Endothelial dysfunction, cellular adhesion molecules and the metabolic syndrome

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Endothelial Dysfunction, Cellular Adhesion Molecules and the Metabolic Syndrome

Abstract

Over the last two decades, it has become evident that the endothelium is more than an inert, single-cell lining covering the internal surface of blood vessels. Normally, the endothelium actively decreases vascular tone, maintains vascular permeability within narrow bounds, inhibits platelet adhesion and aggregation, limits activation of the coagulation system, and stimulates fibrinolysis. Endothelium dysfunction can be considered present when its functions, either in the basal state or after stimulation, are altered in a way that is inappropriate to the preservation of organ function. Endothelial dysfunction has been associated to many cardiovascular risk factors including diabetes, hypertension and hypercholesterolemia. In addition, endothelial dysfunction may play a crucial role in the development and progression of atherosclerosis. This review will give a brief overview of the different methods to assess endothelial function, and then will focus on the current knowledge on soluble cellular adhesion molecules in relation to the metabolic syndrome and type 2 diabetes.

Key words

Type 2 diabetes · Cellular adhesion molecules · Endothelium · Metabolic syndrome · Cardiovascular disease

How to Measure Endothelial Function

Several methods to measure endothelial function *in vivo* are currently known. It should be noted that there is no direct measurement of endothelial function available in humans. The techniques described below provide reasonable but imperfect estimates of endothelial function in humans. Since 1986, direct measurement of coronary artery relaxation after acetylcholine infusions has been used to assess endothelial function in patients with coronary artery disease [1]. However, the invasive nature of this technique means that it is not a suitable method for measuring endothelial function in other patient groups.

Another technique for measuring endothelial function is strain-gauge plethysmography. The response of the forearm vascular bed to infusion of vasodilator or vasoconstrictive agents is determined by direct infusion of these agents into the brachial artery. However, this method is time-consuming and invasive, and therefore not suitable for usage in large populations.

In 1992, a new non-invasive flow-mediated vasodilation technique was introduced by Celermajer et al. [2] This technique has now been used by numerous groups worldwide. The International Brachial Artery Reactivity Task Force has extensively described the technique's methods, along with the technical and interpretive limitations to this technique [3].

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Received 14 October 2004 · **Accepted after revision** 10 February 2005

Bibliography
Horm Metab Res 2005; 37, Supplement 1: 49–55 © Georg Thieme Verlag KG Stuttgart · New York · DOI 10.1055/s-2005-861363 · ISSN 0018-5043

Endothelial function can also be measured using plasma levels of markers of endothelial function such as von Willebrand factor and soluble cellular adhesion molecules. Like other techniques, this concept is based on several assumptions – first, that cell types other than endothelial cells are not an important source of these markers. Second, that synthesis is more important than clearance. Third, that endothelial function in the microcirculatory parallels that in large arteries since microvascular endothelium has a very large surface area and synthetic capacity, and may therefore be the most important source of these endothelial markers. Information on the validity of these assumptions is scarce. However, plasma levels of soluble cell adhesion molecules are easy to determine in large populations. These measurements are relatively independent of observer variability and less time-consuming than other techniques.

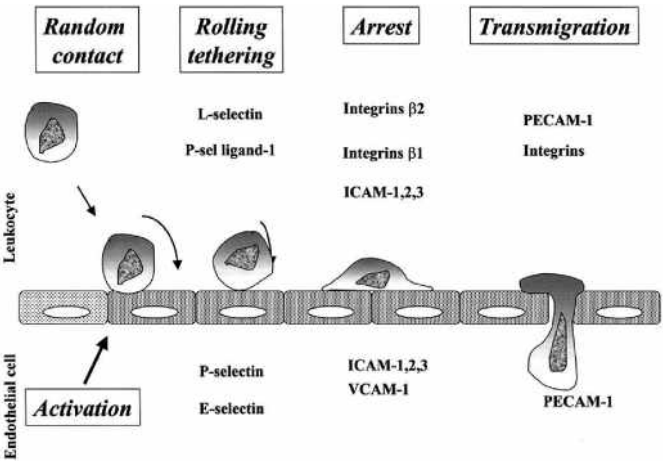

Fig. **1** Leukocyte-endothelial cell interactions during the initial steps of leukocyte migration, and the role of the various adhesion molecules in this process (Reprinted with permission from Blankenberg S et al. Atherosclerosis 170: 191 – 203, 2003).

Endothelial Cell Adhesion Molecules

Cellular adhesion molecules mediate the attachment and transmigration of leukocytes across the endothelial surface in response to several inflammatory cytokines (Fig. **1**), and are hypothesized to play an important role in the initiation of atherosclerosis [4]. Three groups of cellular adhesion molecules have been described: integrins, selectins, and members of the immunoglobulin family. The focus of this review will be on the latter two.

Several selectins have been found on the endothelium – L-selectin, P-selectin, and E-selectin. The latter is exclusively found on the surface of stimulated endothelial cells. This specificity provides an opportunity for studying the pathophysiological aspects of endothelial function. E-selectin binds neutrophils, monocytes, eosinophils, basophils, natural killer (NK) cells, and subsets of lymphocytes. This adhesion molecule has been shown to be important in the initial steps of leukocyte extravasation into inflamed tissues [5]. Levels of soluble E-selectin (sE-selectin) in plasma correlate to its membrane-bound expression [6].

Vascular cell adhesion molecule-1 (VCAM-1) is a membrane-bound adhesion molecule receptor and a member of the immunoglobulin family. VCAM-1 is thought to be a ligand for leukocyte integrins that allow tethering and rolling of monocytes and lymphocytes as well as firm attachment and transendothelial migration of leukocytes. The membrane-bound protein is normally expressed at low levels by endothelial cells, smooth muscle cells, tissue macrophages, lymphoid dendritic cells and renal tubular cells. Soluble forms of VCAM-1 (sVCAM-1) are detectable in plasma, and are reported to parallel the expression of the membrane-bound form on endothelial cells [7]. Several stimuli, including cytokines, modified lipoproteins, advanced glycation end-products, increased blood pressure, and oxidants, can upregulate VCAM-1 expression.

Intercellular adhesion molecule-1 (ICAM-1), also a member of the immunoglobulin family, is a membrane-bound adhesion molecule receptor for monocytes, lymphocytes and neutrophils, and functions as a receptor for soluble fibrinogen. ICAM-1 is expressed by endothelial cells, smooth-muscle cells and monocytes. Like sE-selectin and sVCAM-1 levels, soluble ICAM-1 (sICAM-1) levels are detectable in plasma, and these levels are directly associated with membrane-bound protein expression [6]. ICAM-1 levels can be upregulated by inflammatory cytokines, but can also increase after exposure to high glucose levels. Accumulating data imply that selectins mediate initial rolling of leukocytes along the endothelium, and that VCAM-1 and ICAM-1 play important roles in the firm attachment and transendothelial migration of leukocytes.

Associations Between Cellular Adhesion Molecules and Characteristics of the Metabolic Syndrome

Type 2 diabetes is often accompanied by cardiovascular risk factors such as hypertension, obesity, dyslipidemia, and insulin resistance. The combined presence of these risk factors is referred to as the metabolic syndrome. Many variables included in the metabolic syndrome are associated with endothelial dysfunction. The following section will discuss the associations between endothelial cell adhesion molecules and characteristics of the metabolic syndrome.

Hypertension

High blood pressure increases shear stress on the endothelium, and may result in endothelial cell activation or even damage. Several studies have reported increased levels of sVCAM-1, sICAM-1 and sE-selectin in the presence of hypertension, although conflicting results exist. Some studies only investigated sE-selectin in hypertensive individuals, and found increased levels compared to normotensive individuals [8,9], while others demonstrated elevated sVCAM-1 and/or sICAM-1 levels but no increase in sE-selectin levels in hypertensive individuals [10 – 12]. Two studies found elevations in all three soluble cellular adhesion molecules in hypertensive individuals [13,14]. In addition, a transient elevation of sVCAM-1, sICAM-1 and sE-selectin after a cold-pressor test has been reported in both normotensive and hypertensive individuals [14]. Others investigated the effects of obesity and hypertension, reporting that hypertensive and normotensive obese men showed elevated levels of sVCAM-1, sICAM-1 and sE-selectin [15]. However, these levels were

unrelated to the presence of hypertension, suggesting that the changes in endothelial function were secondary to obesity rather than high blood pressure.

The main problem in the above studies was the relatively small number of individuals included; none of these studies included more than 45 hypertensive individuals. This may, to some extent, explain the conflicting results that have been reported, and some of these may be due to chance. In that respect, larger studies may provide more consistent information. The ARIC study showed significantly elevated levels of sE-selectin in hypertension, while levels of sVCAM-1 and sICAM-1 were similar in hypertensive and normotensive individuals [16]. However, these results were based on a selection of the original population of about 792 individuals based on the presence or absence of coronary heart disease, and therefore do not represent these relationships in the general population. The Physicians' Health Study investigated the association of sICAM-1 levels with measures of blood pressure in a large sample of middle-aged men (n = 948), and showed a strong positive association of sICAM-1 levels with both systolic and diastolic blood pressure [17].

Some reports dealt with specific issues that are important in hypertension. Kuroda et al. [18] showed that sVCAM-1 is a marker of left ventricular hypertrophy in hypertensive individuals, while levels of sICAM-1 and sE-selectin were not. In addition, levels of sE-selectin were shown to be elevated in salt-sensitive compared to salt-resistant hypertensive individuals, while sVCAM-1 and sICAM-1 levels were similar between the groups [19]. These two studies included somewhat more individuals in their analyses; however, the numbers still did not exceed a hundred, and the results were not confirmed by others.

Taken together, we can conclude that results among reports remain conflicting. However, all studies described above showed an increase in at least one of the three cellular adhesion molecules. This seems to imply that increased hemodynamic stress on the endothelium caused by hypertension might raise the expression of endothelial cell adhesion molecules. However, the reverse may also be true – increased expression of endothelial cell adhesion molecules may contribute to the development of hypertension due to failure of the endothelium to perform its tasks correctly in regulating vascular tone.

Obesity

Several studies have investigated the association of obesity with soluble cellular adhesion molecules. Adipose tissue is thought to be able to produce inflammatory markers such as interleukin-6 and tumor necrosis factor α (TNF-α), which in turn are able to stimulate the expression of cellular adhesion molecules. Higher levels of sE-selectin in obesity have been described in both men [16] and women [20], including positive correlations with body mass index or body fat [21 – 23]. Conflicting results exist for the relation of sVCAM-1 and sICAM-1 levels with obesity. Some reports have shown an association between both sVCAM-1 and sICAM-1 on the one hand, and body mass index on the other [15,17,24,25], while others have not [16,26]. However, the latter included a subgroup of the ARIC study with cardiovascular disease [16] and a population of women with polycystic ovary syndrome [26], and may not pertain to the general population. The degree of obesity in the individuals included may of course have an effect on the results of the study. One study investigated sICAM-1 levels in morbid obesity (body mass index above 35 kg/m^2), and showed elevated sICAM-1 levels compared to non-obese individuals [27].

When obesity is accompanied by type 2 diabetes, levels of sE-selectin and, in most cases, sICAM-1 are associated with measures of obesity [22,23,28,29]. Soluble VCAM-1 appears to be associated with obesity in type 2 diabetic Pima Indians [23], while no such association has been found in Caucasian and Japanese individuals [22,28,29]. Another study on non-diabetic Pima Indians demonstrated an association between sICAM-1 and percentage of total body fat, but not sE-selectin levels [21].

Studies on the effects of weight loss on these molecules strongly suggest that obesity is causally involved in elevated levels of endothelial cell adhesion molecules. Levels of all three endothelial cell adhesion molecules have been reported to decrease after weight loss [15,20,27].

Taken together, the evidence suggests that there is indeed an association between obesity and the expression of cellular adhesion molecules. This suggests that obesity is involved in the development of endothelial dysfunction. Studies on the effects of weight loss suggest endothelial dysfunction caused by obesity is reversible. Mechanisms that may explain these relationships include increased stress to the cardiovascular system in overweight patients, increased production of inflammatory markers by adipocytes, or metabolic stimulus such as the effect of insulin on the endothelium.

Dyslipidemia

Hypercholesterolemia (although not a consistent feature of the metabolic syndrome) [30 – 32] has been associated with elevated levels of sVCAM-1, sICAM-1 and sE-selectin. However, in accordance with the previous features of the metabolic syndrome, conflicting results have been published with regard to endothelial cell adhesion molecules and dyslipidemia. No differences in sVCAM-1 levels have been reported for hypercholesterolemia [33 – 36], while levels both elevated [33,37,38] and comparable to controls have been reported for sICAM-1 and sE-selectin [34 – 36,39]. Two reports on hypertriglyceridemia have demonstrated elevated levels of all three endothelial cell adhesion molecules [33,40]. Only one study reported increased sICAM-1 levels in familial hypercholesterolemia (FH) [41], while others showed no differences in sVCAM-1, sICAM-1 or sE-selectin levels between FH and non-FH and control subjects [36,42]. Calabresi et al. [43] specifically investigated the association between low HDL cholesterol and endothelial cell adhesion molecules, and found significant inverse associations of HDL cholesterol and sICAM-1 with sE-selectin, but not with sVCAM-1. However, since only one study has reported this finding, this observation needs to be confirmed.

Taken together, these findings suggest that dyslipidemia does have an effect on cellular adhesion molecule levels. Hypercholesterolemia may have a more specific effect on sICAM-1 and sE-selectin levels, whereas triglycerides and HDL cholesterol levels would also affect sVCAM-1 levels. It seems likely that changes

in lipid profile do have some effect on the expression of endothelial cell adhesion molecules.

Insulin Resistance

Several studies have investigated the association of endothelial cell adhesion molecules with insulin resistance in non-diabetic individuals. These studies showed that levels of sVCAM-1, sICAM-1 and sE-selectin were significantly elevated in insulin-resistant individuals [21,44–47], although not all studies demonstrated this for sVCAM-1 [21,46]. One study investigated this issue in Japanese individuals, and demonstrated increased sE-selectin levels in the insulin-resistant state, while no difference in sVCAM-1 or sICAM-1 levels was found [47].

In Caucasians, some population-based sample studies have investigated the association between insulin resistance and cellular adhesion molecules. Hak et al [46]. investigated a large group of non-diabetic individuals from the Rotterdam study, and found an association of sICAM-1 with post-load insulin levels, but not with sVCAM-1. In contrast, the Hoorn study did show an association of sVCAM-1 with glucose tolerance status in a population that also included diabetic individuals [48]. Somewhat smaller studies including non-diabetic, impaired glucose tolerance and type 2 diabetic individuals in general demonstrated increased levels of sVCAM-1, sICAM-1 and sE-selectin in the insulin-resistant state [49–51], although one study observed no association at all [52]. Studies that included type 2 diabetic individuals only consistently showed increased levels of sVCAM-1 and sE-selectin in insulin-resistant individuals; however, the results on sICAM-1 remain inconclusive [28,53].

In conclusion, there is a trend among studies that shows increased levels of all three endothelial cell adhesion molecules in insulin resistant states whether or not glucose tolerance is normal or type 2 diabetes is present.

Type 2 diabetes

Numerous studies have investigated the association between endothelial cell adhesion molecules and type 2 diabetes. As in the previous sections, conflicting results have been reported. One of the earliest reports showed increased levels of sVCAM-1 and sE-selectin with no difference in sICAM-1 levels in type 2 diabetic individuals compared to controls [54]. Many other findings have been reported; an increase in sICAM-1 with no change in sVCAM-1 and sE-selectin [55], and increase in sVCAM-1 and sICAM-1 with no change in sE-selectin [56], no change in any of the cellular adhesion molecules [52,57], or an increase in all three cellular adhesion molecules [50,58,59]. However, the majority of the studies show increased levels of endothelial cell adhesion molecules in type 2 diabetic compared to non-diabetic individuals. In addition, the larger studies, including over 100 type 2 diabetic patients, consistently show that levels of sVCAM-1, sICAM-1 and sE-selectin are elevated compared to non-diabetic controls [59–61].

Other studies have investigated whether the presence of diabetic complications was associated with cellular adhesion molecules. With regard to nephropathy, Schmidt et al. [62] were among the first to report increased sVCAM-1 levels in diabetic patients with microalbuminuria. Others followed by demonstrating increased sVCAM-1 and/or sICAM-1 levels in the presence of nephropathy [57,63], while Lim et al. [64] could not demonstrate any increase in sVCAM-1 and sICAM-1 levels in diabetic individuals with microalbuminuria compared to those with normoalbuminuria. In addition to these cross-sectional studies, the Hoorn study demonstrated that the development of elevated urinary albumin excretion rate during a follow-up of 6.1 years was significantly associated with levels of sVCAM-1. [65] Apart from that, Stehouwer and colleagues reported sVCAM-1 and sE-selectin to be interrelated to increased urinary albumin excretion in type 2 diabetes during a nine-year follow-up. [66] These two longitudinal studies provide strong evidence that endothelial dysfunction is involved in the early development of nephropathy.

Results are more in agreement with regard to retinopathy; Japanese type 2 diabetic individuals with proliferative retinopathy showed a significant increase in sVCAM-1 compared to those without proliferative retinopathy [67]. This observation was confirmed in diabetic patients with retinopathy but without macrovascular disease [53]. The latter study also investigated sE-selectin levels and found similar results, increased levels in the presence of retinopathy.

Levels of sVCAM-1 and sE-selectin were either increased [53] or remained similar in type 2 diabetes [64]. The Hoorn study provided longitudinal data on this subject, as increased sVCAM-1 levels were significantly associated with increased risk of cardiovascular mortality (relative risk and [95% confidence interval] were 1.10 [1.05–1.15] per 100 μg/l increase in sVACM-1) [48].

Taken together, these results suggest that levels of cellular adhesion molecules are increased in type 2 diabetes compared to levels in non-diabetic individuals. With regard to micro- and macrovascular complications, the indications are that cellular adhesion molecules increase in the presence of retinopathy, nephropathy and cardiovascular disease. Longitudinal studies suggest a pathophysiological role of endothelial function in the development of nephropathy and cardiovascular disease.

Prognostic Information from Cellular Adhesion Molecules

Type 2 diabetes

Only little information is available on the prognostic value of cellular adhesion molecules in the development of type 2 diabetes. Very recently, this issue was investigated in the Nurses' Health Study [68], which included 737 incident cases of type 2 diabetes and 785 age- and race-matched controls followed up for 10 years. These investigators found that elevated sE-selectin and sICAM-1 levels predicted incident type 2 diabetes in these women, independently of known risk factors. Relative risks of diabetes were 7.5 (5.1–11.1) for sE-selectin and 4.3 (3.0–6.2) for sICAM-1 in the highest quintile relative to the lowest quintile of cellular adhesion molecule levels. The association between sVCAM-1 and incident diabetes was not independent of known diabetes risk factors. These results suggest a causal relationship between microvascular dysfunction and insulin resistance as previously implied [69]. This hypothesis is supported by the findings of the ARIC study, which has demonstrated that retinal microangiopathy predicts the development of type 2 diabetes [70].

Cardiovascular disease in type 2 diabetes

Somewhat more information is available on the prognostic value of cellular adhesion molecules in relation to cardiovascular disease in type 2 diabetic individuals. For instance, the Hoorn Study reported that type 2 diabetic individuals with high sVCAM-1 and sICAM-1 levels are at increased risk of cardiovascular death [48,61]. The relative risks for cardiovascular mortality in type 2 diabetic individuals were similar to those in non-diabetic individuals. However, a much larger population would probably be necessary to provide evidence of any interaction between diabetes and adhesion molecule levels in this relationship. In addition, a 10-year follow-up study on type 2 diabetic individuals reported associations between sVCAM-1 and sE-selectin and all-cause mortality [66].

In summary, only few studies have investigated the prognostic value of cellular adhesion molecules in individuals with characteristics of the metabolic syndrome or diabetes. Importantly, the one study that did investigate the role of cellular adhesion molecules in the development of type 2 diabetes showed a markedly high relative risk, suggesting that endothelial dysfunction is indeed an important pathophysiological pathway leading to type 2 diabetes. However, these results would need to be extended and confirmed by others before drawing any final conclusions.

Conclusions

Cellular adhesion molecules may play an important role in the development of the metabolic syndrome and type 2 diabetes, as well as in their cardiovascular complications. All three cellular adhesion molecules, sVCAM-1, sICAM-1 and sE-selectin, are frequently investigated to improve our knowledge on endothelial function. The endothelium is thought to be the major source of the soluble forms of these molecules. Strong evidence exists that increased levels reflect an alteration of endothelial function, which may have pathophysiological consequences on the characteristics of the metabolic syndrome and type 2 diabetes. The strongest evidence is provided by longitudinal studies that show an association between cellular adhesion molecules and development of type 2 diabetes and its cardiovascular complications. Taken together, these results support the concept that endothelial dysfunction is an important pathway leading to type 2 diabetes and cardiovascular disease.

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