The role of ICAM-1 and VCAM-1 in diabetic retinopathy

Chun-Shen Li¹, Rong Miao¹, Qing Cai¹, Tao Zhou¹, Jun-Zhen Tan¹, Xue-Run Wu¹, Bai Chang²

Foundation item: National Natural Science Foundation of China (No. 30973753)
¹Tianjin University of Traditional Chinese Medicine, Tianjin 300193, China
²Metabolic Disease Hospital of Tianjin Medical University, Tianjin 300070, China
Correspondence to: Bai Chang. Metabolic Disease Hospital of Tianjin Medical University, Tianjin 300070, China. changbai1972@126.com
Received: 2011-09-10 Accepted: 2011-12-10

Abstract
- Diabetes causes a lot of abnormalities in the retina including up-regulation of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), and these changes suggest a role for inflammation in the development of diabetic retinopathy (DR). In this paper, we analyzed the important role of ICAM-1 and VCAM-1 on the damage of vascular endothelial cells and the inflammatory response in DR briefly.
- KEYWORDS: diabetic retinopathy; intercellular adhesion molecule-1; vascular cell adhesion molecule-1; inflammatory response

DOI: 10.3969/j.issn.1672-5123.2012.01.01


INTRODUCTION
The pathogenesis of diabetic retinopathy has lately been recognized to involve low-grade, chronic inflammation¹, proposed to be the result of persistent hyperglycemia as well as of dyslipidemia². Up-regulation of inflammatory mediators and adhesion molecules are early features of diabetic retinopathy³, lead to accumulation of leukocytes, altered vessel reactivity and subsequent activation receptors and transcription factors, ultimately result in apoptosis or proliferation of various cell types in retina, e. g., loss of pericytes and proliferation of endothelial cells, and finally the blood - retina barrier (BRB) breakdown. These damages lead to the clinical symptoms of diabetic retinopathy (DR), such as non-perfusion, retinal hemorrhage and retinal edema caused by vascular fragility, each of which can cause serious changes in visual loss.

THE ICAM-1 AND VCAM-1 EXPRESSION IN THE INFLAMMATORY RESPONSE IN THE DIABETIC RETINA
Inflammation in the early stage is characterized by the release of cytokines, which will increase the vascular cell adhesion molecule-1 (VCAM-1) expression. Hyperglycemia triggers an inflammatory response in the retina of normal lipopidemic mice and up-regulation of VCAM-1 in retinal vessels. Hypercholesterolemia effectively promotes VCAM-1 expression without evident stimulation of inflammation. The results also suggest a complex role for TNF-α in the regulation of VCAM-1 expression, being protective under basal conditions but pro-inflammatory in response to diabetes⁵. The initial insult that leads to vascular dysfunction and neurotoxicity in the diabetic retina probably occurs very early. During early stages of experimental diabetes, the activation of endothelial intercellular adhesion molecule-1 (ICAM-1) occurs⁶.

ICAM-1 expression was not significant continuity in normal human retina, and its expression in the diabetic patients was significantly higher, there was a small amount of ICAM-1 expression in the quiescent vascular endothelial cells, no expression of VCAM-1⁷. Endothelial cells were activated due to hypoxia and inflammatory mediators, and they secreted ICAM-1 and VCAM-1⁸.

THE DIFFERENCES BETWEEN ICAM-1 AND VCAM-1 IN DR
Limb et al⁹ found that the vitreous levels of soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) were significantly higher in eyes with proliferative diabetic retinopathy (PDR) than in control cadaverous, and levels of both two molecules did not relate to the type or duration of diabetes mellitus. Hernandez et al⁹ found that the low proportion of VCAM-1 in relation to total vitrill proteins observed in diabetic patients with PDR suggested that VCAM-1 was quenched by diabetic retina. Tang et al¹⁰ observed the expression of ICAM-1 and VCAM-1 of 40 cases with diabetes, the results showed that ICAM-1 was detected in 90% of the cases, VCAM-1 was found in 80% of the cases in the PDR epiretinal membranes; and further, in 77% of the cases ICAM-1 was detected on the
proliferating endothelial cells and VCAM-1 was found in 81% of the cases. The expression of cell adhesion molecules, especially ICAM-1 and VCAM-1 in diabetic epiretinal membranes suggests that cell to cell interactions may play a significant role in the development of PDR membranes. In particular, the expression of ICAM-1 and VCAM-1 on proliferating endothelial cells indicates the activation of these cells, which is the first critical step for lymphocyte/endothelial cell interactions and the initiation of immune responses. Olson et al. studied the serum levels of sVCAM-1 and sICAM-1 in the serum of patients with insulin-dependent diabetes mellitus (IDDM) and varying degrees of retinopathy and healthy age and sex matched control subjects, found that sVCAM-1 levels were raised in all patients with IDDM particularly in those with retinopathy, and sVCAM-1 levels were highest in patients with PDR. In contrast sVCAM-1 levels were the same in patients and control subjects. The study of Yoshizawa et al. suggested that the levels of serum VCAM-1 were not different from normal in the early phase of DR, but into the sVCAM-1 significantly increased in the PDR phase. That sVCAM-1 may be derived from the damaged fragments of the endothelial cells. The levels of serum VCAM-1 may reflect, to some extent, the damage and activity of endothelial cells.

Endothelial cells release multiple inflammatory mediators and express various adhesion molecules such as ICAM-1, VCAM-1, P- and E-selectins. These are membrane proteins necessary for anchoring leukocytes to the vessel wall and are well established markers of endothelial dysfunction in inflammatory conditions such as atherosclerosis. Soluble forms of these adhesion molecules and selectins have been demonstrated in serum of diabetic patients, suggesting that they may play a role in diabetic endothelial activation. Moreover, increased levels of sVCAM-1 have been demonstrated in the vitreous of diabetic patients.

In type 2 diabetic subjects, serum levels of sVCAM-1 and sE-selectin levels are increased both in patients with micro-and macrovascular complications, whereas sICAM-1 levels are higher only in the microvascular group. This suggests potential differential regulation of adhesion molecules and maybe also differential functions. In line with this idea, recent studies have shown associations between sVCAM-1 in human serum and PDR, but not for sICAM-1. ICAM-1 has been widely used as a marker of endothelial activation in experimental studies of DR, but much less is known about VCAM-1 in this context. Dyslipidemia is a well established proinflammatory agent in large arterial vessel disease and could be of importance in the pathogenesis of microvascular complications of diabetes. It was shown that severity of retinopathy was associated with increasing serum triglycerides and inversely associated with high-density lipoprotein (HDL) - cholesterol levels.

**SUMMARY**

ICAM-1 and VCAM-1 play an important role in the damage of vascular endothelial cells and the inflammatory response, both of the expression are also different in the different courses of DR. ICAM-1 and VCAM-1 are closely linked with the occurrence and development of DR. Control of specific adhesion molecules could have important implications in the design of new therapeutic regimens to treat and prevent this sight-threatening complication of diabetes mellitus.

**REFERENCES**


3. Goldberg RB. Cytokine and cytokine-like inflammation markers, endothelial dysfunction, and imbalance coagulation in development of diabetes and its complications. *J Clin Endocrinol Metab* 2009; 94 (9): 3171-3182


ICAM-1 和 VCAM-1 在糖尿病视网膜病变中的作用

李春深1, 范 戈1, 蔡 青1, 周 涛1, 谭俊珍1, 常 涛2

基金项目: 中国国家自然科学基金资助项目(No. 30973753)

通讯作者: 常柏, 博士, 副主任医师, 研究方向: 中西医结合治疗内分泌及代谢病。

糖尿病视网膜病变(DR)发展中发挥了一些作用。本文针对粘附分子 ICAM-1 和 VCAM-1 在 DR 的血管内皮细胞的损伤及其在炎症反应中发挥的重要作用进行了简要分析。

关键词: 糖尿病视网膜病变; 细胞间粘附分子-1; 血管细胞粘附分子-1; 炎症反应