Cardiovascular disease in diabetic nephropathy patients: cell adhesion molecules as potential markers?

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Abstract: Cardiovascular disease is a major complication of diabetes mellitus, especially for patients with diabetic nephropathy. The underlying factor or pathogenic mechanism that links diabetic nephropathy with cardiovascular disease is not known. The endothelial cell adhesion molecules, intercellular adhesion molecule-1 or vascular cell adhesion molecule-1, play a crucial role in the initiation of atherosclerosis. Levels of both cell adhesion molecules are raised by the diabetic and kidney disease states. This review focuses on these important cell adhesion molecules and their role in the pathogenesis of cardiovascular disease in diabetes and diabetic nephropathy.

Keywords: diabetes, kidney disease, cell adhesion

Introduction

Diabetes mellitus (diabetes) affects approximately 100 million people worldwide (Amos et al 1997). Cardiovascular disease is a major chronic complication of both type 1 and type 2 diabetes and people with diabetes have an approximately 2–4-fold increased risk of cardiovascular events, as compared with control populations (Kannel and McGee 1979; Panzram 1987). In addition to cardiovascular disease, people with diabetes are also at high risk of developing microvascular complications, the most clinically important being end-stage kidney disease or diabetic nephropathy. Importantly, the combination of diabetes and nephropathy increases cardiovascular disease risk by 20–40-fold (Mattock et al 1992; Alzaid 1996).

Different stages of kidney disease versus cardiovascular disease risk

Diabetic nephropathy can be classified on its severity. Diabetics initially have no kidney disease at all. The earliest detectable level of kidney disease is microalbuminuria, where there is a minute amount of protein that is excreted in the urine (not detectable by urine dipstick). The next stage is proteinuria, which is defined as easily measurable levels of protein in the urine, but without disturbance of measures that generally mark renal failure (creatinine and urea). Lastly, the disease process may develop into renal failure, otherwise known as uremia (Williams et al 1988; Iseki et al 2003).

Patients who eventually develop end-stage diabetic renal failure will have passed through the stages of normal renal function, microalbuminuria, and proteinuria before reaching uremia. It has long been standard practise to use microalbuminuria as a target for treatment in the prevention of diabetic nephropathy (de Zeeuw et al 2004).

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Less clear, until recently, is the role of microalbuminuria as a marker and therapeutic target in vascular disease (Anavekar et al 2004).

Albuminuria as a marker for cardiovascular disease

In the normal population, cardiovascular risk increases in a continuous fashion along with progression from normal to overt proteinuria levels (Hillege et al 2001, 2002; Romundstad et al 2003; Hunsicker et al 2004). Shown in a prospective 5-year survey of more than 20 000 subjects in the United Kingdom, microalbuminuria and proteinuria were independently associated with risk of cardiovascular disease and death (Romundstad et al 2003). This relationship is also true for people with diabetes, with post-hoc analyses of three recent large clinical trials showing that albuminuria not only determines renal outcomes, but also cardiovascular outcomes (UKPDS 1998; Anavekar et al 2004; de Zeeuw et al 2004). In one of these three studies, the reduction of albuminuria with therapeutic interventions resulted in protection against cardiovascular disease as well as the development of progressive renal impairment (UKPDS 1998).

Albuminuria leading to vascular inflammation

There are many physiological abnormalities that are attendant in end-stage kidney disease that has led to the identification of mechanisms that may link cardiovascular disease and renal failure (Yuyen et al 2004). High on the list of possible mechanisms are factors such as: hypertension; anemia (Rebelink 2004); dyslipidemia (Rebelink 2004); activation of the renin-angiotensin system (Stevens and Levin 2003); medial calcification of the vascular tree (Brewster et al 2003); malnutrition and inflammation (Brewster et al 2003).

However, while these factors are present in end-stage nephropathy, not all of them are universally present in the early stages of albuminuria. Inflammation is associated with the microalbuminuric state, with albuminuria now recognized to reflect generalized vascular damage (Hillege et al 2001). Importantly, inflammation underlies all stages of atherosclerotic lesion formation, including early atherogenesis where inflammatory cells adhere and infiltrate the subendothelium (Liu et al 2004). Critical proteins expressed by endothelial cells that bind the inflammatory cells are the cell adhesion molecules (see Figure 1).

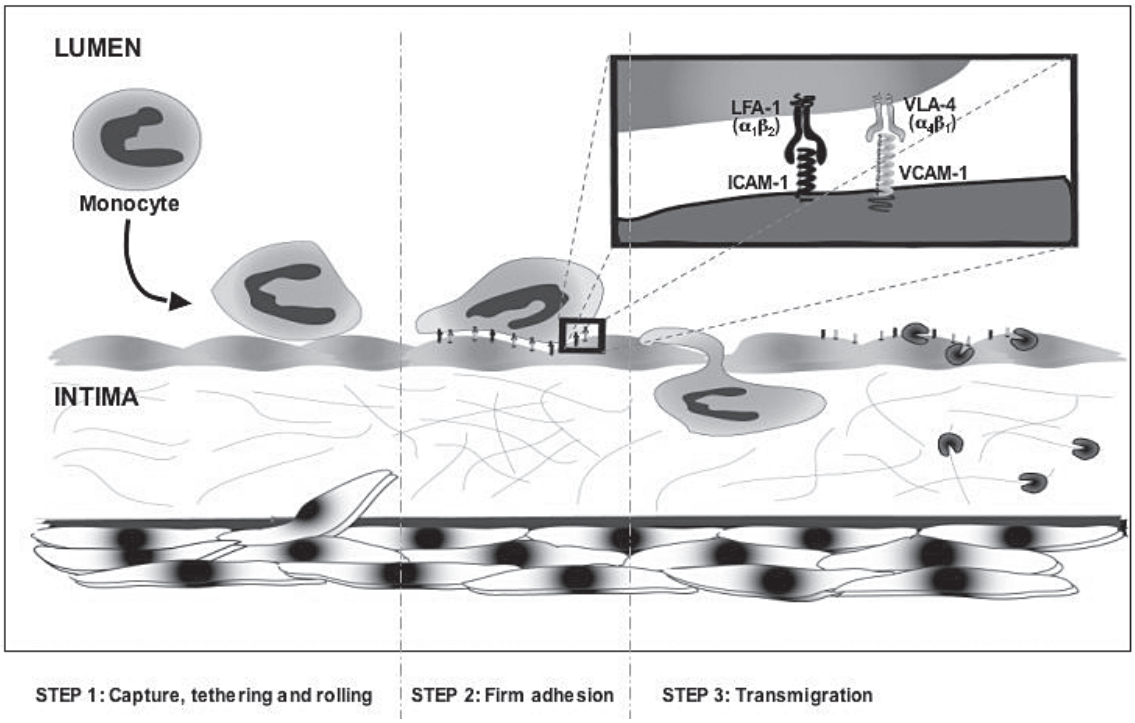

Figure 1 Cell adhesion molecules and early atherosclerotic plaque formation. Cell adhesion molecules, including VCAM-1 and ICAM-1, are expressed on the surface of endothelial cells in response to inflammatory stimuli. Monocytes and other leukocytes bind to the cell adhesion molecules via their own specific cell adhesion molecules called integrins. Integrin leukocyte function antigen-1 (LFA-1) binds ICAM-1 and very-late antigen-4 (VLA-4) binds VCAM-1 (insert). The binding of the monocytes to endothelial cells subsequently triggers the tethering, rolling, and subsequent migration of the monocytes into the subintima.
Abbreviations: ICAM-1, intercellular cell adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

Cell adhesion molecules, inflammation, and atherosclerosis

Two important cell adhesion molecules expressed by endothelial cells that play a major role in the pathogenesis of atherosclerosis are vascular cell adhesion molecule-1 (VCAM-1) and intercellular cell adhesion molecule-1 (ICAM-1). Expression of both ICAM-1 and VCAM-1 have been demonstrated in atherosclerotic plaques (Poston et al 1992; Davies et al 1993; Johnson-Tidey et al 1994; O'Brien et al 1996; DeGraba et al 1998; Blankenberg et al 2003) with focal expression evident at lesion prone areas (O'Brien et al 1996; Nakashima et al 1998) and at the borders of atherosclerotic lesions (Nakashima et al 1998; Iiyama et al 1999). There have been many in vitro studies showing high glucose milieus increase both ICAM-1 and VCAM-1 endothelial cell expression at both the protein (Kim et al 1994; Baumgartner-Parzer et al 1995; Taki et al 1996; Takami et al 1998; Manduteanu et al 1999; Esposito et al 2001; Kado et al 2001; Hoffman et al 2002; Omi et al 2002; Itoh et al 2003) and messenger ribonucleic acid (mRNA) (Kim et al 1994; Chettab et al 2002; Itoh et al 2003; Altannavch et al 2004) levels, via a cell signaling mechanism related to activation of protein kinase C-β (Quagliaro et al 2005). Additionally, human endothelial cells exposed to the serum of nephropathic patients (none of whom had diabetes) had high cell surface ICAM-1 and VCAM-1 expression, correlating with increased mRNA levels (Serradell et al 2002). Our own laboratory has recently shown that exposure of cultured human endothelial cells to serum from diabetic patients with advancing stages of diabetic nephropathy (microalbuminuria progressing to uremia) have a stepwise increase in the expression of both VCAM-1 and ICAM-1, as measured at the levels of gene transcription, mRNA, and protein (Wu et al 2004). This suggests that diabetic/microalbuminuric patients already have underlying pathological signaling that increases key early steps in atherosclerosis using in vitro measures.

Soluble cell adhesion molecules

Although the cell adhesion molecules are firmly anchored on the cell membranes of endothelial cells, cell adhesion molecules may be broken off into the circulation forming soluble VCAM-1 (sVCAM-1) and soluble ICAM-1 (sICAM-1). The underlying physiologic pathway leading to the formation of soluble cell adhesion molecules and their subsequent physiologic function remains unclear. Possible explanations have been proposed, including an increased synthesis of soluble forms via increased gene transcription, altered mRNA stability, and/or the existence of alternate splice variants. However, the favored hypothesis is that enhanced proteolytic cleavage of the cell adhesion molecules from the cell surface leads to soluble cell adhesion molecules, measurable in plasma. This implies that there is a relationship between the degree of cellular expression of cell adhesion molecules and plasma soluble cell adhesion molecule levels. This is yet to be proven. Soluble cell adhesion molecules are easily measurable in plasma and much work has been done in the last 10 years on whether sICAM-1 and sVCAM-1 are useful markers for cardiovascular disease in patients with diabetes and diabetic nephropathy.

Soluble cell adhesion molecules and diabetic kidney disease

There appears to be a strong relationship between sICAM-1/VCAM-1 and diabetic nephropathy. A number of studies have found a general increasing trend in both sICAM-1 and sVCAM-1 with increasing levels of diabetic kidney disease in diabetics (Clausen et al 2000; Guler et al 2002; Wu et al 2004). Importantly, sVCAM-1 and sICAM-1 have been found to be significantly associated with microalbuminuria in type 2 diabetics as compared with controls (Fasching et al 1996; Schmidt et al 1996; Gasic et al 1999; Kado and Nagata 1999; Lim et al 1999; Jager et al 2000; Murakami et al 2001). This has suggested the potential usefulness of plasma sVCAM-1 as a marker of vascular perturbation (Schmidt et al 1996).

Soluble cell adhesion molecules and diabetic cardiovascular disease

Soluble ICAM-1 and/or sVCAM-1 show good correlation with cardiovascular disease in diabetic subjects. In a recent study, type 2 diabetics showed high sICAM-1 levels, independent of known cardiovascular risks, and predicted all cause as well as cardiovascular mortality over 10 years (Becker et al 2002). Increased levels of sVCAM-1 were also associated with increased risk of mortality in type 2 diabetes, as seen in the Hoorn study (Jager et al 2000). In the Hoorn study, 631 type 2 diabetic and control subjects with higher sVCAM-1 levels at the beginning of the study period had increased risk of cardiovascular death during 8 years of follow-up even after adjustment for age, sex, glucose tolerance, hypertension, cardiovascular disease, high density lipoproteins, low density lipoproteins, homocysteine,

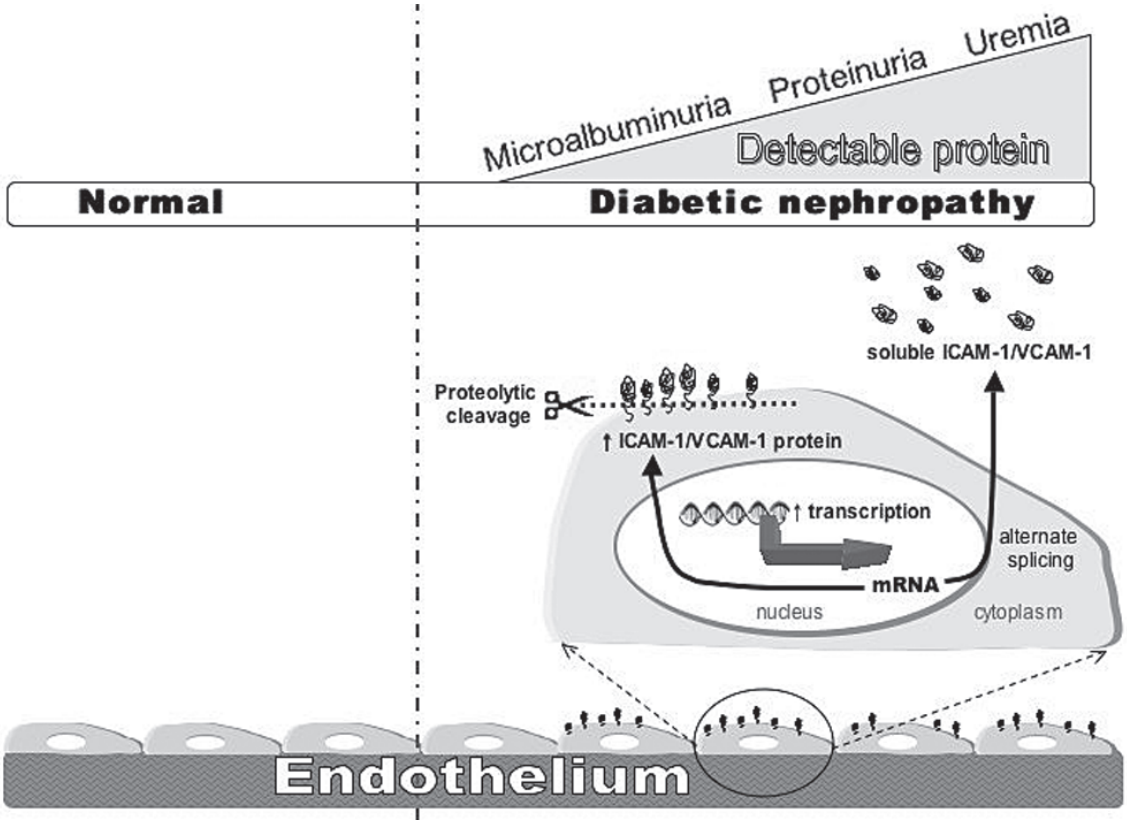

Figure 2 sVCAM-1 and sICAM-1. VCAM-1 and ICAM-1 are expressed on the cell surface of cells. Soluble forms of VCAM-1 and ICAM-1 are measurable in plasma. Several theories for the formation of the soluble forms exist, including alternate splicing, increased transcription, and proteolytic cleavage of the membrane protein (favored). There is an increase in sVCAM-1 and ICAM-1 in plasma of diabetic patients associated with an increase in the severity of kidney disease.
Abbreviations: ICAM-1, intercellular cell adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1.

microalbuminuria, von Willebrand factor, C-reactive protein, and glomerular filtration rate. The effect was magnified in type 2 diabetics, thus indicating that sVCAM-1 is independently associated with the risk of cardiovascular mortality (Jager et al 2000). In another study, Stehouwer et al (2002) also showed that high sVCAM-1 levels were independently associated with increased mortality in type 2 diabetics followed for a mean of 9 years.

These findings are well supported by a number of cross-sectional studies. Both sICAM-1 and sVCAM-1 levels were higher in elderly type 2 diabetics with known cerebrovascular disease (Kawamura et al 1998); and sVCAM-1 levels were higher in type 2 diabetic patients with symptomatic cardiovascular disease as compared with those with no known cardiovascular disease (Otsuki et al 1997). However, one very recent study did not demonstrate any correlation between sICAM-1, sVCAM-1, and known cardiovascular disease, nor with degree of intimamedia thickening (Leinonen et al 2003). It is important to keep in mind that this last survey was smaller than the longitudinal studies outlined above. Overall, sICAM-1 and sVCAM-1 levels have been demonstrated to be predictive for the future development of cardiovascular disease and mortality in diabetic subjects.

Correlations with novel risk factors for atherosclerosis

The cell adhesion molecules are just one of a number of emerging markers for cardiovascular risk factors (Table 1). Additional to cell adhesion molecules, one of the most exciting novel risk factors sparking a lot of research interest is C-reactive protein. The significance of C-reactive protein and inflammation has become increasingly evident recently, and it now appears that C-reactive protein actively contributes to atherosclerotic plaque formation and thrombotic events. Additionally, C-reactive protein is associated with the inflammatory states of not only renal failure, but also microalbuminuria. In a recent study, C-reactive protein was found to be associated with cardiovascular mortality risk rate in patients with end-stage kidney disease, and traditional risk factors including left ventricular hypertrophy

Table 1 Association of kidney disease with risk factors for cardiovascular disease

Traditional cardiovascular disease risk factors
Hypertension
Abnormal lipid profile
Central obesity
Smoking
Left ventricular hypertrophy/dysfunction
Coronary ischemia
Nontraditional cardiovascular disease risk factors
Elevated c-Reactive protein
Elevated von Willebrand factor
Elevated plasminogen activator inhibitor-1
Elevated thromomodulin
Elevated homocysteine
Elevated interleukin-6
Absent nocturnal drop in blood pressure
Insulin resistance
Elevated white blood cell count
Prolonged Q-T interval
Lipoprotein (a)

showed higher associations (Shlipak et al 2005). Similarly, in cell adhesion molecules, recent data reported a linear association between the level of albuminuria and elevations of C-reactive protein. Specific monitoring has been proposed (Bakris 2004). C-reactive protein studies remain in their infancy and prognostic values remain on a case-by-case basis (McCullough 2004). Both sICAM-1 (Ridker et al 1998) and sVCAM-1 (Schalkwijk et al 1999; Jager et al 2000) levels have been shown to significantly correlate with C-reactive protein in the diabetic setting.

The soluble cell adhesion molecules also associate with other prominent novel cardiovascular risk factors including carotid intimamedia thickness (Otsuki et al 1997; Kawamura et al 1998; Matsumoto et al 2002; Takeuchi et al 2002), advanced glycation end-points (Smulders et al 1998; Vlassara et al 2003; Lieuw et al 2004), plasma von Willebrand factor and homocysteine (Ridker et al 1998; Jager et al 2000; Targher et al 2001), fibrinogen, and tissue-type plasminogen-activator antigen (Ridker et al 1998), thereby justifying their consideration as a novel risk marker for cardiovascular disease, especially in diabetic patients.

The effect of treatments on sICAM-1 and sVCAM-1

The effect of glucose control on sICAM-1 and sVCAM-1 is not consistent between studies, with only a minority showing decreasing soluble cell adhesion molecule levels with normalization of glucose (Albertinin et al 1998; Marfella et al 2000). However, diet and dietary supplements can influence soluble cell adhesion molecule levels; eg, ingestion of antioxidants vitamins E and C immediately after a meal can significantly suppress the rapid rise in sICAM-1 and sVCAM-1 seen with a high fat meal (Nappo et al 2002). Additionally, diabetics given RRR-alphatocopheol therapy for 3 months showed a significant fall in sVCAM-1 and sICAM-1 (Devaraj and Jialal 2000). Other antioxidants have also been shown to decrease cell adhesion molecules in type 2 diabetics, such as N-acetyl-L-cysteine which decreased sVCAM-1 (De Mattia et al 1998) and glutathione which decreased sICAM-1 (Ceriello et al 1998).

Pharmacologic treatments can also effect soluble cell adhesion molecule levels; eg, hypertension is a common problem in diabetics and blockade of the renin-angiotensin system is a common method to achieve control of blood pressure. The angiotensin-converting enzyme inhibitor, fosinopril, administered for 12 weeks to microalbuminuric type 2 diabetics, decreased sVCAM-1 to control levels, but did not change sICAM-1 levels (Gasic et al 1999). In a crossover trial in type 2 diabetics, angiotensin-converting enzyme inhibitor, enalapril, and angiotensin receptor II blocker, losartan, both decreased sVCAM-1, but not sICAM-1 (Andersen et al 2000). Even though both decreased blood pressure and urine albumin excretion by the same amount, the enalapril was found to be more effective than losartan in decreasing the level of sVCAM-1 (Andersen et al 2000). In another example, management of dyslipidemia with hydroxymethyl glutaroyl coenzyme A (HMG-coA) reductase inhibitors (statins) is also common in diabetes. Three months of simvastatin therapy was able to significantly decrease both sICAM-1 and sVCAM-1 levels (Ceriello et al 2004). In addition, simvastatin was able to significantly suppress the acute rise in sICAM-1 and sVCAM-1 seen after a glucose load and/or high-fat oral load (Ceriello et al 2004). A similar drug, atorvastatin, significantly decreased sVCAM-1 in type 2 diabetics as compared with placebo (Dalla Nora et al 2003). Cardiovascular patients are often treated with antiplatelet agents, including aspirin and sarpogrelate. Both these drugs have been found to decrease serum sICAM-1 levels (Shouzu et al 2000; Mateos-Careres et al 2002). Lastly, hormone replacement therapy is often used by older women to control the symptoms of menopause and until recently, was thought to have cardioprotective benefit, although this is now very controversial (Prentice et al 2005). Hormone replacement

therapy, whether oestrogen only (Koh et al 2001), or combined oestrogen-progestin based (Manning et al 2002), did not have any effect on sICAM-1 or sVCAM-1 levels in post-menopausal type 2 diabetic women.

In summary, dietary interventions and some medications lower sVCAM-1 and sICAM-1 levels. Therefore cell adhesion molecules could be considered adjunctive factors to monitor, especially in diabetic and diabetic nephropathy patients, as a dual measure of cardiovascular and kidney disease risk.

Summary

The prevalence of cardiovascular disease in diabetic nephropathy patients is high and is a major cause of morbidity and mortality. The cell adhesion molecules, ICAM-1 and VCAM-1, are raised in both cardiovascular disease and diabetic nephropathy, with levels increasing in stepwise fashion with increasing kidney disease. Importantly, sICAM-1 and sVCAM-1 levels are raised even in the earliest stage of diabetic kidney disease; microalbuminuria. They are good predictors of atherosclerotic disease and cardiovascular mortality, and they correlate well with other conventional and nonconventional risk factors. sICAM-1 and sVCAM-1 are lowered by some dietary supplements and pharmacologic agents and therefore represent factors that can be measured to correlate with decreased cardiovascular risk, although more prospective correlative studies would be required for their use as a primary strategy. As early detection of renal impairment and cardiovascular disease in the type 2 diabetic remains a global health priority, soluble cell adhesion molecules may represent a marker of vascular disease, associated closely with early diabetic kidney disease, which if monitored could allow patients to have significant benefit from both reno- and cardioprotective treatment.

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