Potential Clinical Usefulness of Endothelial Adhesion Molecules in Predicting Risk of Type 2 Diabetes

Wei Cui, MD, PhD, Yiqing Song, MD, ScD

Abstract

Early endothelial dysfunction is a common antecedent of the metabolic or insulin resistance syndrome and may thus play an etiologic role in the pathogenesis of type 2 diabetes mellitus and associated complications. Elevated circulating levels of some endothelial adhesion molecules including e-selectin, intercellular adhesion molecule-1 (icam-1), and vascular cell adhesion molecule-1 (vcam-1) may reflect structural microvascular changes related to the pathophysiological processes of impaired insulin action and secretion. Elevated levels of soluble cellular adhesion molecules have been related to insulin resistance and other metabolic syndrome components. Evidence from prospective studies indicates that endothelial biomarkers, particularly e-selectin, may independently predict risk of type 2 diabetes among nondiabetic individuals in multiple populations. Circulating levels of endothelial adhesion molecules appear to have clinically significant prognostic value beyond inflammatory marker-crp in predicting future risk of type 2 diabetes.

[N A J Med Sci. 2009; 2(2):60-63.]

Key Words: *diabetes , endothelial adhesion molecules*

Introduction

Endothelial dysfunction is an integral component of the metabolic syndrome and may play an etiologic role in the development of early atherosclerotic cardiovascular disease and type 2 diabetes as well as diabetic complications.[1,2] There are several directly measures of endothelial function such as flow-mediated dilation of the brachial artery or retinal arteriolar narrowing but with limited clinical utilities. Endothelial function can also be indirectly assessed by measuring circulating levels of endothelial soluble adhesion molecules. When endothelial activation is elicited by several inflammatory cytokines, endothelial cells secrete cellular adhesion molecules including E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) on the cell surface.[1,2] Soluble forms of these molecules released from the endothelial cell surface are considered useful indicators of endothelial dysfunction/activation. Most of available evidence from humans focused on the relation of circulating levels of endothelial biomarkers and diabetic complications. For instance, increasing levels of E-selectin, ICAM-1, and VCAM-1 have also been observed in type 2 diabetes patients with microangiopathy and macroangiopathy. This article aims to summarize epidemiologic data on the temporal relation between endothelial biomarker levels and non-diabetic insulin resistance as well as subsequent risk of type 2 diabetes.

Wei Cui, MD, PhD
Department of Endocrinology & Metabolism, The First Affiliated Hospital, School of Medicine, Xi'an Jiao Tong University, Xi'an, China

Yiqing Song, MD, ScD * (corresponding author)
Division of Preventive Medicine
Brigham and Women's Hospital
Harvard Medical School
900 Commonwealth Avenue East,
Boston, Massachusetts, USA.
Email: ysong3@rics.bwh.harvard.edu

Endothelial Adhesion Molecules and Non-Diabetic Insulin Resistance

In 1997, Pinkney et al.[3] first put forth the hypothesis that endothelial dysfunction is a common antecedent for the insulin resistance/metabolic syndrome and intrinsically related to many of individual metabolic syndrome components. The complex relationship between endothelial dysfunction and insulin resistance is not unidirectional and also reflect their interrelationship with other components of the metabolic syndrome. There are several biological mechanisms that have been hypothesized to explain the reciprocal relationships between endothelial dysfunction and insulin resistance. First, endothelial dysfunction could directly promote the development and progression of insulin resistance. Over-expression of endothelial cellular adhesion molecules promotes the adherence and transmigration of leukocytes into the subendothelial space, ultimately leading to endothelial and subendothelial structural changes. Insulin may act as an important vasodilator by stimulating endothelial production of nitric oxide, a key endothelium-derived relaxing factor.[3,4] The resultant microvascular sclerosis can then reduce insulin delivery to peripheral tissues, which, in turn, leads to impaired nitric oxide-mediated vasodilation and insulin-mediated glucose metabolism in insulin-sensitive tissues.[3,4] Alternatively, impaired insulin action may also directly exaggerate endothelial dysfunction.

Several studies have found that mildly impaired fasting glucose levels within the normoglycemic range accelerate the impairment of endothelial function via adverse effects on oxidative stress, formation of advanced glycation end products, and elevated levels of free fatty acids.[3,4] surrogate for insulin resistance derived from both measures of fasting insulin and glucose.[3,5] The association between circulating soluble adhesion molecules and insulin resistance has also been confirmed by additional cross-sectional studies that provided an accurate assessment of insulin sensitivity and/or secretion using some physiological protocols, such as the intravenous glucose tolerance test. In the Rotterdam Study, post-load insulin levels were used as a good measure of insulin resistance in a random sample of 574 nondiabetic elderly men and women. They reported an association of ICAM-1 with post-load insulin levels but no association with VCAM-1.[6] In 28 healthy, nondiabetic, and normotensive individuals aged 38-75 years, a direct estimate of insulin-mediated glucose disposal based on the measures of steady-state plasma glucose levels (SSPG) was applied to assess insulin resistance. The results showed that the degree of insulin resistance was significantly correlated with levels of soluble adhesion molecules. Correlation coefficients were 0.54 for E-selectin, 0.67 for ICAM-1, and 0.41 for VCAM-1 (all $P<0.05$).[7]

Although insulin resistance may play a central role in the development of the metabolic syndrome, it remains important to consider interaction among a number of metabolic factors contributing to circulating levels of soluble adhesion molecules rather than simply compare their levels between two groups stratified by insulin resistant status alone. In epidemiologic studies, cross-sectional evidence has also shown an elevation in circulating levels of E-selectin, ICAM-1, and VCAM-1 among nondiabetic individuals with insulin resistance, obesity, hypertension, and dyslipidemia.[5] To clarify the independent association between circulating soluble adhesion molecules and insulin resistance, several cross-sectional studies examined the relationship between adhesion molecule levels and insulin sensitivity among nonobese, normotensive, and normolipidemia individuals.[7] These studies found that circulating levels of soluble adhesion molecules would increase in insulin-resistant individuals, independently of the concomitant presence of other metabolic abnormalities, such as hypertension, diabetes, or dyslipidemia. However, the evidence was primarily from cross-sectional studies and does not prove causality. To resolve the controversy about the temporal relationship between elevated levels of adhesion molecules and insulin resistance, prospective data are desirable from future well-designed metabolic studies with accurate assessment of insulin sensitivity using physiological protocols and longitudinal measures of endothelial adhesion molecules.

Of note, lifestyle and pharmacological interventions that improve insulin sensitivity may also improve endothelial function.[4] For example, interventions aimed at reducing individual risk factors correlated with insulin resistance, such as pharmacologic treatments with peroxisome proliferator-activated receptor γ ligands, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (also termed statins), angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, and nonpharmacologic interventions including weight loss, physical activity, and Mediterranean-style diet, have been shown to improve endothelial function or decrease soluble adhesion molecule levels.[4] These studies appeared to not only support the notion that endothelial dysfunction and insulin resistance share common pathophysiological pathways, including oxidative stress and chronic inflammation but also reflect the reciprocal relationships between endothelial dysfunction and insulin resistance.

Endothelial Adhesion Molecules and Risk of Type 2 Diabetes

Endothelial dysfunction is closely related to all features of the metabolic syndrome and its associated metabolic abnormalities, lending support to the "common soil" hypothesis that endothelial dysfunction, as reflected by elevated levels of soluble endothelial adhesion molecules, may precede the development of both atherosclerotic CVD and type 2 diabetes (**Figure 1**).

To address the temporal relationship between endothelial adhesion molecules and type 2 diabetes, a few prospective studies have directly evaluated the role of endothelial biomarkers in predicting future risk of developing type 2 diabetes but have yielded mixed results.8-12 In a nested case-control study of 71 cases and 71 matched controls in the Pima Indian population, none of E-selectin, ICAM-1, and VCAM-1 were associated with type 2 diabetes, partly due to inadequate power. In a larger case-control study of 737 incident cases and 785 age-matched controls during 10 years of follow-up from the Nurses' Health Study, Meigs et al. reported that elevated levels of E-selectin and ICAM-1 were independent predictors of incident diabetes in initially nondiabetic Caucasian women and VCAM-1 was not associated with diabetes.[9] Further adjustment for baseline levels of CRP, fasting insulin, and hemoglobin A1c did not change these associations. Consistent with the findings, E-selectin but not ICAM-1 was an independent predictor of type 2 diabetes risk in a population-based case-cohort study of 532 incident cases of diabetes and 1712 controls involving middle-aged German men and women.[10] E-selectin remained significant association with diabetes risk in men and women after additionally controlling for age, BMI, smoking, alcohol, physical activity, SBP, total cholesterol/HDL cholesterol ratio, parental history of diabetes, and CRP. We prospectively examined the association between baseline levels of three endothelial adhesion molecules and future risk of type 2 diabetes in a case-control study nested within the Women's Health Initiative Observational Study (WHI-OS), an ethnically diverse cohort of U.S. postmenopausal women including whites, blacks, Hispanics, and Asians and Pacific Islanders.[11,12] During a median follow-up of 5.9 years, 1,584 incident diabetes cases were matched with 2,198 controls by age, ethnicity, clinical center, time of blood draw, and follow-up time. Although the results showed ethnic

differences in plasma levels of endothelial adhesion molecules, there was no evidence for ethnic differences and confirmed the predictive role of both E-selectin and ICAM-1 across diverse ethnic groups with different risk factor profiles. Notably, our findings were consistent with previous studies showing that E-selectin was a stronger predictor for type 2 diabetes than ICAM-1 and VCAM-1. The associations were independent of baseline levels of CRP, BMI, and insulin resistance status; the risk of diabetes among women with the highest levels of E-selectin remained 2-fold greater than for women in the lowest quartile.

Overall, prospective data appear to support the strongest predictive role of E-selectin in risk of type 2 diabetes, although the precise mechanisms are not well understood. E-selectin is expressed exclusively by endothelial cells so that soluble E-selection may be a specific marker as a reflection of its membrane-bound form in the activated endothelium. In addition, E-selectin measure appears to be relatively stable as compared to other adhesion biomarkers. Given that elevated levels of endothelial adhesion molecules may to some extent reflect chronic inflammatory state, we also provided additional evidence for the comparative predictive values of each of the three endothelial biomarkers as predictors for type 2 diabetes as compared with CRP.12 In agreement with the findings in previous studies,[9,10] our study clearly showed that circulating levels of E-selectin were independently associated with future diabetes risk irrespective of CRP levels at baseline.

Conclusion

In summary, a large body of cross-sectional evidence has shown strong associations of circulating levels of endothelial adhesion molecules with insulin resistance in nondiabetic individuals or patients with type 2 diabetes. Prospective data have indicated that circulating levels of endothelial adhesion molecules predict risk of type 2 diabetes. However, there are many important questions that require answers before we formally add measures of circulating adhesion molecules in diabetes risk prediction and treatment. For instance, can measurements of three soluble adhesion molecules fully reflect endothelial dysfunction? Are there physiological functions of soluble cellular adhesion molecules in circulation? Most importantly, there is a notable lack of data from prospective studies assessing the clinical utilities of endothelial markers in the comprehensive risk assessment and management for diabetes risk and prognosis in the context of other diabetes biomarkers and traditional risk factors. Although further research is needed, the assessment of circulating levels of endothelial adhesion molecules may possess a potential clinical value in identifying individuals who are at a high risk and justifying pharmacological therapy in diabetes risk reduction.

References

1. Ross R. Atherosclerosis - an inflammatory disease. N Engl J Med. 1999;340(2):115-126.
2. Price DT, Loscalzo J. Cellular adhesion molecules and atherogenesis. Am J Med. 1999;107(1):85-97.
3. Pinkney JH, Stehouwer CD, Coppack SW, Yudkin JS. Endothelial dysfunction: cause of the insulin resistance syndrome. Diabetes. 1997;46(Suppl 2):S9-S13.
4. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation. 2006;113(15):1888-1904.
5. Schram MT, Stehouwer CD. Endothelial dysfunction, cellular adhesion molecules and the metabolic syndrome. Horm Metab Res. 2005;37 (Suppl 1):S49-S55.
6. Hak AE, Pols HA, Stehouwer CD, et al. Markers of inflammation and cellular adhesion molecules in relation to insulin resistance in nondiabetic elderly: the Rotterdam study. J Clin Endocrinol Metab. 2001;86(9):4398-4405.
7. Chen NG, Holmes M, Reaven GM. Relationship between insulin resistance, soluble adhesion molecules, and mononuclear cell binding in healthy volunteers. J Clin Endocrinol Metab. 1999;84(10):3485-3489.
8. Krakoff J, Funahashi T, Stehouwer CD, et al. Inflammatory markers, adiponectin, and risk of type 2 diabetes in the Pima Indian. Diabetes Care. 2003;26(6):1745-1751.
9. Meigs JB, Hu FB, Rifai N, Manson JE. Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. JAMA. 2004;291(16):1978-1986.
10. Thorand B, Baumert J, Chambless L, et al. Elevated markers of endothelial dysfunction predict type 2 diabetes mellitus in middle-aged men and women from the general population. Arterioscler Thromb Vasc Biol. 2006;26(2):398-405.
11. Herder C, Peltonen M, Koenig W, et al. Systemic immune mediators and lifestyle changes in the prevention of type 2 diabetes: results from the Finnish Diabetes Prevention Study. Diabetes. 2006;55(8):2340-2346.
12. Song Y, Manson JE, Tinker L, et al. Circulating levels of endothelial adhesion molecules and risk of diabetes in an ethnically diverse cohort of women. Diabetes. 2007;56(7):1898-1904.

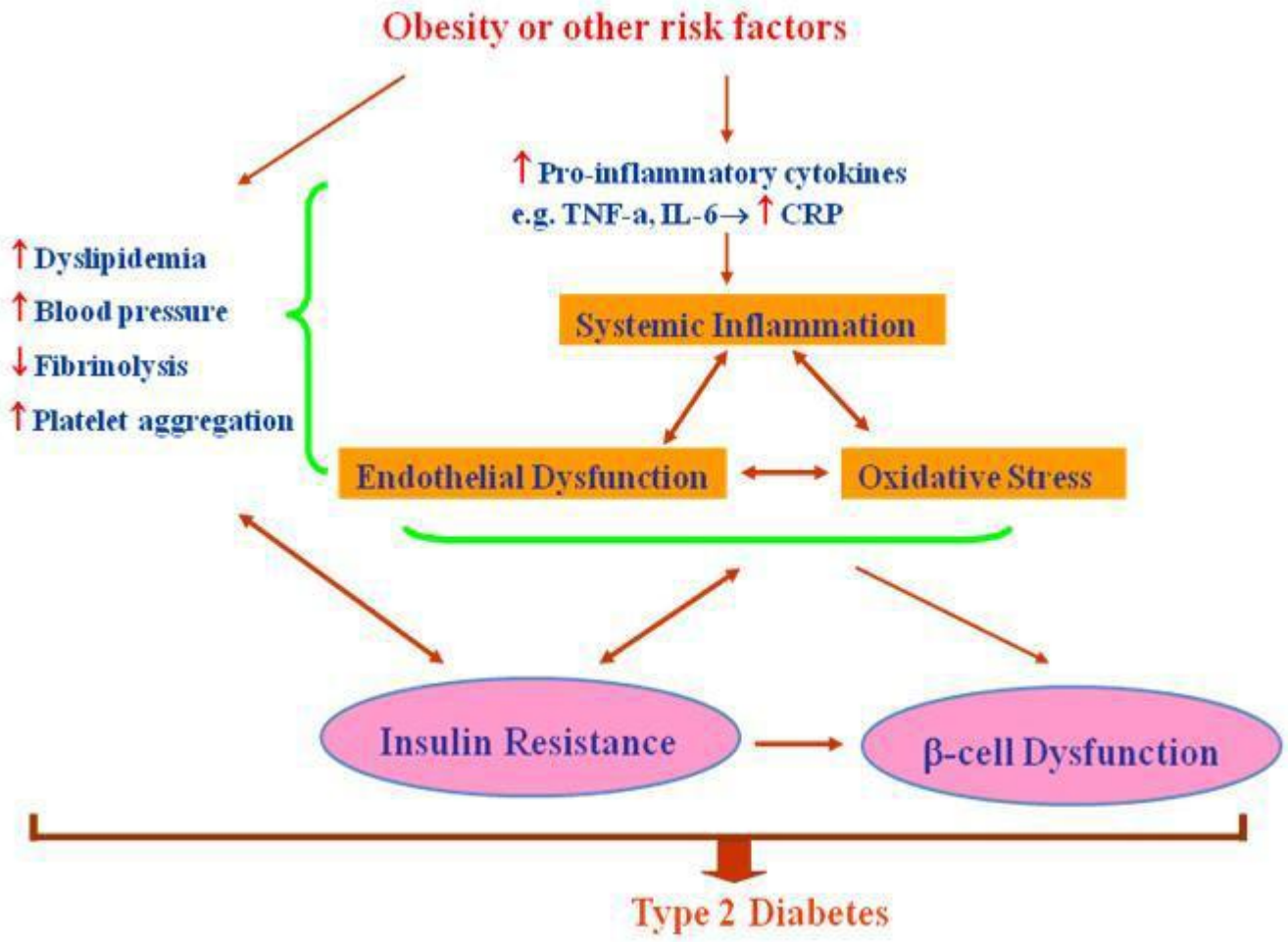

Figure 1. The hzed mechanisms for a link between endothelial dysfunction and type 2 diabetes.