Association of intercellular adhesion molecule-1 gene polymorphism in ischemic stroke patients

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Abstract

Background: Ischemic stroke (IS) is a prevalent disease causing a body disability, the third leading cause of death in Taiwan. It shows that the level of intercellular adhesion molecule-1 (ICAM-1) in IS patients is higher than control subjects. Objective: This study is to investigate the possible association of ICAM-1 (G1548A) polymorphism in IS patients. Materials and Methods: A total of 646 subjects were enrolled in this study, including 312 IS patients, and 334 controls without a history of symptomatic IS. The ICAM-1 (G1548A) polymorphism was analyzed by polymerase chain reaction and restriction fragment length polymorphism. Clinical factors were also determined. Results: The frequencies of the ICAM-1 (G1548A) polymorphism for G/G, G/A, and A/A were 74.8%, 23.9%, and 0.3%, respectively, in healthy controls, and 62.8%, 32.1%, and 5.1%, respectively, in patients. The frequency of the ICAM-1 (G1548A) A allele (21.2% versus 13.2%, respectively; P = 0.007) and the carriers of the ICAM-1 (G1548A) A allele (37.2% versus 25.2%; P = 0.019, OR 1.76, 95% CI 1.1-2.83) are great in IS patients compared with healthy controls. There is a higher risk of IS associated with homozygosity for the ICAM-1 (G1548A) A allele (AA genotype) compared with the control population (5.1% vs. 0.3%, respectively, P = 0.04; OR 5.1, 95% CI 1.19-21.66). We also observed both hypertension and diabetes has shown a positive association with IS. Conclusions: The ICAM-1 (G1548A) polymorphism was associated with independent risk factor for the development of IS.

Key Words

Allele, intercellular adhesion molecular-1, ischemic stroke, polymorphism

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Introduction

Stroke is a prevalent disease and a leading cause to the risk of body disability and death worldwide. The probability of stroke is estimated to be 0.5-1.6% for the adults who are over 36 year old.[1] More therapeutic methods have been progressed tremendously, but still few treatments are available for stroke. An ischemic stroke (IS) happens because of an inadequate supply of oxygen and glucose flowing to the brain to support cellular homeostasis.[2] The etiology and physiology of IS very complex, and other risk factors, including hypertension, diabetes, smoking, drinking, and inflammation, contribute to the development of IS.[3] Recently, several studies have investigated certain genetic polymorphisms associated with IS, but the results still need to be clearly elucidated.[4,5]

Intercellular adhesion molecule-1 (ICAM-1) is a ligand interacted with a receptor leukocyte function-associated antigen-1 (LFA-1) located on leukocytes.[6,7] The leukocytes could bind to endothelial cells via ICAM-1/LFA-1 interaction and then transmigrate into tissues.[8] In the cytokine-mediated immune and inflammatory responses, ICAM-1 played an important role, especially in the progression of IS.[9,10] Ferrarese et al.[11] found the levels of ICAM-1 in peripheral blood and cerebrospinal fluid were higher in IS patients, comparing with that of controls. Orion et al.[12] have also shown that the levels of ICAM-1 were strictly associated with the risk for IS. Moreover, in knock-out mice experiments, ICAM-1 deficiency reduced atherosclerotic lesions after null ICAM-1 mice were fed a high-fat diet. The results has proved that ICAM-1 might be involved in the pathogenesis of ischemic cardiovascular disorders.[13]

The ICAM-1 polymorphisms have been examined, and were associated with various inflammatory diseases.[14,15] For an example, Pola et al.[16] showed the frequency of the EE
genotype of the ICAM-1 (E469K) in the IS patients was twofold, comparing with that of controls. Kitawaki et al.\(^{37}\) reported the ICAM-1 (E469K) and the interleukin-6 (IL-6) (-634C/G) polymorphisms synergistically affected susceptibility to endometriosis. In this study, we are to investigate the association between the occurrence and severity of IS and ICAM-1 (G1548A) polymorphism in the Taiwanese.

**Materials and Methods**

**Subjects**
A total of 646 subjects, including 312 IS patients and 334 healthy controls without a family history of IS, were recruited from the Neurosurgery Division at the Kaohsiung Armed Forces General Hospital, Kaohsiung, Taiwan from March 2009 to March 2011. All subjects agreed and signed an informed consent form to participate in the study. The 312 IS patients included 36 patients with left hemisphere stroke, 140 patients with right hemisphere stroke, and 136 patients with bilateral stroke. The plan was approved by the ethics committee of the Kaohsiung Armed Forces General hospital. Venous blood was taken 2 h after having meal, and plasma and serum sample were either used immediately for analysis or stored frozen at −20°C until DNA extraction.

**DNA extraction**
Total genomic DNA was extracted with the DNeasy\textregistered TM Kit (QIAGEN Group) according to the manufacturer’s instructions. Briefly, the blood was digested with 0.5 mg/mL proteinase K in 400 μL cell lysis solution for 24 h at 55°C until the blood was completely lysed. After adding 200 μL of absolute ethanol to the lysed sample, the mixture was transferred into the DNeasy mini column and centrifuged for 1 min at 8000 rpm. The DNeasy mini column was washed with 500 μL washing buffer and centrifuged for 1 min at 8000 rpm. Finally, the DNA was eluted into a clean 1.5-mL microcentrifuged tube. Quantification of the DNA was performed using a spectrophotometer (GeneQuant), and the sample was stored at −20°C until polymerase chain reaction (PCR) amplification.

**Determination of ICAM-1 polymorphism**
The G/A substitution located at position +1548 in the structural region of the ICAM-1 gene. This region was amplified by PCR, using the primers 5'-CCATCGGGGAATCAGTG-3' (sense) and 5'-'ACAGAGCACCATTACCGTC-3' (antisense). The amplifications were performed as follows: 1 cycle at 95°C for 4 min, 50 cycles at 95°C for 1 min, 61°C for 1 min, 72°C for 1 min and a final extension at 72°C for 3 min in an automated PCR cycler (GeneAmp PCR system 2400; Perkin-Elmer, Darmstadt, Germany). The amplified product was identified by digestion with BstUI (Promega) in a final volume of 10 μL at 37°C overnight. The digested products were separated in a 3% agarose gel followed by staining with ethidium bromide, and the genotypes were determined by analyzing the different bands.

**Statistical analysis**
Demographic and clinical data between groups were compared by analysis of variance. Genotype and allele frequencies between the control and IS groups were compared by the Chi-square test. The \( P \) values, odds ratios (ORs), and 95% confidence intervals were calculated. A \( P \) value of less than 0.05 was considered as significant for all analyses.

**Results**
We recruited 646 subjects, including 312 IS patients, mean age and standard deviation (SD), 68.3 (4.5) years, and 334 controls, mean age and SD, 67.8 (5.3) years [Table 1]. Differences in hypertension and diabetes were significantly different, but there were no significant differences in male : female ratio and hypercholesterolemia.

The distribution of ICAM-1 (G1548A) genotypes and alleles is shown in Table 2. In IS patients, the A/A genotype in ICAM-1 (G1548A) is more frequent than that of controls (5.1% vs. 0.3%; \( P = 0.04 \)). In addition, the G/A genotype is also slightly overrepresented in the IS patients compared to controls (32.1% vs. 23.9%; \( P = 0.001 \)). The frequency of A allele in ICAM-1 (G1548A) is significantly increased in IS patients (21.2% vs. 13.2%, \( P = 0.007 \)). In comparison with controls there are significantly more A allele carriers of the ICAM-1 (G1548A) among IS patients (37.2% versus 25%; \( P = 0.019 \)), with the OR of 1.76 (95% C.I 1.1-2.83), is shown in Table 3.

| Table 1: Demographic and clinical data for subjects |
|-----------------------------------------------|
| IS patients (\(n=312\)) & Controls (\(n=334\)) & \( P \) |
| Age (years±SD) & 68.3±4.5 & 67.8±5.3 | NS |
| Male : female ratio & 153:158 & 161:173 | NS |
| Hypertension & 162 (52.2) & 105 (31.9) | <0.001 |
| Diabetes & 145 (46.5) & 90 (27) | <0.001 |
| Hypercholesterolemia & 96 (31) & 86 (26) | NS |
| IS=Ischemic stroke, NS=Not statistically significant, SD=Standard deviation |

| Table 2: Genotype and allele frequencies of ICAM-1 (G1548A) in subjects |
|-----------------------------|
| ICAM-1 (G1548A) & IS patients (\(n=312\)) & Controls (\(n=334\)) & Odds ratio (95% CI) & \( P \) |
| Genotype |
| GG & 196 (62.8) & 250 (74.8) | 1 (0.90-1.10) | NA |
| GA & 100 (32.1) & 80 (23.9) | 1.63 (0.99-2.00) | 0.051 |
| AA & 16 (5.1) & 2 (0.3) | 5.1 (1.19-21.66) | 0.04 |
| Allele |
| A & 132 (21.2) & 88 (13.2) | 1.77 (1.77-2.68) | 0.007 |
| G & 492 (78.8) & 580 (86.8) |
| IS=Ischemic stroke <0.001, OR=Odds ratio, CI=Confidence interval, ICAM-1=Intercellular adhesion molecular-1, NA=Not available, GG=ICAM-1 GG genotype, GA=ICAM-1 GA genotype, AA=ICAM-1 AA genotype |

| Table 3: A allele frequencies of ICAM-1 (G1548A) in subjects |
|-----------------------------|
| ICAM-1 (G1548A) & IS patients (\(n=312\)) & Controls (\(n=334\)) & Odds ratio (95% CI) & \( P \) |
| GA=AA & 116 (37.2) & 84 (25.2) | 1.76 (1.10-2.83) | 0.019 |
| GG & 196 (62.8) & 250 (74.8) | |
| IS=Ischemic stroke, OR=Odds ratio, CI=Confidence interval, ICAM-1=Intercellular adhesion molecular-1, AA=ICAM-1 AA genotype, GA=ICAM-1 GA genotype, AA=ICAM-1 AA genotype |
Discussion

The leading causes of IS are associated with many clinical disorders, including myocardial infarction, circulatory shock, lacunar infarction, and inflammatory cytokines. Among these risk factors, cytokines are thought to play a vital role in the regulation of the immune response. Previous studies have reported the levels of cytokines in IS patients, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), IL-6, and ICAM-1, were higher than that of healthy controls. In addition, genetic risk factors might have important contributions in the pathogenesis of IS. Likewise, several studies have shown that the synergistic effect of the IL-6 promoter and ICAM-1 polymorphisms could be the lead cause of serious immune diseases IS or endometriosis in the world.

ICAM-1, induced by IL-1 and TNFα, is a cellular adhesion protein located at the cell membrane of leukocytes and endothelial cells. The expressed ICAM-1 has led to various inflammatory and cardiovascular disorders. Gaetani et al. first demonstrated that the ICAM-1 (G1548A) polymorphism was associated with the peripheral arterial occlusive disease. Kamiuchi et al. found the ICAM-1 polymorphism was associated with diabetic retinopathy in Type 2 diabetes mellitus. Longoni et al. also reported the ICAM-1 (K469E) polymorphism was highly represented in a spontaneous cervical artery dissection subgroup. Other studies have analyzed the relationship between the ICAM-1 variation and the risk of IS. In Italian patients, Pola et al. showed the existence of a synergistic effect of the IL-6 (-174G/C) polymorphism and the ICAM-1 (469 E/K) polymorphism in patients with a history of IS. ICAM-1 possesses an amino-terminal extracellular domain, a single transmembrane domain, and a carboxy-terminal cytoplasmic domain. Staunton et al. described how the ICAM-1 (K469E) could affect the arrangement of the immunoglobulin-like domain 5 of the protein's structure. The domain 5 of ICAM-1 bond to the Macrophage Adhesion Ligand-1 (Mac-1), LFA-1, and fibrinogen. In addition, in the Japanese population, Yamada et al. reported that the ICAM-1 (K469E) polymorphism was more predictive of IS. This study found that this genotypic variant in the IS patients could differentiate between Western and Asian populations. However, more clinical results are needed for confirmation of these results.

Campanella et al. showed that cerebral ischemia was associated with the infiltration of inflammatory cells into the ischemic region. The recruitment of inflammatory cells seemed to increase ischemic brain injury and the pathogenesis of IS. Leukocyte-endothelial cell adhesion was an important step in the recruitment of leukocytes into post-ischemic brain tissue. In this inflammatory environment, cerebral endothelial cells increased their expression of cell surface adhesion molecules, such as ICAM-1, that mediate the recruitment of leukocytes and platelets to the ischemic region. Several studies have reported that the expression of ICAM-1 is induced by IL-1, IL-6, and TNF-α in IS patients. Experiments have also shown that ICAM-1 ligation produced inflammatory leukocyte recruitment by signaling though signaling cascades involving a number of kinases, including the Src tyrosine kinase, Raf-1, and the mitogen-activated protein kinases (MAPKs).

In this study, we noted that the frequency of IS was positively associated with the level of plasma glucose. The results were consistent with previous studies by Tanne et al. who found a J-shaped association between fasting plasma glucose and the incidence of ischemic cerebrovascular events in patients with plasma glucose levels (>100 mg/dL). However, Targher et al. reported that in diabetic subjects, the plasma ICAM-1 and E-selectin were negatively associated with total glucose disposal during the insulin clamp. In these patients, acute hyperinsulinemia did not contribute any significant effect on plasma adhesion molecules. The possibility was proposed that adipose tissue releases one or more factors that adversely affect endothelial function.

In summary, the ICAM-1 (G1548A) polymorphism was a genetic factor that could influence the severity of IS in Taiwanese patients. Furthermore, both plasma glucose and hypertension was associated with the risk of IS. In conclusion, this study indicated that the ICAM-1 (G1548A) polymorphism was significantly associated with IS, and the result suggested this polymorphism was an independent risk factor for IS.

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References

1. Lee TH, Hsu WC, Chen CJ, Chen ST. Etiologic study of young ischemic stroke in Taiwan. Stroke 2002;33:1950-5.
2. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997;349:1269-76.
3. del Zoppo G, Ginis I, Hallenbeck JM, Iadecola C, Wang X, Feuerstein GZ. Inflammation and stroke: Putative role for cytokines, adhesion molecules and iNOS in brain response to ischemia. Brain Pathol 2000;10:95-112.
4. Balding J, Livingstone WJ, Pittcoke SJ, Mynett-Johnson L, Ahern T, Hodgson A, et al. The IL-6 G-174C polymorphism may be associated with ischaemic stroke in patients without a history of hypertension. Ir J Med Sci 2004;173:200-3.
5. Tso AR, Merino JG, Warach S. Interleukin-6 174G/C polymorphism and ischemic stroke: A systematic review. Stroke 2007;38:3070-5.
6. Rothlein R, Dustin ML, Marlin SD, Springer TA. A human intercellular adhesion molecule (ICAM-1) distinct from LFA-1. J Immunol 1986;137:1270-4.
7. Hess DC, Bhuftala T, Sheppard JC, Zhao W, Smith J. ICAM-1 expression on human brain microvascular endothelial cells. Neurosci Lett 1994;168:201-4.
8. Yang L, Froio RM, Scuito TE, Dvorak AM, Alon R, Luscinskas FW. ICAM-1 regulates neutrophil adhesion and transcellular migration of TNF-alpha-activated vascular endothelium under flow. Blood 2005;105:584-92.
9. Bourdillon MC, Poston RN, Covacho C, Chignier E, Bricca G, McGregor JL. ICAM-1 deficiency reduces atherosclerotic lesions in double-knockout mice (apoE(-/-)/ICAM-1(-/-)) fed a fat or a Chow diet. Arterioscler Thromb Vasc Biol 2000;20:2630-5.
10. Lee SJ, Drabik K, Van Wagoner NJ, Lee S, Choi C, Dong Y, et al. ICAM-1-induced expression of proinflammatory cytokines in astrocytes: Involvement of extracellular signal-regulated kinase and p38 mitogen-activated protein kinase pathways. J Immunol 2000;165:4658-66.
et al. Increased cytokine release from peripheral blood cells after acute stroke. J Cereb Blood Flow Metab 1999;19:1004-9.

12. Orion D, Schwammenthal Y, Reshef T, Schwartz R, Tsabari R, Merzeliak O, et al. Interleukin-6 and soluble intercellular adhesion molecule-1 in acute brain ischemia. Eur J Neurol 2008;15:323-8.

13. Bourdillon MC, Poston RN, Covacho C, Chignier E, Bricca G, McGregor JL. ICAM-1 deficiency reduces atherosclerotic lesions in double-knockout mice (ApoE(-/-)/ICAM-1(-/-)) fed a fat or a chow diet. Arterioscler Thromb Vasc Biol 2000;20:2630-5.

14. Pontiheux A, Lambert D, Herbeth B, Droesch S, Pfister M, Vinckius S. Association between Gly241Arg ICAM-1 gene polymorphism and serum sICAM-1 concentration in the Stanislas cohort. Eur J Hum Genet 2003;11:679-86.

15. Dore Al, Santana-Lemos BA, Coser VM, Santos FL, Dalmazoo LF, Lima AS, et al. The association of ICAM-1 Exon 6 (E469K) but not of ICAM-1 Exon 4 (G241R) and PECAM-1 Exon 3 (L125V) polymorphisms with the development of differentiation syndrome in acute promyelocytic leukemia. J Leukoc Biol 2007;82:1340-3.

16. Pola R, Flex A, Gaetani E, Fiore R, Serricchio M, Pola P. Synergistic effect of -174 G/C polymorphism of the interleukin-6 gene promoter and 469 E/K polymorphism of the intercellular adhesion molecule-1 gene in Italian patients with history of ischemic stroke. Stroke 2003;34:881-5.

17. Kitawaki J, Kyomizu M, Obayashi H, Ohta M, Ishihara H, Hasegawa G, et al. Synergistic effect of interleukin-6 promoter (IL6-634C/G) and intercellular adhesion molecule-1 (ICAM-1 1469K/E) gene polymorphisms on the risk of endometriosis in Japanese women. Am J Reprod Immunol 2006;56:267-74.

18. Gaetani E, Flex A, Pola R, Papaleo P, De Martini D, Pola E, et al. The K469E polymorphism of the ICAM-1 gene is a risk factor for peripheral arterial occlusive disease. Blood Coagul Fibrinolysis 2002;13:483-8.

19. Kamiuchi K, Hasegawa G, Obayashi H, Kitamura A, Ishii M, Yano M, et al. Intercellular adhesion molecule-1 (ICAM-1) polymorphism is associated with diabetic retinopathy in Type 2 diabetes mellitus. Diabet Med 2002;19:371-6.

20. Longoni M, Grond-Ginsbach C, Grau AJ, Genius J, Debette S, Lima AS, et al. Increased cytokine release from peripheral blood cells after acute stroke. J Cereb Blood Flow Metab 1999;19:1004-9.

21. Orion D, Schwammenthal Y, Reshef T, Schwartz R, Tsabari R, Merzeliak O, et al. Interleukin-6 and soluble intercellular adhesion molecule-1 in acute brain ischemia. Eur J Neurol 2008;15:323-8.

22. Bourdillon MC, Poston RN, Covacho C, Chignier E, Bricca G, McGregor JL. ICAM-1 deficiency reduces atherosclerotic lesions in double-knockout mice (ApoE(-/-)/ICAM-1(-/-)) fed a fat or a chow diet. Arterioscler Thromb Vasc Biol 2000;20:2630-5.

23. Pontiheux A, Lambert D, Herbeth B, Droesch S, Pfister M, Vinckius S. Association between Gly241Arg ICAM-1 gene polymorphism and serum sICAM-1 concentration in the Stanislas cohort. Eur J Hum Genet 2003;11:679-86.

24. Dore Al, Santana-Lemos BA, Coser VM, Santos FL, Dalmazoo LF, Lima AS, et al. The association of ICAM-1 Exon 6 (E469K) but not of ICAM-1 Exon 4 (G241R) and PECAM-1 Exon 3 (L125V) polymorphisms with the development of differentiation syndrome in acute promyelocytic leukemia. J Leukoc Biol 2007;82:1340-3.

25. Pola R, Flex A, Gaetani E, Fiore R, Serricchio M, Pola P. Synergistic effect of -174 G/C polymorphism of the interleukin-6 gene promoter and 469 E/K polymorphism of the intercellular adhesion molecule-1 gene in Italian patients with history of ischemic stroke. Stroke 2003;34:881-5.

26. Kitawaki J, Kyomizu M, Obayashi H, Ohta M, Ishihara H, Hasegawa G, et al. Synergistic effect of interleukin-6 promoter (IL6-634C/G) and intercellular adhesion molecule-1 (ICAM-1 1469K/E) gene polymorphisms on the risk of endometriosis in Japanese women. Am J Reprod Immunol 2006;56:267-74.

27. Gaetani E, Flex A, Pola R, Papaleo P, De Martini D, Pola E, et al. The K469E polymorphism of the ICAM-1 gene is a risk factor for peripheral arterial occlusive disease. Blood Coagul Fibrinolysis 2002;13:483-8.

28. Kamiuchi K, Hasegawa G, Obayashi H, Kitamura A, Ishii M, Yano M, et al. Intercellular adhesion molecule-1 (ICAM-1) polymorphism is associated with diabetic retinopathy in Type 2 diabetes mellitus. Diabet Med 2002;19:371-6.

29. Longoni M, Grond-Ginsbach C, Grau AJ, Genius J, Debette S, Schwanger M, et al. The ICAM-1 E469K gene polymorphism is a risk factor for spontaneous cervical artery dissection. Neurology 2006;66:1273-5.

30. Staunton DE, Dustin ML, Erickson HP, Springer TA. The arrangement of the immunoglobulin-like domains of ICAM-1 and the binding sites for LFA-1 and thioninovirus. Cell 1990;61:243-54.

31. Stoolman LM. Adhesion molecules controlling lymphocyte migration. Cell 1989;56:907-10.

32. Osborn L. Leukocyte adhesion to endothelium in inflammation. Cell 1990;62:3-6.

33. Yamada Y, Metoki N, Yoshida H, Satoh K, Ichihara S, Kato K, et al. Genetic risk for ischemic and hemorrhagic stroke. Arterioscler Thromb Vasc Biol 2006;26:1920-5.

34. Campanella M, Sciorati C, Tarozzo G, Beltramo M. Flow cytometric analysis of inflammatory cells in ischemic rat brain. Stroke 2002;33:586-92.

35. Fassbender K, Rossol S, Kammer T, Daffertshofer M, Wirth S, Dölman M, et al. Proinflammatory cytokines in serum of patients with acute cerebral ischemia: Kinetics of secretion and relation to the extent of brain damage and outcome of disease. J Neurol Sci 1994;122:135-9.

36. Fassbender K, Mössner R, Motsch L, Kischka U, Grau A, Hennerici M. Circulating selectin- and immunoglobulin-type adhesion molecules in acute ischemic stroke. Stroke 1995;26:1361-4.

37. Tarkowski E, Rosengren L, Blomstrand C, Wikkelso C, Jensen C, Ekholm S, et al. Early intrathecal production of interleukin-6 predicts the size of brain lesion in stroke. Stroke 1995;26:1393-8.

38. Tarkowski E, Rosengren L, Blomstrand C, Wikkelso C, Jensen C, Ekholm S, et al. Intrathecal release of pro-and anti-inflammatory cytokines during stroke. Clin Exp Immunol 1997;110:492-9.

39. Wang Q, Pfeiffer GR 2nd, Gaarde WA. Activation of SRC tyrosine kinases in response to ICAM-1 ligation in pulmonary microvascular endothelial cells. J Biol Chem 2003;278:47731-43.

40. Holland J, Owens T. Signaling through intercellular adhesion molecule 1 (ICAM-1) in a B cell lymphoma line. The activation of Lyn tyrosine kinase and the mitogen-activated protein kinase pathway. J Biol Chem 1997;272:9108-12.

41. Lee SJ, Drabik K, Van Wagoner NJ, Lee S, Choi C, Dong Y, et al. ICAM-1-induced expression of proinflammatory cytokines in astrocytes: Involvement of extracellular signal-regulated kinase and p38 mitogen-activated protein kinase pathways. J Immunol 2000;165:4658-66.

42. Tanne D, Koren-Morag N, Goldbourt U. Fasting plasma glucose and risk of incident ischemic stroke or transient ischemic attacks: A prospective cohort study. Stroke 2004;35:2351-5.

43. Targher G, Bonadonna RC, Alberiche M, Zenere MB, Muggeo M, Bonora E. Relation between soluble adhesion molecules and insulin sensitivity in type 2 diabetic individuals: Role of adipose tissue. Diabetes Care 2001;24:1961-6.