Original Article

Association of Polymorphism of Estrogen Receptor-α Gene with Circulating Levels of Adiponectin in Postmenopausal Women with Type 2 Diabetes

Rie Yoshihara[1], Kazunori Utsunomiya[1], Atsushi Gojo[1], Sho Ishizawa[1], Yasushi Kanazawa[1], Keiichiro Matoba[1], Kanta Taniguchi[1], Tamotsu Yokota[1], Hideaki Kurata[1], Jun-ichi Yokoyama[1], Mitsuyoshi Urashima[2], and Naoko Tajima[1]

[1]Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan
[2]Division of Clinical Research and Development, Jikei University School of Medicine, Tokyo, Japan

***Aim*: Menopause is a risk factor for cardiovascular disease (CVD) in women because of the reduction in endogenous estrogen. Recently, single nucleotide polymorphisms (SNPs) of the estrogen receptor α (ESR-1) gene (c.454-397T>C) associated with the prognosis of myocardial infarction in postmenopausal women were identified; however, the mechanism by which genetic variation of ESR-1 contributes to the pathogenesis of CVD is unknown. Circulating levels of adipokines and inflammatory cytokines predict CVD risk; hence, this study aimed to investigate whether ESR-1 genotypes (c.454-397T>C) might influence circulating levels of adipokines and inflammatory cytokines in postmenopausal women with type 2 diabetes.**
***Methods*: Sixty-three postmenopausal women with type 2 diabetes were recruited. Serum levels of adiponectin, resistin, interleukin-6 (IL-6), and high-sensitive C-reactive protein (hs-CRP) were determined.**
***Results*: The genotype of ESR-1 was closely associated with serum adiponectin, which was decreased in subjects with the T allele and was lowest in those with the T/T genotype. Multiple logistic regression analysis revealed independent contribution of the homozygote for the T allele to low serum levels of adiponectin.**
***Conclusion*: The T allele of the c.454-397T>C SNP of ESR-1 is associated with low serum levels of adiponectin, which may lead to a high risk of CVD in postmenopausal women.**

J Atheroscler Thromb, 2009; 16:250-255.

Key words; Estrogen, Adiponectin, Diabetes, SNP, Atherosclerosis

Introduction

It is well known that the incidence of cardiovascular disease (CVD) is lower in women than men because of the protective effect of estrogen on atherosclerosis, and menopause is risk factor of CVD in women. On the other hand, the increased relative risk of CVD associated with diabetes is greater in women than in men[1, 2], indicating that the role of estrogen in the pathogenesis of diabetic vascular disease is complicated. The effects of estradiol on vascular lineage cells are mediated via two different receptors, estrogen receptor (ER)-α and -β. Recently, single nucleotide polymorphisms (SNPs) of the estrogen receptor-α gene (ESR-1) (c.454-397T>C, also known as the PvuII polymorphism) associated with the prognosis of myocardial infarction in women were identified[3, 4]; however, the underlying mechanism whereby these genetic variations in ESR-1 contribute to the risk of myocar-

Address for correspondence: Kazunori Utsunomiya, Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Jikei University School of Medicine, 3-25-8 Nishi-shinbashi, Minato-ku, Tokyo 105-8461, Japan
E-mail: kazu-utsunomiya@jikei.ac.jp
Received: September 7, 2008
Accepted for publication: December 10, 2008

dial infarction in women is unknown.

A series of recent investigations have revealed that adipokines and inflammatory mediators secreted by visceral adipose tissue profoundly contribute to the pathogenesis of insulin resistance and atherosclerosis, and that circulating levels of adipokines, especially adiponectin and resistin, predict the development of CVD[5, 6]. Circulating levels of these adipokines become more proatherogenic during menopause[7], and low serum adiponectin is a risk of CVD in postmenopausal women with diabetes[8]. Hence, this study aimed to investigate whether ESR-1 genotypes might influence circulating levels of these adipokines and inflammatory mediators in postmenopausal women with type 2 diabetes.

Material and methods

Subjects and Determination of Genotype

Sixty-three postmenopausal women with type 2 diabetes but no diabetic renal complication, identified as having elevated serum creatinine or proteinuria, were recruited. Patients taking thiazolidinedione were excluded. Serum levels of the following parameters were determined: adiponectin by enzyme-linked immunosorbent assay (ELISA) (Otsuka Assay, Tokushima, Japan), resistin by ELISA (BioVender Laboratory Medicine, Brno, Czech Republic), interleukin-6 (IL-6) by chemiluminescent enzyme immunoassay (CLEIA) (Fujirebio, Tokyo, Japan), and high-sensitive C-reactive protein (hs-CRP) by ELISA (Date Behring, Marburg, Germany). DNA extracted from white blood cells was used to characterize ER-α genotypes. All subjects were genotyped for the c.454-397T>C (rs2234693) polymorphism using the sequence-specific primer cycle elongation and fluorescence correlation spectroscopy (SSPCE-FCS) method described elsewhere[9]. SSPCE primers were designed by NovusGene (for details, see http//www.novusgene.co.jp) as follows: GAGTTCCAAATGTCCCAGCT for 5' labeling by TARMA and GTTCCAAATGTCCCAGCC for 5' labeling by Cy5. This study was approved by the Institutional Review Board of Jikei University School of Medicine and all subjects gave written informed consent.

Statistical Analysis

Correlation between parameters was evaluated by Spearman's rank test. To avoid a type 1 error due to multiple testing, genotype associations with other parameters (resistin, hs-CRP, IL-6, body mass index, adiponectin, hemoglobin A1c) were determined by a permutation test, where the distribution of maximum t statistics based on 100,000 random permutations was compared with the observed values to determine the p value and its 95% confidence interval for each gene. Multiple logistic regression analysis was performed to determine factors independently contributing to serum levels of adiponectin. For all statistical analysis, Stata 8.0 (Stata Corp. College Station, TX) was used and $p<0.05$ was considered significant.

Table 1. Demographic characteristics of patients

	Mean	S.D.
Age (years)	63.2	6.1
Postmenopausal age (years)	49.8	5.1
BMI (kg/m^2)	23.9	3.4
HbA1c (%)	7.4	1.0
Adiponectin (μg/mL)	11.5	6.8
hs-CRP (ng/mL)	705.5	737.2
IL-6 (pg/mL)	1.2	0.6
Resistin (ng/mL)	3.5	1.9
Treatment (n)		
No medication	3	
OHA	35	
Insulin therapy	25	

BMI: body mass index, hs-CRP: high-sensitive CRP, IL-6: interleukin-6, OHA: oral hypoglycemic agents

Results

Demographic characteristics of the patients are presented in **Table 1**. Serum levels of adiponectin showed a significant negative correlation with body mass index (BMI) ($p=0.048$, $r=-0.30$) (**Fig. 1**). Resistin showed a significant positive correlation with IL-6 ($p=0.031$, $r=0.32$) (**Fig. 2**), but not with BMI. There was no significant correlation between serum levels of adiponectin and resistin.

Changes in variables according to each genotype of ESR-1 are shown in **Table 2**. The incidence of each genotype of c.454-397T>C SNP was T/T 32%, T/C 55% and C/C 13%, respectively. There was no difference in BMI, hemoglobin A1c (HbA1c) or age among the 3 genotypes. Serum levels of adiponectin were decreased in the patients with T allele and were significantly lower in patients with T/T genotype than in those with other genotypes (T/C+C/C). These genotypes showed no association with serum levels of resistin, IL-6 or hs-CRP.

Consequently, the contribution of T/T genotype to serum levels of adiponectin was investigated by multiple logistic regression analysis. Because the median value of serum adiponectin of the patients in this study was 9.6 μg/mL, we identified patients with serum

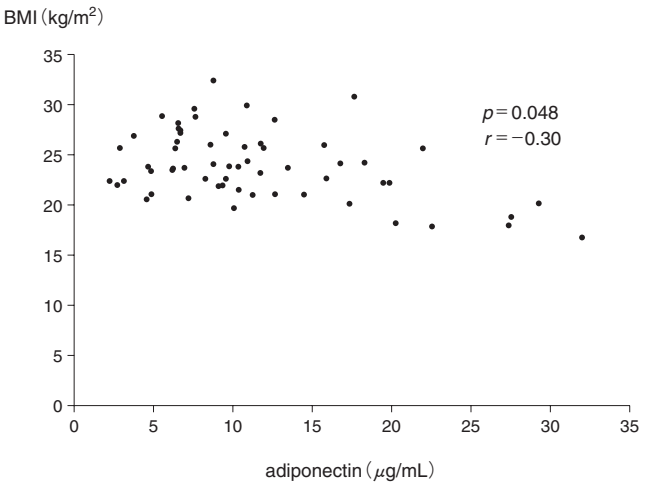

Fig. 1. Relationship between serum levels of adiponectin and BMI

BMI: body mass index

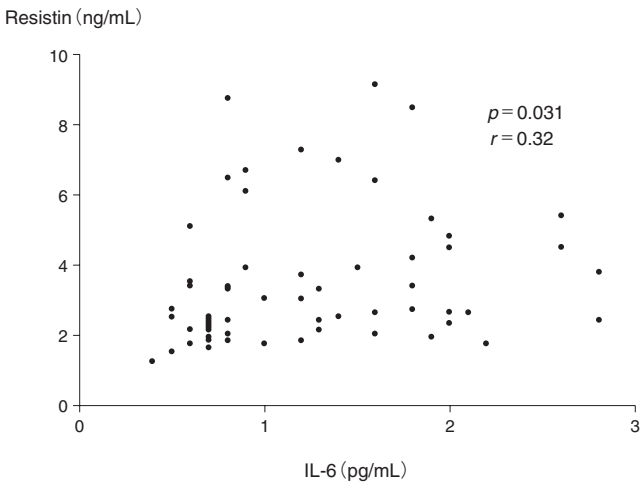

Fig. 2. Relationship between serum levels of resistin and IL-6

IL-6: interleukin-6

Table 2. Genotype of ESR-1 and clinical parameters

	T/T (n=20)	T/C (n=35)	C/C (n=8)	p value	95%CI of p value
Age (years)	63.7±6.7	63.1±5.8	63.0±6.8	0.663	0.660–0.666
BMI (kg/m^2)	23.9±3.6	23.9±3.3	24.0±4.0	0.951	0.950–0.952
HbA1c (%)	7.2±1.0	7.4±0.9	7.6±1.6	0.443	0.440–0.446
Adiponectin (μg/mL)	9.1±6.1	12.3±7.2	14.5±5.1	0.019	0.018–0.020
hs-CRP (ng/mL)	712±781	726±787	599±372	0.667	0.664–0.670
IL-6 (pg/mL)	1.2±0.6	1.3±0.6	1.2±0.7	0.716	0.713–0.718
Resistin (ng/mL)	3.1±1.8	3.5±1.9	4.8±2.1	0.211	0.209–0.214

Figures are expressed as the mean±S.D. *P* values denote comparison between T/T and T/C+C/C.
CI: confidence interval, BMI: body mass index, hs-CRP: high-sensitive CRP, IL-6: interleukin-6

Table 3. Multiple logistic regression analysis for independent contributors to low serum levels of adiponectin

	Odds Ratio	Standard Erorr	p value	95%CI
T/T genotype	5.80	4.10	0.013	1.446–23.245
BMI (kg/m^2)	1.28	0.13	0.013	1.054–1.560
Age (years)	0.96	0.05	0.417	0.870–1.059
Postmenopausal age (years)	0.92	0.06	0.172	0.870–1.059

BMI: body mass index, CI: confidence interval

adiponectin ≤10 μg/mL (n=33) as having low circulating levels of adiponectin, and examined the factors independently involved in low circulating levels of adiponectin as shown in **Table 3**. T/T genotype was an independent contributor to low circulating levels of adiponectin besides BMI.

Discussion

Various anti-atherosclerotic effects of estrogen on vascular cells are believed to be mediated mainly by estrogen receptor (ER)-α, which binds estradiol and regulates gene expression by acting as a transcription factor[10]. Menopause is a risk of CVD in women, exacerbating the known cardiovascular risk factors,

including hypertension, dyslipidemia and insulin resistance[11, 12]. ESR-1 SNP, c.454-397T>C (rs2234693, or PvuII polymorphism), is recognized as a marker that identifies the risk of CVD in women[3, 4]; however, the investigators were not able to explain this effect by changes in the known CVD risk factors[3], and the mechanism whereby this SNP is involved in the progression of CVD is still unknown.

Visceral adipose tissue produces tissue-specific adipokines and inflammatory cytokines[13, 14]. Both adipokines and inflammatory cytokines are implicated in obesity-associated inflammation, insulin resistance and, consequently, atherosclerosis. Of adipokines, adiponectin plays an important role in the regulation of insulin action via its own receptors in the liver and muscle[15]. Adiponectin has anti-atherosclerotic action on endothelial cells and vascular muscle cells[16, 17]. Thus, low circulating levels of adiponectin could be a risk factor for developing type 2 diabetes[18, 19] and CVD[5, 20]. In contrast, resistin causes insulin resistance[21] and shows proatherogenic properties[16, 22]. Circulating levels of resistin are closely associated with the severity of CVD[23, 24]. In addition to these adipokines, obesity-associated induction of adipose IL-6 production stimulates the liver to secrete CRP, which is not only prognostic for the development of CVD, but also for the risk of type 2 diabetes[25, 26]. The present study investigated a possible contribution of the specific ESR-1 SNP to circulating levels of these cytokines.

In this study, serum levels of adiponectin correlated significantly with BMI, as is already known (**Fig. 1**). In contrast, serum levels of resistin correlated significantly with IL-6 (**Fig. 2**), but not BMI, indicating that the circulating levels of these adipokines are regulated by a different mechanism, which was also suggested in a previous study[27]. A novel finding of our study is that the c.454-397T>C SNP of ESR-1 is closely associated with serum levels of adiponectin that were decreased in the patients with the T allele and were lowest in those with the T/T genotype (**Table 2**). In contrast, this SNP showed no association with serum resistin, IL-6 or hs-CRP. Independent contribution of the T/T genotype to serum levels of adiponectin was confirmed by multiple logistic analysis (**Table 3**), where odds ratio of having the T/T genotype for low circulating levels of adiponectin reached 5.8. This study indicates that genetic variation in the action of estrogen plays a role in regulating circulating levels of adiponectin; hence, a homozygote for the T allele could be a risk of CVD in women, as previous investigations identified, because of low circulating levels of adiponectin.

The mechanism whereby this type of ESR-1 SNP is involved in the regulation of circulating levels of adiponectin remains to be elucidated. This SNP reportedly affects the promoter activity of ER-α and expression of the ER-α promoter containing the T allele results in reduced ER-α expression compared to the C allele[28]. Interestingly, recent studies suggested a close relationship between ESR-1 SNPs and obesity or metabolic syndrome. Okura *et al*. investigated the association of ESR-1 SNPs with body fat distribution and reported that XbaI polymorphism, which is in close linkage disequilibrium with PvuII polymorphism, was an independent contributor to fat mass and waist-to-hip ratio in middle-aged Japanese women[29]. The Framingham Heart Study also investigated the sex-specific association of ESR-1 SNPs with adiposity[30] and described that waist circumference of homozygous men for C allele of PvuII polymorphism was significantly lower than in homozygous men for the T allele, while this association was not found in women. More recently, Gallagher *et al*. investigated the association of 17 SNPs of ESR-1 with metabolic syndrome and its components in African-American families and found a significant association of c.454-397T>C (rs2234693) with insulin sensitivity[31]. These studies indicate that ESR-1 polymorphisms are involved in the accumulation of visceral fat, which may lead to reduced adiponectin synthesis in visceral adipose tissue; however, it is uncertain whether estrogen affects circulating levels of adiponectin via a direct action.

An animal study using ovariectomized mice investigated the role of estrogen in the regulation of adiposity and lipolytic enzymes. In ovariectomized mice, replacement of estrogen decreased adiposity and adipocyte size, which was associated with the up-regulation of lipolytic enzymes in adipose tissue[32]. Estrogen may regulate adiposity via its direct effect on lipolytic enzymes, which would be followed by a change in circulating levels of adiponectin. On the other hand, it is reported that 17-β estradiol enhances adipogenic differentiation of human mesenchymal stem cells and adipose-derived stromal cells[33, 34]. ER-α plays a role in regulating nuclear factor of activated T-cell (NFAT) 3, which is involved in diverse cellular functions, including adipocyte differentiation[35]. These findings suggest that estrogen may affect circulating levels of adiponectin, enhancing the differentiation of visceral adipocytes. More recently, estrogen-related receptor α (ERRα) was identified as an orphan nuclear receptor on the basis of its homology with ER-α[36]. ERRα function is linked to at least three pathways: estrogen signaling, bone formation and oxidative metabolism[37]. Interestingly, ERRα and peroxisome proliferator-activated receptor γ (PPARγ) coactivator (PGC)-1α are

involved in the modulation of adipogenesis-related genes, such as the activation of PPARγ during adipocyte differentiation[38]. Collaboration between ER-α and ERRα in adipocyte differentiation is not well recognized; however, it is likely that ER-α modulates circulating levels of adiponectin in association with the upregulation of adipogenesis-related genes in visceral adipose tissue. The role of the genetic variation of ESR-1 as a contributor to serum adiponectin can be recognized from this view point. Nevertheless, further investigation is required to determine whether this speculation is reasonable.

There are several limitations of the present study. Firstly, the number of patients under investigation was small; however, it is noteworthy that the homozygote for T allele was present in over 30% of women enrolled in this study. We believe that contribution of the T allele of this SNP to circulating levels of adiponectin could be confirmed in a study with more subjects. Secondly, this study is cross sectional and the true risk of CVD in patients homozygous for the T allele should be evaluated by an observational study with prospective follow up.

In conclusion, this study demonstrated that the T allele of the c.454-397T>C SNP of ESR-1 is associated with low serum levels of adiponectin in postmenopausal women with type 2 diabetes, which may lead to a high risk of CVD.

References

1) Asao K, Sarti C, Forsen T, Hyttinen V, Nishimura R, Matsushima M, Reunanen A, Tuomilehtho J, Tajima N for Diabetes Epidemiology Research International (DERI) Mortality Study Group: Long-term mortality in nationwide cohorts of childhood-onset type 1 diabetes in Japan and Finland. Diabetes Care, 2003; 26:2037-2042
2) Juutilainen A, Kortelainen S, Lehto S, Rönnemaa T, Pyörärä K, Laakso M: Gender difference in the impact of type 2 diabetes on coronary heart disease risk. Diabetes Care, 2004; 27:2898-2904
3) Schuit SCE, Oei HH, Witteman JC, Geurts van Kessel CH, van Merurs, JB, Nijhuis RL, van Leeuwen JP, de Jong FH, Zillikens MC, Hofman A, Pols HA, Uitterlinden AG: Esrogen receptor α gene polymorphisms and risk of myocardial infarcton. JAMA, 2004; 291:2969-2977
4) Ferrero V, Ribichini F, Matullo G, Carturan S, Vado A, Vassanelli C, Piazza A, Uslenghi E, Wijins W: Estrogen receptor-α polymorphisms and angiographic outcome after coronary artery stenting. Aretrioscler Thromb Vasc Biol, 2003; 23:2223-2228
5) Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi H, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y: Plasma concentration of a novel, adipose-spcific protein, adiponectin, in type 2 diabetic patients. Arterioscler thromb Vasc Biol, 2000; 20:1595-1599
6) Weikert C, Westphal S, Berger K, Dierkers J, Möhlig M, Spranger J, Rimm EB, Willich SN, Boeing H, Pischon T: Plasma resistin levels and risk of myocardial infarction and ischemic stroke. J Clin Endocrinol Metab, 2008; 93:2647-2653
7) Soweres MR, Wildman RP, Mancuso P, Eyvazzadeh AD, Karvonen-Gutierrez CA, Rillamas-Sun E, Jannausch ML: Change in adipocytokines and ghrelin with menopause. Maturitas, 2008; 59:149-157
8) Jaleel F, Jaleel A, Aftab J, Rahman MA: Relationship between adiponectin, glycemic control and blood lipids in diabetic type 2 postmenopausal women with and without complication of ischemic heart disease. Clinica Chimica Acta, 2006; 370:76-81
9) Hori K, Shin WS, Hemmi C, Toyo-oka T, Makino T: High fidelity SNP genotyping using sequence-specific primer elongation and fluorescence correlation spectroscopy. Curr Pharm Biote, 2003; 4:477-484
10) Mendelsohn ME, Karas RH: The protective effects of estrogen on the cardiovascular system. N Engl J Med, 1999; 340:1801-1811
11) Welty FK: Women and cardiovascular risk. Am J Cardiol, 2001 88:48J-52J
12) Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, Daida H, Biro S, Hirobe K, Funahashi T, Yokote K, Yokode M: Risk factors of atherosclerotic diseases. Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerosis cardiovascular diseases for Japanese. J Atheroscler Thromb, 2007; 14:267-277
13) Berg AH, Sherer PE: Adipose tissue, inflammation, and cardiovascular diseae. Circ Res, 2005; 96:939-949
14) Yatoh S, Tamada N: Insulin sensitizer and atherosclerosis. J Atheroscler Thromb, 2007; 9:276-279
15) Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, Sugiyama T, Miyagishi M, Hara K, Tsunoda M, Murakami K, Ohteki T, Uchida S, Takekawa S, Waki H, Tsuno NH, Shibata Y, Terauchi Y, Froguel P, Tobe K, Koyasu S, Taira K, Kitamura T, Shimizu T, Nagai R, Kadowaki T: Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature, 2003; 423:762-769
16) Kawanami D, Maemura K, Takeda N, Harada T, Nojiri T, Imai Y, Manabe I, Utsunomiya K, Nagai R: Direct reciprocal effects of resistin and adiponectin on vascular endothelial cells: a new insight into adipocytokine-endothelial cell interactions. Biochem Biophys Res Commun, 2004; 314:415-419
17) Goldstein BJ, Scalia R: Adiponectin: A novel adipokine linking adipocytes and vascular function. J Clin Endocrinol Metb, 2004; 89:2563-2568
18) Mather KL, Funahashi T, Matsuzawa Y, Edelstein S, Bray GA, Kahn SE, Crandall J, Marcovina S, Goldstein B, Goldberg R; Diabetes Prevention Program: Adiponectin, change in adiponectin, and progression to diabetes in the Diabetes Prevention Program. Diabetes, 2008; 57:980-986
19) Hara K, Boutin P, Mori Y, Tobe K, Yasuda K, Yamauchi T, Otabe S, Okada T, Eto K, Kadowaki H, Hagura R,

Akanuma Y, Yazaki Y, Nagai R, Taniyama M, Matsubara K, Yada M, Nakano Y, Kimura S, Tomita M, Kimura S, Ito C, Froguel P, Kadowaki T: Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population. Diabetes, 2002; 51:536-540
20) Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB: Plasma adiponectin levels and risk of myocardial infarction in men. JAMA, 2004; 291:1730-1737
21) Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA: The hormone resistin links obesity to diabetes. Nature, 2001; 409:307-312
22) Jung HS, Park KH, Cho TM, Chung SS, Cho HJ, Cho SY, Kim SJ, Kim SY, Lee HK, Park KS: Resistin is secreted from macrophages in atheromas and promotes atherosclerosis. Cardiovasc Res, 2006; 69:76-85
23) Ohmori R, Moniyama Y, Kato R, Taniguchi H, Ogura M, Ayaori M, Nakamura H, Ohsuzu F: Associations between serum resistin levels and insulin resistance, inflammation, and coronary artery disease. J Am Coll Cardiol, 2005; 46:379-380
24) Reilly MP, Lehrke ML, Wolfe ML, Rohatgi A, Lazar MA, Rader DJ: Resistin is an inflammatory marker of atherosclerosis in humans. Circulation, 2005; 111:932-939
25) Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA, 2001; 286:327-334
26) Doi Y, Kiyohara Y, Kubo M, Ninomiya T, Wakugawa Y, Yonemoto K, Iwase M, Iida M: Elevated C-reactive protein is a predicator of the development of diabetes in a general Japanese population: the Hisayama study. Diabetes Care, 2005; 28:2497-2500
27) Shetty GK, Economides PA, Horton ES, Mantzoros CS, Veves A: Circulating adiponectin and resistin lvels in relation to metabolic factors, inflammatory markers, and vascular reactivity in diabetic patients and subjects at risk for diabetes. Diabetes Care, 2004; 27:2450-2457
28) Herrington DM, Howard TD, Brosnihan KB, McDonnell DP, Li X, Hawkins GA, Reboussin DM, Xu J, Zheng SL, Meyers DA, Bleecker ER: Common estrogen receptor polymorphism augments effects of hormone replacement therapy on E-selectin but not C-reactive protein. Circulation, 2002; 105:1879-1882
29) Okura T, Koda M, Ando F, Niino N, Ohta S, Shimokata H: Association of polymorphisms in the estrogen receptor alpha gene with body fat distribution. Int J Obes Relat Metab Disord, 2003; 27:1020-1027
30) Fox CS, Yang Q, Cupples AL, Guo CY, Atwood LD, Murabito JM, Levy D, Mendelsohn ME, Housman DE, Shearman AM: Sex-specific association between estrogen receptor-alpha gene variation and measures of adiposity; The Framingham Heart Study. J Clin Endocrinol Metab, 2005; 90:6257-6262
31) Gallagher CJ, Langefeld CD, Gordon CJ, Campbell JK, Mychaleckyj JC, Bryer-Ash M, Rich SS, Bowden DW, Sale MM: Association of the estrogen-α gene with the metabolic syndrome and its component traits in African-American families. Diabetes, 2007; 56:2135-2141
32) D'Eon TM, Souza SC, Aronovitz M, Obin MS, Fried SK, Greenberg AS: Estrogen regulation of adiposity and fuel partitioning. Evidence of genomic and non-genomic regulation of lipogenic and oxidative pathways. receptor-alpha J Biol Chem, 2005; 280:35983-35991
33) Hong L, Colpan A, Peptan IA: Modulations of 17-beta estradiol on osteogenic and adipogenic differentiations of human mesenchymal stem cells. Tissue Eng, 2006; 12:2747-2753
34) Hong L, Colpan A, Peptan IA, Daw J, George A, Evans CA: 17-beta estradiol enhances osteogenic and adipogenic differentiation of human adipose-derived stromal cells. Tissue Eng, 2007; 13:1197-1203
35) Qin X, Wang XH, Yang ZH, Ding LH, Xu XJ, Cheng L, Niu C, Sun HW, Zhang H, Ye QN: Repression of NFAT3 transcriptional activity by estrogen receptors. Cell Mol Life Sci, 2008; 65:2752-2762
36) Laganière J, Tremblay GB, Dufour CR, Giroux S, Rousseau F, Giguère V: A polymorphic autoregulatory hormone response element in the human estrogen-related receptor alpha (ERRalpha) promoter dictates peroxisome proliferator-activated receptor gamma coactivator-1alpha control of ERRalpha expression: J Biol Chem, 2004; 279:18504-18510
37) Villena J, Hock MB, Chang WY, Barcas JE, Giguère V, Kralli A: Orphan nuclear receptor estrogen-related receptor alpha is essential for adaptive thermogenesis. Proc Natl Acad Sci USA, 2007; 104:1418-1423
38) Ijichi N, Ikeda K, Horie-Inoue K, Yagi K, Okazaki Y, Inoue S: Estrogen-related receptor alpha modulates the expression of adipogenesis-related genes during adipocyte differentiation. Biochem Biophys Res Commun, 2007; 358:813-818