

Vascular and Endovascular Surgery

<http://ves.sagepub.com/>

The Influence of Diabetes on Degree of Abdominal Aortic Aneurysm Tissue Inflammation

Vassilis Arapoglou, Agathi Kondi-Pafiti, Demetrios Rizos, Eleni Carvounis, Matrona Frangou-Plemenou, Thomas Kotsis and Konstantinos Katsenis

VASC ENDOVASCULAR SURG 2010 44: 454

DOI: 10.1177/1538574410363748

The online version of this article can be found at:

<http://ves.sagepub.com/content/44/6/454>

Published by:



<http://www.sagepublications.com>

Additional services and information for *Vascular and Endovascular Surgery* can be found at:

Email Alerts: <http://ves.sagepub.com/cgi/alerts>

Subscriptions: <http://ves.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

Citations: <http://ves.sagepub.com/content/44/6/454.refs.html>

The Influence of Diabetes on Degree of Abdominal Aortic Aneurysm Tissue Inflammation

Vascular and Endovascular Surgery
44(6) 454-459
© The Author(s) 2010
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1538574410363748
http://ves.sagepub.com


**Vassilis Arapoglou, MD, PhD¹, Agathi Kondi-Pafiti, MD, PhD²,
Demetrios Rizos, PhD³, Eleni Carvounis, MD, PhD²,
Matrona Frangou-Plemenou, DSc, PhD², Thomas Kotsis, MD, PhD¹, and
Konstantinos Katsenis, MD, PhD¹**

Abstract

Abdominal aortic aneurysm (AAA) progression and disease resistance are related to transmural degenerative processes and an inflammatory infiltration (INF). Diabetes is associated with low prevalence and growth rate of AAA. We sought to characterize INF in established AAA (INFAAA), in diabetic patients. From 89 male patients aged 52 to 83 years, aneurysm specimens obtained at open asymptomatic nonruptured AAA repair were graded for INF and immunostained using antibodies against T-lymphocytes (CD3) and macrophages (CD68). Diabetic patients had an odds ratio (OR) 3.8, 95% confidence interval ([CI] 1.14-12.96), $P = .03$, of experiencing above-median INFAAA. These associations were affected by serum glucose (SG) levels (OR 3.6, 95% CI [0.72-18.77]; $P = .1$). Macrophage subpopulations higher in diabetic patients (1.44 ± 0.78 versus 0.98 ± 0.76 ; $P = .02$) were correlated with SG ($r = .21$, $P = .044$). Abdominal aortic aneurysms in diabetic patients are associated with higher INF. Macrophage densities are correlated with SG.

Keywords

abdominal aortic aneurysm, inflammation, diabetes

Introduction

Aneurysmal degeneration is a common and frequently fatal disease of the abdominal aorta. With the current computed tomography (CT), morphologic parameters, such as maximum aortic diameter >5.5 cm, aneurysm shape, abdominal aortic aneurysm (AAA) expansion, computed wall stress, and 18F fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT, the rupture risk can be determined.¹ Studies have assessed pathophysiological events currently thought to contribute to aneurysmal degeneration, based on human end-stage AAA tissues histology and several different experimental animal models, gene expression, circulating markers, and protein abundance in patients and controls.² The pathologic features of human AAA, including mural inflammatory cell infiltration, smooth muscle cell loss, and the destruction of structural matrix proteins, elastin, and collagen, begin years before rupture or elective repair.³ However, the combination of a high-pressured vessel located deep in the body makes repeated biopsies impossible in prospective cohorts and progress difficult. The chronic infiltration, mainly in the outer part of the aorta, consists of the most part of macrophages, lymphocytes, and plasma cells. The dominant cells are T helper cell type 2 (Th2) restricted CD3+ lymphocytes.⁴ Adventitial

macrophages and neocapillaries predominate in larger, advanced aneurysms, whereas smaller AAAs have fewer macrophages and retain more medial smooth muscle cells.⁵ Mononuclear phagocyte infiltration is associated with production of proinflammatory cytokines, prostaglandin derivatives, and reactive oxygen species as part of an innate inflammatory response. These macrophages are the principle source of metalloproteinases (MMPs), which can also be secreted by neutrophils, lymphocytes, and resident mesenchymal cells. Gelatinase B (MMP-9) and many other MMPs, endogenous tissue inhibitors of MMPs (TIMPs), and the secretion of the immunoregulatory cytokine interleukin 10 (IL-10) have also

¹ Vascular Surgical Unit, 2nd Surgical Department, Aretaeion Hospital, Medical School, University of Athens, Greece

² Pathology Laboratory, Areteion Hospital, Medical School, University of Athens, Greece

³ Hormone Laboratory, Areteion Hospital, Medical School, University of Athens, Greece

Corresponding Author:

Vassilis Arapoglou, Vascular Surgical Unit, Areteion Hospital, 76, Vas Sofias Str, 115 28 Athens, Greece
Email: arapoglu@aretaieio.uoa.gr

been described. Animal models of aortic aneurysm confirm that MMPs produced by chronic inflammatory cells are mediators of elastin and collagen degradation. These processes result in progressive dysfunction of aortic elastin and collagen, with gradual aortic expansion and the potential for rupture.^{3,4} Genetic and developmental factors were involved in the natural history of AAA, inflammation, dilatation, and terminal rupture.^{6,7} Patients with large AAAs were found to have an elevated inflammatory status compared to patients with small AAAs.^{8,9} Abdominal aortic aneurysms were traditionally attributed to atherosclerosis.¹⁰ Dominant atherosclerotic risk factors for AAA, male gender, increasing age,¹¹ and smoking¹² were associated with increased AAA tissue inflammation in humans. Hypercholesterolemia and hypertension, also known as atherosclerotic risk factors for AAA, were contributed to infiltration of cells into the adventitia in experimental AAA.^{13,14} Diabetes is a primary risk factor for cardiovascular disease,¹⁵ however, AAA is an exceptional expression of atherosclerotic disease in type 2 diabetes.¹⁶ A screening study of older diabetic men found the prevalence of AAAs to be 2.3%, compared with a 7% in all men older than 65 years of age. In other studies, diabetes has not proved to be a significant independent risk factor for the progression of AAAs. It has also shown that aortic diameter throughout its range has an inverse relationship with fasting glucose concentration.¹⁷ Furthermore, a large recent study demonstrated that the impact of diabetes on AAA surgical patients was higher for intact AAA versus ruptured AAA and that the incidence of ruptured AAA in surgical diabetic patients by gender was similar.¹⁸ The cause of the negative associations between diabetes and AAA is unknown. As vascular inflammation is important in diabetes,¹⁹ it might be expected that aortic inflammation would be more common in diabetic patients with AAA.¹⁷ However, evidence for the role of diabetes in total amount of inflammatory cells and inflammatory cell subpopulations in the AAA wall is lacking. We investigated the influence of diabetes on the degree of tissue inflammation and the predominant inflammatory cell subpopulations in aneurysm specimens obtained at open asymptomatic nonruptured end-stage AAA repair.

Methods

Our institutional review board allowed a retrospective exempt review of patients' database for this study and waived informed consent. All Greek patients undergoing elective open repair of an AAA between June 2002 and December 2007, in Vascular Surgery Unit of Areteion Hospital, were retrospectively studied. Patients with symptomatic or ruptured AAA were excluded. A total of 126 male and 4 female patients underwent elective open repair. Mean diameter of AAAs, measured by CT abdominal scan, in male patients was 5.5 cm. In female patients, the mean diameter of AAAs was 4.9 cm. Full thickness sections from the proximal anterolateral portion of the aneurysm were available for histologic study in 89 male patients at the time of aneurysm repair and at the discretion

of the surgeon. In 27 male and 4 female patients, tissue was not obtained because of surgeon discretion.

Cross-sections of aneurysm wall were dissected of luminal thrombus and peripheral tissue and immersed in 10% neutral buffered formalin for 24 hours and then embedded in paraffin. Aortic 5- μ m cross-sections were mounted and stained with hematoxylin and eosin for regular histology.

For immunohistochemistry, paraffin sections were baked at 58°C for 2 hours and dewaxed in xylene and rehydrated through graded ethanol (100%-70%) and distilled water. Immunohistochemistry was performed using the Bond-Max automatic system (Leica Microsystems, Newcastle Upon Tyne, UK). Primary antibody solution was added for 20 minutes and antigen retrieval was performed by epitope retrieval solution ER1 provided by the manufacturer. Localization studies were done for macrophages (mouse monoclonal antihuman CD68, clone KP1; Biocare Medical, Concord, California) and T-lymphocytes (mouse monoclonal antihuman CD3; Vision Biosystems, Victoria, Australia). After the primary antibody incubation, visualization was performed using the Bond Polymer Refine Detection Kit (Leica Biosystems), according to the manufacturer's instructions. All sections were evaluated by 3 experienced observers blinded to clinical characteristics and to each other.

According to accentuated distribution of histopathologic patterns, semiquantitative analyses were performed to describe the predominant histologic characteristics in the entire sample. The total amount of inflammatory cells in the AAA wall was evaluated by conventional hematoxylin and eosin staining. Furthermore, inflammatory cell subpopulations were specified by CD68 (macrophages) and CD3 (T-lymphocytes) immunostaining.

The degree of inflammatory infiltration (INF; absent inflammation to severe inflammation) was evaluated using a score of 0 to 3, with 0 indicating *no*, 1 indicating *weakly positive*, 2 indicating *intermediate positive*, and 3 indicating *massive positive staining* and the mean $\pm$ standard deviation score was calculated, as has been described by a previous study.²⁰

Clinical data were obtained from the medical records of all 89 patients including age, atherosclerotic risk factors history, obvious atherosclerosis of any territory assessed clinically: coronary (myocardial infarction or unstable angina, revascularization procedures), cerebral (ischemic noncardioembolic stroke or transient ischemic attack or revascularization procedures on the carotids), peripheral vascular (claudication grade II or revascularization procedures on the peripheral arteries), ankle-brachial index < 0.9, AAA diameter; and drug history. Kidney function was evaluated by glomerular filtration rate (GFR) estimated from serum creatinine levels using the Modification of Diet in Renal Disease (MDRD) study prediction equation.²¹

Atherosclerotic Risk Factors

Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, or a diastolic blood pressure ≥ 90 mm Hg, or the use of any antihypertensive medication. Hypercholesterolemia was

Table 1. Demographic and Lifestyle Characteristics of Male Abdominal Aortic Aneurysm Patients With and Without Diabetes^a

	No Diabetes, n = 18	Diabetes, n = 71	P Value
Age (years)	72.5 (6.2)	69.9 (6.8)	.1
Aneurysm diameter (cm)	5.4 (1.0)	5.5 (1.2)	.6
Atherosclerosis, n (%)			
CHD	8 (44.4)	26 (36.6)	.6
PAD	4 (22.2)	16 (22.5)	.9
CVD	4 (22.2)	5 (7.0)	.08
Smoking status, n (%)			
Never	4 (22.2)	12 (16.9)	.7
Current	9 (50.0)	42 (59.1)	.6
Former	5 (27.7)	17 (23.9)	.7
Hypertension, n (%)	13 (72.2)	55 (77.4)	.7
Hypercholesterolemia, n (%)	8 (44.4)	41 (57.7)	.4

Abbreviations: CHD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral artery disease.

^a Mean value (standard deviation) for quantitative variables; number of participants (percentages) for qualitative variables.

defined as total serum cholesterol levels >200 mg/dL, low-density lipoprotein cholesterol >140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, triglyceride >150 mg/dL, or the use of antilipidemic medication.

Diabetes mellitus was defined as a fasting blood glucose >126 mg/dL²² or the use of antidiabetic medication. Smoking history was categorized based on self-report. Smokers were considered current, former, or never. Duration of smoking was estimated in a pack years calculation.

Biochemical Analysis

After an overnight fast, venous blood samples were taken between 8:30 and 9:30 AM. Serum glucose (SG), total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride, and creatinine were determined on an RA5 automated analyzer (Technicon Instrument Corporation, Tarrytown, New York), according to the manufacturer's recommendations.

Statistical Analysis

All continuous variables were presented as mean $\pm$ standard deviation. Categorical and continuous variables were compared between patients with and without diabetes using Fisher exact test and the Student *t* test. For normality of variables, Kolmogorov-Smirnov test was used. Data that were not normally distributed were analyzed using the Mann-Whitney *U* test.

Binary logistic regression was used to assess determinants of above-median tissue inflammation. Determinants that had previously been shown to be associated with AAA tissue inflammation were included to adjust for these in the analysis. These factors were age, smoking history, AAA diameter, pack year smoked, hypertension, and hypercholesterolemia. For the reason that SG was greater in patients with diabetes, a further logistic regression model including SG in addition to age, smoking history, AAA diameter, hypertension, and hypercholesterolemia was also put together. Serum concentrations of glucose were associated with tissue inflammation score,

CD68 (macrophages), and CD3 (T-lymphocytes) densities, using Spearman correlation. A *P* value of less than .05 was considered statistically significant in 2-sided tests. Statistical analyses were performed using SPSS 13.0 for Windows software.

Results

In our cohort, 18 (20.2%) of the 89 patients had diabetes. The clinical characteristics of the patients with and without diabetes were similar (Table 1). Pack years smoked (52.2 ± 48.1), serum cholesterol (214.7 ± 42.6 mg/dL), high-density lipoprotein (45.1 ± 10.7 mg/dL), triglycerides (150 ± 58.6 mg/dL), systolic blood pressure (130 ± 11.3 mm Hg), diastolic blood pressure (81.2 ± 4.8 mm Hg), and estimated GFR (80.1 ± 21.3 mL/min per 1.73 m²) were similar in patients with and without diabetes. Fasting glucose concentration (151.5 ± 42.2 mg/dL) (104.5 ± 11.8 mg/dL) was higher in patients with than without diabetes, *P* < .0001.

Histology Characteristics

Increasing outer media and adventitial inflammatory cell infiltrates were found in diabetic patients. The mean tissue inflammation score was 1.8 ± 1.1 and 1.3 ± 0.9 in patients with and without diabetes, *P* = .03. After adjusting for other factors known associated with AAA tissue inflammation (age, smoking history, AAA diameter, hypertension, and hypercholesterolemia), patients with diabetes had an odds ratio (OR) of 3.8 (1.14-12.96), *P* = .03, experiencing above-median tissue inflammation when compared with those without diabetes (Table 2). These associations were affected by including SG in the model. Patients with diabetes had an OR of 3.6 (0.72-18.77), *P* = .1, experiencing above-median tissue inflammation when compared with those without diabetes. Furthermore, inflammatory cell subpopulations densities specified by CD68 (macrophages) immunostaining were significantly higher in diabetic patients versus nondiabetic patients (1.44 ± 0.78 vs 0.98 ± 0.76 , *P* = .02). CD3-positive cells (T-lymphocytes)

Table 2. Binary Logistic Regression Analysis Results of Clinical Factor Association With Above-Median Aortic Aneurysm Tissue Inflammation (n = 89)

Clinical Factors	Odds Ratio (95% Confidence Interval)	P Value
Age	0.9 (0.9-1.06)	.7
Diabetes	3.8 (1.13-12.96)	.03
Aneurysm diameter	1.08 (0.7-1.6)	.6
Smoking status		
Never		
Former	0.2 (0.04-1.5)	.1
Current	1.2 (0.3-5.4)	.7
Pack years smoked	1 (0.98-1.01)	.9
Hypertension	0.7 (0.3-2.1)	.5
Hypercholesterolemia	1.4 (0.6-3.7)	.4

densities were not significantly different in diabetic patients versus nondiabetic patients (0.89 ± 0.67 vs 0.66 ± 0.65 , $P = .2$). Both the densities of T-lymphocytes and macrophages in the aortic media and adventitia were not related to the age of patients ($r = -.113$, $P = .29$; $r = -.13$, $P = .09$, respectively).

Significant correlation was obvious in serum levels of glucose with CD68 (macrophages; $r = .21$, $P = .044$) but not with total tissue inflammation and CD3 (T-lymphocytes) inflammatory infiltrate ($r = .17$, $P = .1$; $r = .051$, $P = .6$, respectively)

Discussion

In this study, we confirm the suggestion that aortic inflammation might be expected to be more common in diabetic patients with AAA.¹⁷ Moreover, we found that these increased infiltrating inflammatory cells in the wall of advanced AAAs in diabetic patients were independently associated with factors known to be connected with AAA tissue inflammation and were affected by SG concentration. Macrophage densities, in the aortic adventitia and outer media in diabetic patients, were higher and positively correlated with SG concentration.

In industrialized Westernized countries, the incidence of diabetes, particularly type 2 diabetes, is dramatically rising. Diabetes affects approximately 7.8% of the European population and 19% of all persons aged 60 years or older. Cardiovascular complications are the leading cause of morbidity and mortality in patients with diabetes.¹⁵ In contrast, studies favored a lower prevalence of AAA in patients with diabetes, even though, all data were not in agreement with this conclusion, however, no study showed an increase in prevalence^{23,24} and a difference between genders.²⁴ In our cohort, 18 (20.2%) of the 89 male patients, with an AAA mean diameter 5.5 cm, had diabetes.

Atherosclerosis per se probably does not directly cause AAA; but in genetically susceptible individuals, it may provide the first inflammatory trigger to recruit inflammatory cells and direct their subsequent heightened elaboration of further mediators (eg, proteases, reactive oxygen species).¹⁰

Endothelial dysfunction seems to be the trigger for AAA tissue inflammation. Aging is one of the risk factors for AAA. Most literature suggests that circulating levels of

proinflammatory cytokines are elevated in the aged, and macrophages have been assumed the primary producer of these cytokines. Upregulation of Th2 cytokines are also known to be elevated in elderly human patients.¹¹ Smoking is a potent risk factor for AAA. Exposure of animals to tobacco smoke after a relatively minor aortic elastase injury produces significantly more tissue inflammation and elastin degradation, demonstrating that smoking can act as a synergistic factor in AAA development.²⁰ Active cigarette smoking in humans is associated with increased inflammation within the wall of AAAs, suggesting an acute and not a cumulative effect.¹² Mechanical stretch present in AAA may exacerbate inflammation.¹⁴ It is also known that hypercholesterolemia was contributed to infiltration of cells, mostly foamy macrophages, into the adventitia, which was involved in AAA formation in animal models.^{13,14}

The independent, of all the above factors, association of INF in established AAA (INFAAA) with diabetes, found in our study, might be related to additional monocytes that migrated across the endothelium linked to diabetes. We found these associations to be affected by SG and that SG levels were correlated with macrophage densities but not with total tissue inflammation and T-lymphocytes inflammatory infiltrate. In our patients, blood glucose measurements were determined after an overnight fast. Although the prebreakfast and prelunch measurements have been shown to detect the largest proportion of hypoglycemic readings in patients with type 2 diabetes,²⁵ short-term low-glucose concentration might not be expected to reduce the already increased number of monocytes that had migrated on the subendothelium and differentiated into macrophages, during prior postprandial, endothelium exposure to high-glucose concentration. A study on an in vitro human vascular tissue model showed that short-term high-glucose concentration increased the number of monocytes migrating across the endothelium by 70% and also increased the number of these monocytes differentiating into macrophages by 28%. Also, there were nearly 2.5 times more T-lymphocytes that migrated across the endothelium, along with significant cell proliferation, compared to cell migration and differentiation across the endothelium exposed to low-glucose concentration.²⁶ Moreover, a recent study demonstrated that repetitive fluctuation in blood glucose in animals induced more deleterious effects on monocyte-aortic endothelial cell interaction than did consistent glycemic exposure in vivo.²⁷ The assessment of blood glycated hemoglobin (HbA1c), which reflects the average level of glycemic exposure to the vascular wall may have been more revealing, but this was not available from the records of our retrospectively studied patients. Alterations in the vascular endothelium connected to diabetes that contribute to endothelial dysfunction include elevated expression and plasma levels of vasoconstrictors such as angiotensin II and endothelin 1, increased expression of adhesion molecules and associated enhanced adhesion of platelets and monocytes to vascular endothelium, and impairment of nitric oxide (NO) release and reduced NO responsiveness. Endothelial expression of adhesion molecules is enhanced by exposure to dyslipidemia, hypertensive plasma vasoconstrictor concentrations,

and elevated adipose-derived proinflammatory cytokine levels and promotes leukocyte adhesion, migration, and vascular extravasation.¹⁹ An inflammatory vascular state is also induced by advanced glycation end products ([AGEs]; proteins or lipids that become glycated after exposure to sugars). This leads to an induction of reactive oxygen species and promotes endothelial expression of adhesion molecules and proinflammatory cytokines. Soluble AGEs are chemotactic for human blood monocytes both in vitro and in vivo. Advanced glycation end products on the subendothelium induce monocyte migration across an endothelial cell monolayer.²⁸ However, receptor for AGEs also implicate in T-lymphocyte endothelial dysfunction, migration, and infiltration.²⁹

Accumulating evidence suggests that the adventitial and medial inflammatory responses cannot be considered merely as markers of the ongoing pathological process. Indeed, it is believed that the adventitial responses influence, directly or indirectly, the biology of the entire aortic wall and are directly related to aneurysm expansion and size.³⁰ In our asymptomatic AAA patients, with similar clinical characteristics between diabetic patients and nondiabetic patients, tissue inflammation and particularly macrophage subpopulation infiltrate at the outer part of aortic wall was higher in diabetic patients. However, the role of the increased macrophages in the natural history of AAAs, large enough (mean diameter 5.5 cm) to require surgical repair, in diabetic patients is unknown. Could they provide any beneficial effect in the stability of AAAs, in diabetic patients? Macrophages are renown for their apparent phenotypic heterogeneity and for the diverse activities in which they engage. Many of these activities appear to be opposing in nature: proinflammatory versus anti-inflammatory activities, immunogenic versus tolerogenic activities, and tissue-destructive versus tissue-restorative activities.³¹ Increasing rates of gene expression and macromolecular synthesis place large bioenergetic demands on all immune cells. Glucose is readily used by cells of the immune system and is used to generate energy and biosynthetic precursors. However, the exact nature of the demands and how they are met may differ among immune cells, whether they are proliferative cells, like T-lymphocytes, or secretory cells, like macrophages.³² Subset of infiltrating monocyte-derived macrophages in the microenvironment of AAA wall in diabetic patients, in a specific glucose concentration and time frame, could undergo progressive shifts in functional activities in response to regulatory oscillations and mediate their beneficial activity through secretion of the immunoregulatory cytokine IL-10 to control the local immune response,³³ as at least some of the protective effects of IL-10 may occur within the vessel wall,³⁴ or increase collagen synthesis and reduce proteolysis.^{17,24,29} In this context, defining macrophage subsets by membrane protein and functional phenotype in diabetic patients AAA might enable the development of novel approaches to manipulate and refine the endogenous repair mechanisms in AAA. We expect that future research will provide some answers to these points.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research and/or authorship of this article.

References

1. Choke E, Cockerill G, Wilson WR, et al. A review of biological factors implicated in abdominal aortic aneurysm rupture. *Eur J Vasc Endovasc Surg*. 2005;30(3):227-244.
2. Curci JA, Thompson RW. Adaptive cellular immunity in aortic aneurysms: cause, consequence, or context? *J Clin Invest*. 2004; 114(2):168-171.
3. Davies MJ. Aortic aneurysm formation lessons from human studies and experimental models. *Circulation*. 1998;98(3):193-195.
4. Lindholt S, Shi GP. Chronic inflammation, immune response, and infection in abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg*. 2006;31(5):453-463.
5. Sho E, Sho M, Nanjo H, Kawamura K, Masuda H, Dalman RL. Comparison of cell-type-specific vs transmural aortic gene expression in experimental aneurysms. *J Vasc Surg*. 2005;41(5):844-852.
6. Marian AJ. On genetics, inflammation, and abdominal aortic aneurysm: can single nucleotide polymorphisms predict the outcome? *Circulation*. 2001;103(18):2222-2224.
7. Eriksson P, Jormsjo-Pettersson S, Brady A, Deguchi H, Hamsten A, Powell J. Genotype-phenotype relationships in an investigation of the role of proteases in abdominal aortic aneurysm expansion. *Br J Surg*. 2005;92(11):1372-1376.
8. Brady AR, Fowkes FG, Thompson SG, Powell JT. Aortic aneurysm diameter and risk of cardiovascular mortality. *Arterioscler Thromb Vasc Biol*. 2001;21(7):1203-1207.
9. Schouten O, Kok NF, Hoedt MT, van Laanen JH, Poldermans D. The influence of aneurysm size on perioperative cardiac outcome in elective open infrarenal aortic aneurysm repair. *J Vasc Surg*. 2006;44(3):435-441.
10. Shimizu K, Mitchell RN, Libby P. Inflammation and cellular immune responses in abdominal aortic aneurysms. *Arterioscler Thromb Vasc Biol*. 2006;26(5):987-994.
11. Plackett TP, Boehmer ED, Faunce DE, Kovacs EJ. Aging and innate immune cells. *J Leukoc Biol*. 2004;76(2):291-299.
12. Rasmussen TE, Hallett JW Jr, Tazelaar HD, et al. Human leukocyte antigen class II immune response genes, female gender, and cigarette smoking as risk and modulating factors in abdominal aortic aneurysm. *J Vasc Surg*. 2002;35(5):988-993.
13. Freestone T, Turner RJ, Higman DJ, Lever MJ, Powell JT. Hypercholesterolemia and adventitial inflammation on the development of aortic aneurysm in rabbits. *Arterioscler Thromb Vasc Biol*. 1997;17(1):10-17.
14. McCormick ML, Gavrilu D, Weintraub NL. Role of oxidative stress in the pathogenesis of abdominal aortic aneurysms. *Arterioscler Thromb Vasc Biol*. 2007;27(3):461-469.
15. Uemura S, Matsushita H, Li W, et al. Diabetes mellitus enhances vascular matrix metalloproteinase activity: role of oxidative stress. *Circ Res*. 2001;88(12):1291-1298.
16. Rensing KL, Twickler TB. Abdominal aorta aneurysm: an exceptional expression of atherosclerotic disease in type II diabetes. *Eur Heart J*. 2008;29(5):581-582.

17. Norman PE, Davis TM, Le MT, Golledge J. Matrix biology of abdominal aortic aneurysms in diabetes: mechanisms underlying the negative association. *Connect Tissue Res.* 2007;48(3):125-131.
18. McPhee JT, Hill JS, Eslami MH. The impact of gender on presentation, therapy, and mortality of abdominal aortic aneurysm in the United States, 2001-2004. *J Vasc Surg.* 2007;45(5):891-899.
19. Haertge MM, Unger T, Kintscher U. The endothelium and vascular inflammation in diabetes. *Diab Vasc Dis Res.* 2007;4(2):84-88.
20. Bergoeing MP, Arif B, Hackmann AE, Ennis TL, Thompson RW, Curci JA. Cigarette smoking increases aortic dilatation without affecting matrix metalloproteinase-9 and -12 expression in a modified mouse model of aneurysm formation. *J Vasc Surg.* 2007;45(6):1217-1227.
21. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39(2 suppl 1):S1-S266.
22. Diagnosis and classification of diabetes mellitus. American Diabetes Association. *Diabetes Care.* 2006;29(suppl 1):S43-S48.
23. Weiss JS, Sumpio BE. Review of prevalence and outcome of vascular disease in patients with diabetes mellitus. *Eur J Vasc Endovasc Surg.* 2006;31(2):143-150.
24. Golledge J, Karan M, Moran CS, et al. Reduced expansion rate of abdominal aortic aneurysms in patients with diabetes may be related to aberrant monocyte-matrix interactions. *Eur Heart J.* 2008;29(5):665-672.
25. Harris MI. Frequency of blood glucose monitoring in relation to glycemic control in patients with type 2 diabetes. *Diabetes Care.* 2001;24(6):979-982.
26. Gappa-Fahlenkamp H, Shukla AS. The effect of short-term, high glucose concentration on endothelial cells and leukocytes in a 3D in vitro human vascular tissue model. *In Vitro Cell Dev Biol Anim.* 2009;45(5-6):234-242.
27. Azuma K, Kawamori R, Toyofuku Y, et al. Repetitive fluctuations in blood glucose enhance monocyte adhesion to the endothelium of rat thoracic aorta. *Arterioscler Thromb Vasc Biol.* 2006;26(10):2275-2280.
28. Goldin A, Beckman JA, Schmidt AM, Creager MA. Advanced glycation end products: sparking the development of diabetic vascular injury. *Circulation.* 2006;114(6):597-605.
29. Ramasamy R, Yan SF, Herold K, Clynes R, Schmidt AM. Receptor for advanced glycation end products: fundamental roles in the inflammatory response: winding the way to the pathogenesis of endothelial dysfunction and atherosclerosis. *Ann N Y Acad Sci.* 2008 Apr;1126:7-13.
30. Michel JB, Thaumat O, Houard X, Meilhac O, Caligiuri G, Nicoletti A. Topological determinants and consequences of adventitial responses to arterial wall injury. *Arterioscler Thromb Vasc Biol.* 2007;27(6):1259-1268.
31. Stout DR, Suttles J. Functional plasticity of macrophages: reversible adaptation to changing microenvironments. *J Leukoc Biol.* 2004;76(3):509-513.
32. Calder PC, Dimitriadis G, Newsholme P. Glucose metabolism in lymphoid and inflammatory cells and tissues. *Curr Opin Clin Nutr Metab Care.* 2007;10(4):531-540.
33. Shechter R, London A, Varol C, et al. Infiltrating blood-derived macrophages are vital cells playing an anti-inflammatory role in recovery from spinal cord injury in mice. *PLoS Med.* 2009;6(7):e1000113.
34. Didion SP, Kinzenbaw DA, Schrader LI, Chu Y, Faraci FM. Endogenous interleukin-10 inhibits angiotensin II-induced vascular dysfunction. *Hypertension.* 2009;54(3):619-624.