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Circulating cellular adhesion molecules and risk of diabetes: the Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Aims—To test the hypothesis that soluble cellular adhesion molecules would be positively and independently associated with risk of diabetes.

Methods—Soluble levels of six cellular adhesion molecules (ICAM-1, E-selectin, VCAM-1, E-cadherin, L-selectin and P-selectin) were measured in participants in the Multi-Ethnic Study of Atherosclerosis, a prospective cohort study. Participants were then followed for up to 10 years to ascertain incident diabetes.

Results—Sample sizes ranged from 826 to 2185. After adjusting for age, sex, race/ethnicity, BMI and fasting glucose or HbA_{1c}, four cellular adhesion molecules (ICAM-1, E-selectin, VCAM-1 and E-cadherin) were positively associated with incident diabetes and there was a statistically significant trend across quartiles. Comparing the incidence of diabetes in the highest and lowest quartiles of each cellular adhesion molecule, the magnitude of association was largest for E-selectin (hazard ratio 2.49; 95% CI 1.26–4.93) and ICAM-1 (hazard ratio 1.76; 95% CI 1.22–2.55) in fully adjusted models. Tests of effect modification by racial/ethnic group and sex were not statistically significant for any of the cellular adhesion molecules (P>0.05).

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Competing interests

None declared.

Conclusions—The finding of significant associations between multiple cellular adhesion molecules and incident diabetes may lend further support to the hypothesis that microvascular endothelial dysfunction contributes to risk of diabetes.

Introduction

Microvascular complications, such as retinopathy, are a hallmark of diabetes, and have been used to help establish clinical thresholds for the diagnosis of diabetes [1]; however, epidemiological research also indicates that dysfunction of the microvasculature involving endothelial or smooth muscle cells precedes and predicts the development of Type 2 diabetes, and may represent an intermediate step linking central obesity or chronic inflammation and Type 2 diabetes [2]. In particular, impaired function of endothelial cells has been hypothesized to play a role in the development of insulin resistance, possibly through a reduced capacity of insulin to redirect blood flow in skeletal muscle from non-nutritive to nutritive capillaries [3]. Once established, insulin resistance may foster a metabolic environment favouring the production of free fatty acids, advanced glycation end products, and mediators of oxidative stress that, in turn, may further impair endothelial function [3].

Cellular adhesion molecules (CAMs), such as ICAM-1 and E-selectin, are released from cell membranes by shedding or proteolytic cleavage. Circulating levels of CAMs have been identified as surrogate markers of endothelial dysfunction or activation. Because the microvasculature accounts for 98% of total vascular surface area [4], these soluble CAMs may largely reflect microvascular endothelial dysfunction. Epidemiological studies have generally supported an independent and positive association between levels of soluble CAMs and incident Type 2 diabetes. For example, a recent systematic review and meta-analysis [2] found that plasma soluble ICAM-1 and E-selectin were independently associated with Type 2 diabetes after accounting for other risk factors. Most prospective studies of diabetes have been restricted to just a few CAMs and have predominantly been conducted in populations of European descent. We evaluated the associations between six CAMs (ICAM-1, E-selectin, VCAM-1, E-cadherin, L-selectin and P-selectin) and risk of diabetes, and determined whether race/ethnicity modified any of these associations. We hypothesized that soluble CAMs would be positively and independently associated with risk of diabetes.

Patients and methods

Study participants

Participants in the Multi-Ethnic Study of Atherosclerosis (MESA) were recruited from six field sites in the USA: Forsyth County, NC (Wake Forest), Northern Manhattan/Bronx, NY (Columbia), Baltimore/Baltimore County, MD (Johns Hopkins), St Paul, MN (University of Minnesota), Chicago, IL (Northwestern), and Los Angeles County, CA (UCLA). Details of recruitment have been previously published [5]. Briefly, MESA recruited 6814 men and women, aged 45–84 years and free of known cardiovascular disease, excluding those who reported a medical history of heart attack, angina, coronary revascularization, pacemaker or defibrillator implantation, valve replacement, heart failure or cerebrovascular disease. The

cohort was 53% women, with a racial/ethnic composition of approximately 38% white, 28% black, 23% Hispanic and 11% Asian (primarily of Chinese descent). The baseline examination (Exam 1) occurred from 2000 to 2002, with Exam 2 from 2002 to 2004, Exam 3 from 2004 to 2005, Exam 4 from 2005 to 2007, and Exam 5 from 2010 to 2011. Institutional review board approval was obtained at all MESA sites and participants gave informed consent.

Measurement of cellular adhesion molecules

A total of six CAMs were evaluated. Four CAMs (VCAM-1, E-cadherin, L-selectin and P-selectin) were measured in a race-stratified random subset of participants, using stored samples from Exam 2. Soluble VCAM-1 was measured in serum by enzyme-linked immunosorbent assay (ELISA) using the Quantikine Human Soluble VCAM Immunoassay kit (R&D Systems, Minneapolis, MN, USA). The minimum detection limit was 0.6 ng/ml, and the inter-assay coefficient of variation was 3.6% at a mean concentration of 564 ng/ml. Soluble E-cadherin was measured in serum by ELISA using the Quantikine Human Soluble E-Cadherin Immunoassay kit (R&D Systems). The minimum detection limit was 0.04 ng/ml, and the inter-assay coefficient of variation was 7.8% at a mean concentration of 197 ng/ml. Soluble L-selectin was measured in serum with a quantitative sandwich ELISA using the Human Soluble L-selectin/CD62L Immunoassay kit (R&D Systems). The minimum detection limit was 0.3 ng/ml, and the inter-assay coefficient of variation was 6.7% at a mean concentration of 943 ng/ml. Soluble P-selectin was measured in plasma using the Human Soluble P-Selectin/CD62P Immunoassay kit (R&D Systems). The minimum detection limit was 0.5 ng/ml, and the inter-assay coefficient of variation was 6.7% at a mean concentration of 182 ng/ml. Two additional proteins of interest (ICAM-1, E-selectin) were measured in serum collected at Exam 1 in a random sample of participants. Soluble ICAM-1 was measured by ELISA (Parameter Human sICAM-1 Immunoassay, R&D Systems). The minimum detection limit was 0.35 ng/ml and the inter-assay coefficient of variation was 5% at a reference mean of 326 ng/ml. Soluble E-selectin was measured by an ELISA (Parameter Human sE-Selectin Immunoassay, R&D Systems). The minimum detection limit was 0.1 ng/ml and inter-assay coefficients of variation ranged from 5.7 to 8.8%.

Incident diabetes

Diabetes was defined as use of insulin or oral diabetes medication or fasting glucose ≥ 7.0 mmol/l (126 mg/dl). Incident cases met at least one of these criteria at one of the follow-up examinations, and non-cases did not meet these criteria at any of the available follow-up examinations.

Other measurements

Information on age, sex, race/ethnicity, education, smoking history and use of medications was obtained via interview and questionnaires. Education was categorized as lower than high school level, high school level (high school completed), some college education/ technical school certificate or associate degree level, bachelor’s degree level, and graduate or professional school level. Smoking status was categorized as current, former or never smoker. Standing height, weight and waist circumference at the level of the umbilicus were

measured by trained technicians using standardized instruments, and BMI was calculated [weight (kg)/height^2 (m^2)]. Physical activity was assessed as the sum of walking for exercise, sports/dancing and conditioning metabolic equivalent task (MET) h per week. Seated blood pressure was measured using a Dinamap® automated blood pressure device. Fasting blood samples were collected and serum glucose was measured at a central laboratory by the glucose oxidase method on the Vitros Analyzer (Johnson & Johnson Clinical Diagnostics, Rochester, NY, USA). HbA_{1c} was measured at Exam 2 in EDTA plasma using the Tosoh HPLC Glycohemoglobin Analyzer (Tosoh Medics Inc., San Francisco, CA, USA). C-reactive protein and interleukin-6 were measured at Exam 1 by the BNII nephelometer (N High Sensitivity CRP, Dade Behring Inc., Deerfield, IL, USA) and an ultrasensitive ELISA (Quantikine HS Human IL-6 Immunoassay, R&D Systems), respectively. Insulin was measured in serum at Exam 1 by an immunoenzymatic sandwich assay (Beckman Instruments Inc.). Genotyping of rs5491 in *ICAM-1* was performed by Illumina Genotyping Services (Illumina Inc., San Diego, CA, USA) using their proprietary GoldenGate assay.

Statistical analysis

For CAMs measured on samples collected at Exam 1 (i.e. ICAM-1 and E-selectin), we excluded subjects with prevalent diabetes at Exam 1 as well as those with no follow-up information at Exams 2–5 that was necessary to classify incident diabetes status. For CAMs measured on samples collected at Exam 2 (i.e. VCAM-1, E-cadherin, L-selectin and P-selectin), we excluded subjects with prevalent diabetes at Exams 1 or 2 as well as those with no follow-up information at Exams 3–5 that was necessary to classify incident diabetes status. Cox proportional hazards models were used to estimate the hazard ratio of incident diabetes by quartile of each CAM, with time at-risk estimated as time from baseline until date of the examination at which diabetes was first ascertained or administrative censoring at the last available examination. Associations with a P value < 0.05 were considered statistically significant. A test of trend was performed by testing a linear association across quartiles. Analyses were minimally adjusted for age, sex and race/ethnicity (Model 1), and then more fully adjusted in models that included other diabetes risk factors (Models 2 and 3). Covariate values were taken from the same examination at which the CAM was assayed (either Exam 1 or Exam 2). The proportional hazards assumption was tested by adding a term to each model, reflecting the product of CAM level and (log) time. Heterogeneity in the strength of association by race/ethnicity or sex was tested by including relevant multiplicative interaction terms in the Cox models with CAMs expressed as continuous variables. Because the T-allele of the *ICAM1* single nucleotide polymorphism (SNP) rs5491 has been reported to interfere with the monoclonal antibody used in the R&D Systems assay for ICAM-1 [6,7], we also conducted a sensitivity analysis for ICAM-1 restricted to individuals homozygous for the AA genotype.

Results

Sample sizes ranged from 826 in analyses of E-selectin to 2185 in analyses of ICAM-1. Table 1 shows unadjusted participant characteristics by quartile of each CAM. On average, men had higher levels of E-selectin and P-selectin, while women had higher levels of L-

selectin. VCAM-1 and E-cadherin were most strongly associated with age, with higher mean levels among older participants.

The mean (SD) length of follow-up was 8.1 (2.7) years for CAMs measured at MESA Exam 1 and 6.5 (2.3) years for CAMs measured at Exam 2. Among cases, the mean follow-up time from baseline to ascertainment of diabetes was 5.1 years for CAMs measured at Exam 1 and 4.6 years for CAMs measured at Exam 2. In a model adjusting for age, sex, race/ethnicity (Model 1), four CAMs (ICAM-1, E-selectin, E-cadherin and P-selectin) were positively associated with incidence of diabetes and there was a statistically significant trend across quartiles (Table 2). After additional adjustment for BMI and fasting glucose or HbA_{1c} (Model 2), the hazard ratios for ICAM-1, E-selectin and P-selectin were substantially attenuated. The test for trend in Model 2 remained significant for ICAM-1 (P=0.002), E-selectin (P=0.02) and E-cadherin (P=0.03), but not for P-selectin (P=0.35). By contrast, the association between VCAM-1 and diabetes became stronger and statistically significant after additional adjustment for BMI and fasting glucose (hazard ratio 1.00, 1.48, 1.41 and 1.66 for quartiles 1–4, respectively; P=0.04 for trend). Comparing the incidence of diabetes in the highest and lowest quartiles of each CAM, the magnitude of association in Model 2 was strongest for E-selectin (hazard ratio 2.16; 95% CI 1.14–4.09) and ICAM-1 (hazard ratio 1.87; 95% CI 1.33–2.65). The pattern of results for ICAM-1 were largely unchanged in a sensitivity analysis restricting to individuals with the AA genotype for *ICAM1* SNP rs5491 (314 subjects excluded). Hazard ratios for model 2 were 1.58, 1.31 and 1.93 across quartiles 2–4, respectively (P=0.02 for trend). With the exception of VCAM- and E-cadherin, the magnitude and pattern of association for each CAM was not materially different after additional adjustment for examination site, waist circumference, physical activity, education, smoking status, systolic blood pressure, use of hypertension medications, C-reactive protein, interleukin-6 or fasting insulin (Model 3).

Similar results were obtained when CAMs were modelled as continuous variables (Table 3): strongest associations were found for ICAM-1 (hazard ratio 1.14 per standard deviation), E-selectin (hazard ratio 1.24) and VCAM-1 (hazard ratio 1.22), when each CAM was included in a separate model. VCAM-1 remained significantly associated with incident diabetes (hazard ratio 1.29 per SD; 95% CI 1.09–1.53) in a model that included the other CAMs measured at Exam 2. Using the final model with CAMs represented as continuous variables, tests of effect modification by racial/ethnic group or sex were not significant for any of the CAMs (P>0.05). No violations of the proportional hazards assumption were detected.

Discussion

In the present study we found that several circulating CAMs were independently associated with incident diabetes in an ethnically diverse sample from the MESA. Associations were strongest for ICAM-1, E-selectin, VCAM-1 and E-cadherin, and all were positively related to diabetes risk. The magnitude and direction of association between these CAMs and incidence of diabetes were found to be largely similar across four racial/ethnic groups.

ICAM-1, E-selectin and VCAM-1 have been the most widely studied CAMs in relation to Type 2 diabetes in epidemiological cohort studies [8–14]. Soluble ICAM-1 is formed by

proteolytic cleavage of ICAM-1, a transmembrane glycoprotein constitutively expressed on leukocytes, vascular endothelial cells, fibroblasts and epithelial cells, where it plays a key role in leukocyte recruitment to inflamed sites [15]. E-selectin is expressed by endothelial cells after stimulation by inflammatory molecules and also helps recruit leukocytes to a site of injury. Soluble E-selectin is produced by proteolytic cleavage or through shedding of cell surface proteins by activated cells [16]. Soluble VCAM-1 is derived from a transmembrane protein induced by cytokines and expressed by endothelial cells, where it facilitates the adhesion of leukocytes to the vascular endothelium [17]. A recent systematic review and meta-analysis [5] found relative risks of incident Type 2 diabetes were 1.5 (95% CI 1.4–1.6) per standard deviation of plasma E-selectin and 1.2 (95% CI 1.1–1.3) per standard deviation of plasma ICAM-1 after accounting for other diabetes risk factors. Consistent with these previous studies, both ICAM-1 and E-selectin were found to be independently associated with incident diabetes in the MESA cohort, with a magnitude of association similar to that estimated in the prior meta-analysis [2]. We also found a significant association between VCAM-1 levels modelled continuously and incident diabetes. In contrast to the present study, no association between VCAM-1 and incidence of diabetes was reported in the Women's Health Initiative Observational Study [11], the Nurses' Health Study [10], or a study of Pima Indians [12].

To our knowledge, the present study is the first to evaluate the association of soluble E-cadherin with incident diabetes. Soluble E-cadherin is a 80 kDa fragment formed by the proteolytic cleavage of the extracellular domain of E-cadherin expressed at the cell surface of epithelial cells, possibly in response to pro-inflammatory cytokines and growth factors [18]. E-cadherin helps maintain adhesion of epithelial cells and may regulate immune response through targeting of T lymphocytes. Once cleaved, E-cadherin may disrupt cell–cell interactions, and serum levels have been associated with disease states, including various types of cancer, severity of acute pancreatitis, and sepsis or organ dysfunction [18]. Two cross-sectional studies found mean levels of soluble E-cadherin were 10–20% higher in the serum or urine of individuals with diabetes compared with control subjects, but differences were not statistically significant [19›20]. One of these studies also found that urine levels of soluble E-cadherin were markedly higher in subjects with more severe forms of diabetic nephropathy [19].

Soluble L-selectin is a fragment formed by the proteolytic cleavage of the extracellular domain of L-selectin expressed on most leukocytes. L-selectin facilitates the initial attachment of leukocytes to the endothelium in inflammation, and is shed from the surface after cell activation. Soluble L-selectin may competitively inhibit the binding of leukocytes to ligands on endothelial cells [21]. It has been hypothesized that L-selectin shedding may serve to limit leukocyte recruitment during inflammation, with higher levels of soluble L-selectin conferring a lower risk of conditions with an inflammatory aetiology [21]. One small cross-sectional study that reported lower soluble L-selectin in cases with Type 2 diabetes compared with control subjects [22]; to our knowledge there are no published prospective studies of L-selectin and incident diabetes. Soluble L-selectin levels and gene variants were not associated with clinical or subclinical cardiovascular disease in MESA [23›24].

P-selectin is produced by platelets and endothelial cells, with platelets being the main source of circulating P-selectin [25]. It is important in the recruitment of leukocytes to the site of injury during inflammation, and recruitment and aggregation of platelets at areas of vascular injury. In the present analysis we found a similar positive association between P-selectin and incident diabetes in sex-, age- and race/ethnicity-adjusted models; however, the hazard ratios for P-selectin were substantially attenuated and no longer statistically significant after adjustment for BMI and HbA_{1c}. Relatively few studies have explored relations of soluble P-selectin and diabetes. In a cross-sectional analysis of the Chennai Urban Rural Epidemiology Study, P-selectin levels were found to be higher in those with prevalent diabetes compared with those with normal or impaired glucose tolerance [26]. Similarly, in an earlier analysis of the MESA cohort, we found that prevalence of diabetes increased from lower to higher categories of P-selectin level, and there was heterogeneity across racial/ethnic groups in the strength of association between P-selectin and outcomes such as prevalent diabetes and coronary artery calcium [27]. In the Framingham Study, no associations were found between P-selectin and incident diabetes in adjusted models, in accordance with the present results [28]. Discrepant results between cross-sectional and longitudinal studies could occur if elevated P-selectin level was a consequence rather than a cause of diabetes.

The observation that multiple soluble CAMs were independently associated with incident diabetes in this study may point to a broader role for endothelial dysfunction in the pathophysiology of Type 2 diabetes rather than a direct role for any specific CAM. A possible mechanism linking CAMs and diabetes involves reduced capacity of insulin to redirect blood flow in skeletal muscle from non-nutritive to nutritive capillaries in the context of endothelial impairment [3], leading to peripheral insulin resistance. Central obesity and accompanying chronic inflammation may exacerbate endothelial dysfunction.

The strengths of the present study include the population-based design, regular follow-up and standardized data collection procedures and measurements to ascertain diabetes, and racial/ethnic diversity of the sample. With a few exceptions [11⁻13], many previous prospective studies of CAMs and Type 2 diabetes have been conducted in study populations that were predominantly of European descent [8⁻10،14], a significant gap in the literature acknowledged in a recent review [2]. Limitations include one-time measurements of CAMs, and restriction to soluble forms of CAMs measured in the circulation, which may be less biologically relevant than the cellular forms of these proteins. In addition, the number of incident diabetes events may have been too few to detect significant heterogeneity in associations across ethnic racial/groups for some CAMs. We were not able to replicate an interaction between soluble E-selectin and race/ethnicity as reported in the Women's Health Initiative Observational Study [11].

In conclusion, results from long-term follow-up of the MESA cohort lend further support to the hypothesis that microvascular endothelial dysfunction contributes to the development diabetes. Associations between soluble ICAM-1 and E-selectin and incident diabetes were consistent with previous studies; results for other CAMs need to be replicated and confirmed in other prospective studies.

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References

1. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 1997; 20:1183–97. [PubMed: 9203460]
2. Muris DMJ, Houben A, Schram MT, Stehouwer CDA. Microvascular dysfunction is associated with a higher incidence of type 2 diabetes mellitus a systematic review and meta-analysis. Arterioscler Thromb Vasc Biol. 2012; 32:3082–3094. [PubMed: 23042819]
3. Muniyappa R, Iantorno M, Quon MJ. An integrated view of insulin resistance and endothelial dysfunction. Endocrinol Metab Clin North Am. 2008; 37:685–711. [PubMed: 18775359]
4. Wolinsky H. A proposal linking clearance of circulating lipoproteins to tissue metabolic-activity as a basis for understanding atherogenesis. Circ Res. 1980; 47:301–311. [PubMed: 6996862]
5. Bild DE, Bluemke DA, Burke GL, Detrano R, Roux AVD, Folsom AR, et al. Multi-ethnic study of atherosclerosis: Objectives and design. Am J Epidemiol. 2002; 156:871–81. [PubMed: 12397006]
6. Bielinski SJ, Pankow JS, Li N, Hsu FC, Adar SD, Jenny NS, et al. ICAM1 and VCAM1 polymorphisms, coronary artery calcium, and circulating levels of soluble ICAM-1: the multi-ethnic study of atherosclerosis (MESA). Atherosclerosis. 2008; 201:339–344. [PubMed: 18420209]
7. Register TC, Burdon KP, Lenchik L, Bowden DW, Hawkins GA, Nicklas BJ, et al. Variability of serum soluble intercellular adhesion molecule-1 measurements attributable to a common polymorphism. Clin Chem. 2004; 50:2185–2187. [PubMed: 15502096]
8. Stranges S, Rafalson LB, Dmochowski J, Rejman K, Tracy RP, Trevisan M, et al. Additional contribution of emerging risk factors to the prediction of the risk of type 2 diabetes: Evidence from the Western New York Study. Obesity. 2008; 16:1370–76. [PubMed: 18356828]
9. Thorand B, Baumert J, Chambless L, Meisinger C, Kolb H, Doring A, 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; 26:398–405. [PubMed: 16322530]
10. Meigs JB, Hu FB, Rifai N, Manson JE. Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. JAMA. 2004; 291:1978–1986. [PubMed: 15113816]
11. Song Y, Manson JE, Tinker L, Rifai N, Cook NR, Hu FB, et al. Circulating levels of endothelial adhesion molecules and risk of diabetes in an ethnically diverse cohort of women. Diabetes. 2007; 56:1898–1904. [PubMed: 17389327]
12. Krakoff J, Funahashi T, Stehouwer CDA, Schalkwijk CG, Tanaka S, Matsuzawa Y, et al. Inflammatory markers, adiponectin, and risk of type 2 diabetes in the Pima Indian. Diabetes Care. 2003; 26:1745–1751. [PubMed: 12766104]
13. Hoogeveen RC, Ballantyne CM, Bang H, Heiss G, Duncan BB, Folsom AR, et al. Circulating oxidised low-density lipoprotein and intercellular adhesion molecule-1 and risk of type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. Diabetologia. 2007; 50:36–42. [PubMed: 17136392]
14. Sattar N, Murray HM, Welsh P, Blauw GJ, Buckley BM, de Craen AJ, et al. Are elevated circulating intercellular adhesion molecule 1 levels more strongly predictive of diabetes than vascular risk? Outcome of a prospective study in the elderly. Diabetologia. 2009; 52:235–239. [PubMed: 19030842]
15. Hua S. Targeting sites of inflammation: intercellular adhesion molecule-1 as a target for novel inflammatory therapies. Front Pharmacol. 2013; 4:127. [PubMed: 24109453]

16. Telen MJ. Cellular adhesion and the endothelium: E-selectin, L-selectin, and pan-selectin inhibitors. Hematol Oncol Clin North Am. 2014; 28:341–354. [PubMed: 24589270]
17. Gearing AJ, Hemingway I, Pigott R, Hughes J, Rees AJ, Cashman SJ. Soluble forms of vascular adhesion molecules, E-selectin, ICAM-1, and VCAM-1: pathological significance. Ann N Y Acad Sci. 1992; 667:324–331. [PubMed: 1285023]
18. Grabowska MM, Day ML. Soluble E-cadherin: more than a symptom of disease. Front Biosci (Landmark Ed). 2012; 17:1948–1964. [PubMed: 22201848]
19. Jiang H, Guan G, Zhang R, Liu G, Cheng J, Hou X, et al. Identification of urinary soluble E-cadherin as a novel biomarker for diabetic nephropathy. Diabetes Metab Res Rev. 2009; 25:232–241. [PubMed: 19177462]
20. Katayama M, Hirai S, Kamihagi K, Nakagawa K, Yasumoto M, Kato I. Soluble E-cadherin fragments increased in circulation of cancer patients. Br J Cancer. 1994; 69:580–585. [PubMed: 8123491]
21. Hafezi-Moghadam A, Thomas KL, Prorock AJ, Huo Y, Ley K. L-selectin shedding regulates leukocyte recruitment. J Exp Med. 2001; 193:863–872. [PubMed: 11283159]
22. Mastej K, Adamiec R. Serum level of sL-selectin and leukocyte surface expression of L-selectin in patients with type 2 diabetes. Przegl Lek. 2011; 68:140–145. Article in Polish. [PubMed: 21812228]
23. Berardi C, Decker PA, Kirsch PS, de Andrade M, Tsai MY, Pankow JS, et al. Plasma and serum L-selectin and clinical and subclinical cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). Transl Res. 2014; 163:585–592. [PubMed: 24631064]
24. Berardi C, Larson NB, Decker PA, Wassel CL, Kirsch PS, Pankow JS, et al. Multi-ethnic analysis reveals soluble L-selectin may be post-transcriptionally regulated by 3′UTR polymorphism: the Multi-Ethnic Study of Atherosclerosis (MESA). Hum Genet. 2015; 134:393–403. [PubMed: 25576479]
25. Semenov AV, Romanov YA, Loktionova SA, Tikhomirov OY, Khachikian MV, Vasil'ev SA, et al. Production of soluble P-selectin by platelets and endothelial cells. Biochemistry (Mosc). 1999; 64:1326–1335. [PubMed: 10611541]
26. Gokulakrishnan K, Deepa R, Mohan V, Gross MD. Soluble P-selectin and CD40L levels in subjects with prediabetes, diabetes mellitus, and metabolic syndrome - the Chennai Urban Rural Epidemiology Study. Metabolism. 2006; 55:237–242. [PubMed: 16423632]
27. Bielinski SJ, Berardi C, Decker PA, Kirsch PS, Larson NB, Pankow JS, et al. P-selectin and subclinical and clinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis. 2015; 240:3–9. [PubMed: 25744700]
28. Dallmeier D, Larson MG, Wang N, Fontes JD, Benjamin EJ, Fox CS. Addition of Inflammatory Biomarkers Did Not Improve Diabetes Prediction in the Community: The Framingham Heart Study. J Am Heart Assoc. 2012; 1(4)

What's new?

- Most prospective studies of cellular adhesion molecules and incident diabetes have been limited to a few cellular adhesion molecules and have predominantly been conducted in populations of European descent.
- We tested the associations between six different cellular adhesion molecules and risk of diabetes in a diverse, population-based sample.
- Significant associations between multiple cellular adhesion molecules and incident diabetes may indicate an important role of microvascular endothelial dysfunction in the pathophysiology of Type 2 diabetes.

Table 1

Unadjusted baseline* characteristics (mean or percentage) by quartile of cellular adhesion molecules

Characteristic	Quartile 1	Quartile 2	Quartile 3	Quartile 4
	ICAM-1			
No. of subjects	554	542	546	553
Age, years	57	59	60	60
Gender, % male	44	43	43	41
BMI, kg/m^2	27	27	28	29
Fasting glucose, mmol/l	4.8	4.8	4.7	4.8
	E-selectin			
No. of subjects	205	210	204	207
Age, years	59	59	59	58
Gender, % male	32	41	47	47
BMI, kg/m^2	27	28	28	30
Fasting glucose, mmol/l	4.8	4.8	4.9	5.0
	VCAM-1			
No. of subjects	436	465	449	448
Age, years	58	60	64	67
Gender, % male	47	42	46	52
BMI, kg/m^2	28	27	27	27
Fasting glucose, mmol/l	5.1	5.1	5.1	5.1
HbA1c, mmol/mol (%)	37 (5.5)	37 (5.5)	36 (5.4)	36 (5.4)
	E-cadherin			
No. of subjects	449	448	458	443
Age, years	60	62	62	66
Gender, % male	40	46	51	50
BMI, kg/m^2	27	28	28	27
Fasting glucose, mmol/l	5.1	5.1	5.2	5.1
HbA1c, mmol/mol (%)	36 (5.4)	36 (5.4)	37 (5.5)	37 (5.5)
	L-selectin			
No. of subjects	452	445	453	448
Age, years	64	63	61	61
Gender, % male	62	50	39	35
BMI, kg/m^2	27	27	28	28
Fasting glucose, mmol/l	5.1	5.1	5.2	5.1
HbA1c, mmol/mol (%)	37 (5.5)	37 (5.5)	36 (5.4)	36 (5.4)
	P-selectin			
No. of subjects	478	465	472	479
Age, years	61	63	63	62

Characteristic	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Gender, % male	36	43	46	59
BMI, kg/m^2	27	27	27	28
Fasting glucose, mmol/l	5.1	5.1	5.1	5.2
HbA1c, mmol/mol (%)	36 (5.4)	36 (5.4)	37 (5.5)	37 (5.5)

MESA, Multi-Ethnic Study of Atherosclerosis.

*Baseline is MESA Exam 1 for ICAM-1 and E-selectin and Exam 2 for VCAM-1, E-cadherin, L-selectin and P-selectin; HbA_{1c} was not measured at Exam 1.

Table 2

Incidence of diabetes by cellular adhesion molecules, in quartiles

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
	ICAM-1*, ng/ml				***P* trend**
Mean (range)	188 (18–227)	246 (228–264)	286 (265–307)	365 (308–734)	
Diabetes cases	56	72	59	99	
Rate per 1000 person-years	12.2	16.4	13.2	23.7	
Model 1 hazard ratio (95% CI)	1.00 (reference)	1.69 (1.18–2.42)	1.40 (0.96–2.06)	2.44 (1.73–3.45)	<0.001
Model 2 hazard ratio (95% CI)	1.00 (reference)	1.64 (1.14–1.91)	1.30 (0.89–1.91)	1.87 (1.33–2.65)	0.002
Model 3 hazard ratio (95% CI)	1.00 (reference)	1.61 (1.12–2.32)	1.24 (0.84–1.83)	1.76 (1.22–2.55)	0.02
	E-selectin*, ng/ml				
Mean (range)	27 (5–35)	44 (36–50)	57 (51–64)	84 (65–201)	
Diabetes cases	13	21	28	45	
Rate per 1000 person-years	7.5	12.1	17.3	30.6	
Model 1 hazard ratio (95% CI)	1.00 (reference)	1.54 (0.76–3.11)	2.41 (1.24–4.70)	3.76 (1.99–7.08)	<0.001
Model 2 hazard ratio (95% CI)	1.00 (reference)	1.64 (0.80–3.34)	1.57 (0.80–3.08)	2.16 (1.14–4.09)	0.02
Model 3 hazard ratio (95% CI)	1.00 (reference)	1.78 (0.85–3.75)	1.85 (0.91–3.73)	2.49 (1.26–4.93)	0.01
	VCAM-1†, ng/ml				
Mean (range)	503 (252–583)	639 (584–692)	758 (693–834)	1012 (835–2643)	
Diabetes cases	43	46	38	45	
Rate per 1000 person-years	14.2	14.9	13.0	16.8	
Model 1 hazard ratio (95% CI)	1.00 (reference)	1.23 (0.80–1.88)	1.10 (0.69–1.74)	1.40 (0.89–2.21)	0.22
Model 2 hazard ratio (95% CI)	1.00 (reference)	1.48 (0.96–2.29)	1.41 (0.89–2.26)	1.66 (1.05–2.62)	0.04
Model 3 hazard ratio (95% CI)	1.00 (reference)	1.39 (0.90–2.17)	1.27 (0.79–2.04)	1.49 (0.93–2.39)	0.14
	E-cadherin†, ng/ml				
Mean (range)	157 (106–177)	193 (178–207)	225 (208–245)	292 (246–836)	
Diabetes cases	39	31	56	46	
Rate per 1000 person-years	12.7	10.4	18.6	17.2	
Model 1 hazard ratio (95% CI)	1.00 (reference)	0.86 (0.53–1.38)	1.51 (0.99–2.29)	1.44 (0.92–2.26)	0.02
Model 2 hazard ratio (95% CI)	1.00 (reference)	0.89 (0.55–1.43)	1.56 (1.02–2.38)	1.43 (0.90–2.28)	0.03

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
	ICAM-1*, ng/ml				*P* trend
Model 3 hazard ratio (95% CI)	1.00 (reference)	0.79 (0.49–1.29)	1.30 (0.84–2.01)	1.24 (0.77–2.00)	0.13
	L-selectin†, ng/ml				
Mean (range)	673 (281–762)	823 (763–883)	943 (884–1012)	1156 (1013–2106)	
Diabetes Cases	44	51	41	36	
Rate per 1000 person-yrs	15.3	17.5	13.8	12.1	
Model 1 hazard ratio (95% CI)	1.00 (reference)	1.15 (0.77–1.73)	0.90 (0.58–1.39)	0.81 (0.51–1.28)	0.23
Model 2 hazard ratio (95% CI)	1.00 (reference)	1.01 (0.67–1.53)	0.91 (0.59–1.42)	0.83 (0.52–1.31)	0.37
Model 3 hazard ratio (95% CI)	1.00 (reference)	1.01 (0.67–1.53)	0.88 (0.56–1.39)	0.79 (0.49–1.26)	0.27
	P-selectin†, ng/ml				
Mean (range)	18.4 (8.4–22.1)	24.8 (22.2–27.4)	30.3 (27.5–33.4)	40.4 (33.5–63.7)	
Diabetes cases	38	39	50	57	
Rate per 1000 person-years	12.0	12.7	16.3	18.7	
Model 1 hazard ratio (95% CI)	1.00 (reference)	1.10 (0.70–1.73)	1.36 (0.89–2.09)	1.62 (1.06–2.48)	0.01
Model 2 hazard ratio (95% CI)	1.00 (reference)	1.04 (0.66–1.64)	1.26 (0.82–1.94)	1.17 (0.76–1.80)	0.35
Model 3 hazard ratio (95% CI)	1.00 (reference)	0.98 (0.63–1.57)	1.23 (0.80–1.89)	1.14 (0.73–1.77)	0.40

MESA, Multi-Ethnic Study of Atherosclerosis.

*Baseline is MESA Exam 1; Model 1: adjusted for gender, age, and race/ethnicity; Model 2: adjusted for model 1 variables + BMI, BMI^2, and fasting glucose. Model 3: adjusted for Model 2 variables + examination site, waist circumference, physical activity, education, smoking status, systolic blood pressure, use of hypertension medications, C-reactive protein, interleukin-6, and fasting insulin.

†Baseline is MESA Exam 2; Model 1: adjusted for gender, age, and race/ethnicity; Model 2: adjusted for Model 1 variables + BMI, BMI^2 and HbA_{1C}; Model 3: adjusted for model 2 variables + examination site, waist circumference, physical activity, education, smoking status, systolic blood pressure, and use of hypertension medications.

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Table 3

Adjusted hazard ratio for incident diabetes per standard deviation increment in cellular adhesion molecules

Adhesion molecule	SD for adhesion molecule	Hazard ratio (95% CI)	
		Model 1*	Model 2†
Measured at Exam 1			
ICAM-1	75 ng/ml	1.14 (1.02–1.27)	–
E-selectin	24 ng/ml	1.24 (1.04–1.49)	–
Measured at Exam 2			
VCAM-1	216 ng/ml	1.22 (1.05–1.41)	1.29 (1.09–1.53)
E-cadherin	58 ng/ml	1.11 (0.95–1.29)	1.04 (0.88–1.23)
L-selectin	194 ng/ml	0.91 (0.77–1.08)	0.82 (0.69–0.98)
P-selectin	9 ng/ml	1.06 (0.91–1.22)	1.04 (0.89–1.21)

*Adjusted for age, gender, race/ethnicity, exam site, BMI, BMI^2, waist circumference, physical activity, education, smoking status, systolic blood pressure, use of hypertension medications, C-reactive protein, interleukin-6, fasting insulin, and fasting glucose (Exam 1 CAMs) or HbA_{1c} (Exam 2 CAMs).

†Additionally adjusted for other adhesion molecules measured at same examination.