta-cells in type II diabetes mellitus. *Diabetes* 40 : 166-80, 1991
  - 16) Stout RW : Overview of the association between insulin and atherosclerosis. *Metabolism* 34 : suppl 1 : 7-12, 1985
  - 17) Williams JK, Adams MR, Klopfenstein HS : Oestrogen modulates responses of atherosclerotic coronary arteries. *Circulation* 81 : 1680-1687, 1990
  - 18) Weiner CP, Lizasoain I, Baylis SA, Knowles RG, Charles IG, Moncada S : Induction of calcium-dependent nitric oxide synthases by sex hormones. *Proc Natl Acad Sci USA* 91 : 5212-5216, 1994
  - 19) Sack MN, Rader DJ, Cannon RO III : Oestrogen and inhibition of oxidation of low-density lipoproteins in postmenopausal women. *Lancet* 343 : 269-270, 1994
  - 20) Francis RB, Kawashishi D, Baruchi T, et al : Impaired fibrinolysis in coronary artery disease. *Am Heart J* 115 : 776-780, 1988
  - 21) Meade TW, Mellows S, Brozovic M, et al : Haemostatic function and ischaemic heart disease : Principal results of the Northwick Park Heart Study. *Lancet* ii.533-537, 1986
  - 22) Paramo JA, Colucci M, Collen D, et al : Plasminogen activator inhibitor activity and other fibrinolytic variables in patients with coronary artery disease. *BMJ* 291 : 575-576, 1985
  - 23) Grimaudo V, Hauert J, Bachmann F, Kruithof EKO : Diurnal variation of the fibrinolytic system. *Thromb Haemost* 59 : 495, 1988
  - 24) Angleton P, Chandler WL, Schmer G : Diurnal variation of tissue-type plasminogen activator and its rapid inhibitor (PAI-1). *Circulation* 79 : 101, 1989
  - 25) Ranby M, Sundelb, Nilsson TK : Blood collection in strong acidic citrate anticoagulant used in a study of dietary influence on basal tPA activity. *Thromb Haemost* 62 : 917, 1989
  - 26) Meijer P, Boon R, Jie AFH, Rosen S, Kluft C : Bioimmunoassay for tissue-type plasminogen activator (tPA) in human plasma : Evaluation of blood sampling and handling procedures and comparison with other tPA activity methods. *Fibrinolysis* 6 (Suppl 3) : 99, 1992
  - 27) Aznar J, Estelles A : Role of plasminogen activator inhibitor type 1 in the pathogenesis of coronary artery disease. *Hemostasis* 24 : 243-251, 1994
  - 28) Hamsten A, Wiman B, de Faire U, et al : Increased plasma levels of rapid inhibitor of tissue plasminogen activator in young survivors of myocardial infarction. *N Engl J Med* 313 : 1557-1563, 1985
  - 29) Ihnken K, Speiser W, Ruf W, Thiel W, Schlepfer M, Muller-Berghaus G : High PAI activity with correlation to triglyceride and HDL cholesterol values in patients with coronary artery disease with no difference in survivors of myocardial infarction. *Ann Hematol* 67 (5) : 237-244, 1993
  - 30) Sawdey MS, Loskutoff DJ : Regulation of murine type I plasminogen activator inhibitor gene expression in vivo : tissue specificity and induction by lipopolysaccharide, tumor necrosis factor-alpha, and transforming growth factor-beta. *J Clin Invest* 88 : 1346-1353, 1991
  - 31) Konkle BA, Schick PK, He X, Liu RJ, Mazur EM : Plasminogen activator inhibitor-1 is present in human platelets and is produced in the megakaryoblastic cell line. *Thromb Haemost* 69 : 547, 1993. Abstract
  - 32) Erickson LA, Ginsburg MH, Loskutoff DJ : Detection and partial characterization of an inhibitor of plasminogen activator in human platelets. *J Clin Invest* 74 : 1465-1472, 1984
  - 33) Wagner OF, de Vries C, Hohmann C, Veerman H, Pannekoek H : Interaction between plasminogen activator inhibitor-1 (PAI-1) bound to fibrin and either tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA). *J Clin Invest* 84 : 647-657, 1989
  - 34) Reilly FR, Hutzelmann JE : Plasminogen activator inhibitor-1 binds to fibrin and inhibits tissue-type plasminogen activator-mediated fibrin dissolution. *J Biol Chem* 267 : 17128-17135, 1992
  - 35) Gram J, Jespersen J : A selective depression of tissue-type plasminogen activator (t-PA) in euglobulin characterizes a risk group among survivors of myocardial infarction. *Thromb Haemost* 57 : 137-139, 1987
  - 36) Munkvad S, Gram J, Jespersen J : A depression of active tissue-type plasminogen activator in plasma characterizes patients with unstable angina pectoris who develop myocardial infarction. *Eur Heart J* 11 : 525-528, 1990
  - 37) Jansson JH, Nilsson TK, Olofsson BO : Tissue plasminogen activator and other risk factors of cardiovascular disease in patients with severe angina pectoris. *Eur Heart J* 12 : 157-161, 1991
  - 38) Ridker PM, Vaughan DE, Stampfer MJ, et al : Endogenous tissue-type plasminogen activator and risk of myoc-

- ardial infarction. *Lancet* 341 : 1165-1168, 1993
- 39) Thompson SG, Kienast J, Pyke SDM, et al : *For the ECAT Angina Pectoris Study : Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. N Eng J Med* 332 : 635-641, 1995
- 40) Wilhelmsen L, Svardsudd K, Korsan-Bengtson K, et al : *Fibrinogen as a risk factor for stroke and myocardial infarction. N Engl J Med* 311 : 501-505, 1984
- 41) Ernst E, Resch KL : *Fibrinogen as a cardiovascular risk factor : A meta-analysis and review of the literature. Ann Intern Med* 118 : 956-963, 1993
- 42) Lee AJ, Lowe GDO, Woodward M, Tunstall-Pedoe H : *Fibrinogen in relation to personal history of prevalent hypertension, diabetes, stroke, intermittent claudication, coronary heart disease and family history : the Scottish Heart Health Study. Br Heart J* 69 : 338-42, 1993
- 43) Qizilbash N, Jones L, Warlow C, Mann J : *Fibrinogen and lipid concentrations as risk factors for transient ischaemic attacks and minor ischaemic strokes. BMJ* 303 : 605-9, 1991
- 44) Ernst E, Resch KL : *Fibrinogen as a cardiovascular risk factor : a metaanalysis and review of the literature. Ann Intern Med* 118 : 956-63, 1993
- 45) Sweetnam PM, Thomas HF, Yarnell WG, Beswick AD, Baker IA, Elwood PC : *Fibrogen, viscosity and 10-year incidence of ischemic heart disease. Eur Heart J* 17 : 1814-1820, 1996
- 46) Meade TW, Vickers MV, Thompson SG, et al : *Epidemiological characteristics of platelet aggregability. BMJ* 290 : 428-32, 1985
- 47) Krobot K, Hense HW, Cremer P, Eberle E, Keil U : *Determinants of plasma fibrinogen : relation to body weight, waist-to-hip ratio, smoking, alcohol, age, and sex : results from the Second MONICA Augsburg Survey 1989-90. Arterioscler Thromb* 12 : 780-8, 1992
- 48) Balleisen L, Bailey J, Epping PH, Schulte H, van de Loo J : *Epidemiological study on factor VII, factor VIII and fibrinogen in an industrial population. I. Baseline data on the relation to age, gender, bodyweight, smoking, alcohol, pillusing, and menopause. Thromb Haemost* 54 : 475-9, 1985