Eur J Vasc Endovasc Surg (2010) **39**, 200–207

REVIEW

Diabetes and the Abdominal Aortic Aneurysm

S. Shantikumar [a], **R. Ajjan** [a], **K.E. Porter** [b], **D.J.A. Scott** [a,*]

[a] *Division of Cardiovascular and Diabetes Research, Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Leeds LS2 9JT, UK*
[b] *Division of Cardiovascular and Neuronal Modelling, Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Leeds LS2 9JT, UK*

Submitted 15 June 2009; accepted 19 October 2009
Available online 30 November 2009

KEYWORDS
Diabetes;
Glycaemia;
Abdominal aortic aneurysm;
Pathogenesis

Abstract *Objective:* The aim of this review is to delineate the association between abdominal aortic aneurysms (AAAs) and diabetes mellitus. Mechanisms for the underlying association are then discussed.
Methods: A systematic review of the English-language literature using PubMed, EMBASE and Cochrane databases was undertaken up to September 2009. Studies reporting appropriate prevalence data were identified and a meta-analysis performed.
Results: Eleven studies were identified. The prevalence of diabetes mellitus in studied patients with AAA ranged from 6% to 14%. The prevalence of diabetes in control patients without AAA ranged from 17% to 36%. Pooled analysis suggested a reduced rate of diabetes amongst people with AAA compared to those without (OR 0.65, 0.60–0.70, $p < 0.001$).
Conclusions: Studies so far suggest a protective role for diabetes on the development of AAA. Further research is required to demarcate the underlying mechanisms for this possible association.

Introduction

Diabetes mellitus affects around 4% of the UK population.[1] The prevalence of diagnosed type 2 diabetes in men over 60 – the group most at risk of developing abdominal aortic aneurysms (AAAs) – is estimated between 10–15%.[2,3] The prevalence of both diabetes and AAA has risen in recent years.[4–6] Abdominal aortic aneurysm (AAA) is defined as a permanent dilatation of the abdominal aorta and is the tenth leading cause of death in older men.[7]

Despite theoretical common pathogenic mechanisms, the association between AAA and diabetes remains unclear and published work in this area is limited, incomplete and often conflicting. In this review, we scan the literature aiming to further delineate the prevalence of diabetes in people with AAA. In addition, we outline possible factors that explain the link between diabetes and AAA.

* Corresponding author. Tel.: +44 07786 250 850; fax: +44 0113 392 3196.
E-mail address: d.j.a.scott@leeds.ac.uk (D.J.A. Scott).

1078-5884/$36
doi:10.1016/j.ejvs.2009.10.014

Methods

A literature search was performed using PubMed, Embase and the Cochrane databases. The last search was performed in September 2009. Results were limited to human studies written in the English language in the last thirty years. The key search words used were AAA, aneurysm, diabetes and glycaemia. The titles and relevant abstracts were screened for studies which included statistically analysed prevalence data for diabetes in AAA. In addition, the references of eligible papers were screened for further relevant studies. Statistics were performed using Comprehensive Meta Analysis version 2 (Hewlett—Packard 2008).

Prevalence of Abdominal Aortic Aneurysm in Diabetes

Eleven papers were identified that analysed the association between diabetes and AAA (Table 1), of which the first three produced conflicting results. Simoni et al.[8] performed a population-based, prospective screening program in one district in Italy on patients aged 65—75 years. Of the 1601 patients screened, the prevalence of diabetes was 14% in individuals with normal aortas (<2.5 cm; $n = 1504$), and 14% in those with AAA (>3 cm, $n = 70$; $p = 0.964$).[8] A similar screening study carried out in the UK, which compared the co-morbidities in people aged 65—80 years, found no significant difference in the prevalence of diabetes in patients with or without AAA (OR 0.8, 95% CI 0.41—1.58; $p = 0.50$).[9] Both of these studies had approximately equal numbers of men and women (Table 1). Conversely, a retrospective case—control trial undertaken in two teaching hospitals in Boston[10] compared the rates of diabetes in patients who had aortic surgery against patients of a similar age range who were admitted for appendicectomy. They demonstrated a significantly negative association between AAA and diabetes (OR 0.78, 0.62—0.98; $p = 0.03$).[10] This study, however, included people of a younger age group (50—84 years). In all three of these early studies, no mention was made on the criteria used to diagnose diabetes or concurrent medications.

A subsequent Australian study analysed the prevalence of AAA in a group of known diabetic men over 60 years who had no previous history of aortic disease.[11] Seven of the 300 men screened were found to have AAA (2.3%). Although they had no control group with which to compare this figure, they reported that when measured against the prevalence of AAA in non-diabetic populations in other studies the result was significantly lower.[11]

Lederle et al.[12] reported early results of the Aneurysm Detection and Management (ADAM) study, a large ongoing population-based screening trial which aims to compare a conservative observation strategy with a surgical repair approach for small aneurysms. In this study 73,451 subjects aged 50—79 with no previous history of AAA were screened of whom 97% were males. A negative association was demonstrated between diabetes and AAA measuring between: (i) 3.0—3.9 cm (OR 0.68, 95% CI 0.60—0.77); and (ii) ≥4 cm (OR 0.54, 0.44—0.65).[12] The authors claimed that this negative association was unexpected as atherosclerosis traditionally shares many risk factors with AAA. The same group published further results using 52,745 new subjects recruited to the same trial three years later.[13] These results confirmed the negative relationship between diabetes and AAA in small (3.0—3.9 cm) aneurysms (OR 0.60, 0.50—0.71) and larger (>4 cm) aneurysms (OR 0.50, 0.39—0.65).[13] Neither of these two reports investigated the association between diabetes and large aneurysms (>5.5 cm). It is possible that diabetes is only protective at early stages of AAA and that after a certain size mechanical factors play a greater role in aneurysm expansion. Similarly to earlier studies, the criteria used for the diagnosis of diabetes were unclear.

Since the publication of the ADAM data, three more studies demonstrated similar results. Blanchard et al.[14] compared the rates of diabetes in patients with newly diagnosed AAA with control subjects who underwent ultrasound examination for similar indications, but were not found to have aneurysmal disease (12% *vs.* 17%, OR 0.32, 0.12—0.88). A sub-analysis compared the rates of diabetes in aneurysms <4 cm (OR 0.50, 0.17—1.46) and aneurysms ≥4 cm (OR 0.15, 0.03—0.79) with rates in non-aneurysmal subjects.[14] This study had a clear advantage by explicitly defining diabetes as a fasting blood glucose above 7 mmol/l or a physician's diagnosis with concurrent hypoglycaemic or insulin use.

Kang et al.[15] examined the role of routine ultrasound screening for patients with carotid artery stenosis for AAA, as some studies have found that patients with carotid stenosis have a higher prevalence of AAA compared with the general population.[16] In patients with >50% carotid stenosis, the prevalence of AAA ≥ 3.0 cm was 21.9% in non-diabetics *vs.* 9.2% in diabetics (OR 0.58; $p = 0.002$), and the prevalence of AAA ≥ 4.0 cm was 10.2% in non-diabetics *vs.* 2.8% in diabetics (OR 0.32; $p = 0.002$). The authors found a significant negative association between the development of AAA and diabetes within this subset. They concluded that non-diabetic patients with carotid stenosis should be screened for AAA disease.[15] This study provided no criteria for the diagnosis of diabetes.

In order to look more closely at the differences in risk factors between AAA and aorto-iliac occlusive disease, Shteinberg et al.[17] conducted a prospective study comparing patients undergoing AAA surgery and those having operative intervention for aorto-occlusive disease (AOD). They reported a 6% prevalence of diabetes in AAA and a 36% prevalence in AOD ($p < 0.001$).[17] In this hospital-based population, the patients with AOD would represent a group with more advanced disease of which diabetes would be a significant factor. The reported difference is therefore likely to represent an overestimation.

The Health in Men study, a large, population-based study conducted in Western Australia, assessed the relationship between diabetes and AAA in men over the age of 65.[18,19] They reported that diabetes was a negative risk factor for AAA development (OR = 0.79, 95% CI 0.63—0.98), with a diminishing risk with increasing duration of diabetes: 3—5 years (OR 0.50, 0.27—0.89), 6—12 years (OR 0.57, 0.33—0.97), over 12 years (OR 0.37, 0.19—0.70).[19]

A recent analysis by Lederle et al. looked at AAA events in a cohort of 161,808 post-menopausal women followed-up for a mean of 7.8 years.[20] The study found that women who suffered an AAA event had a lower prevalence of diabetes

(OR = 0.29, 0.13–0.68). The authors concluded that the negative association between diabetes and AAA seen in men is also evident in women.[20]

In summary, nine studies found a lower prevalence of AAA in individuals with diabetes,[10–15,7–19] whereas 2 studies found no difference.[8,9] Of the studies reporting diabetes as a negative risk factor for AAA development, three included data from the Aneurysm Detection and Management trial.[12,13,15]

We performed a meta-analysis of the above studies (Fig. 1). Of the eleven data sets, four were excluded because there was no control group,[11] there was a poor

Table 1 Summary of studies reporting prevalence rates of diabetes in abdominal aortic aneurysms.

Author	Study type	Subjects	Results
Simoni et al., 1995[8]			
	Population-based screening study (over 3 years) Italy	$n = 1601$ 46% male Age 65–75 years DM not defined	14.1% of patients normal aortas (<2.5 cm, $n = 1504$)) had DM 14.1% of patients with AAA (>3.0 cm, $n = 70$) had DM No significant difference ($p = 0.964$) (Note 27 patients had aortas between 2.5 and 3.0 cm)
Kanagasabay et al., 1996[9]			
	Population-based screening study (over 2 years) London	$n = 5392$ 43% male Age 65–80 years DM not defined	218 people had AAA No significant difference in diabetes prevalence (OR 0.8, 95% CI 0.41–1.58; $p = 0.50$)
LaMorte et al., 1995[10]			
	Case–control study (from 4 years) Boston	(1) Patients with AAA ($n = 4682$) (2) Appendicectomy admissions ($n = 3188$) 71% male Age 50–84 DM not defined	Significantly lower rate of DM in AAA compared to appendicectomy (OR 0.78, 95% CI 0.62–0.98; $p = 0.03$)
Mattes et al., 1997[11]			
	Population-based screening study Australia	Diabetic men $n = 300$ Over 60 years DM not defined	7 of 300 diabetic men screened had AAA (2.3%) No control group with which to calculate significance
Lederle et al., 1997[12]			
	Population-based screening study Boston	$n = 73,451$ 97% male Age 50–79 DM not defined	12% of those with AAA ($n = 3366$) had DM 19% of those without AAA had DM Significantly lower rate of DM in AAA compared to no-AAA OR 0.68 (95% CI 0.60–0.77) for small AAA (3.0–3.9 cm) OR 0.54 (95% CI 0.44–0.65) for larger AAA (>4.0 cm)
Lederle et al., 2000[13]			
	Population-based screening study (over 3 years) Boston	$n = 52,745$ 97% male Age 50–79 DM not defined	1917 had AAA Significantly lower rate of DM in AAA compared to no-AAA OR 0.60 (95% CI 0.50–0.71) for small AAA (3.0–3.9 cm) OR 0.50 (95% CI 0.39–0.65) for larger AAA (>4.0 cm)
Blanchard et al., 2000[14]			
	Case–control study Canada	(1) Newly diagnosed AAA ($n = 98$) (2) Controls ($n = 102$) DM defined as fasting glucose >7 or use of insulin/hypoglycaemics	12% of those with AAA had DM 17% of those without AAA had DM (OR 0.32, 95% CI 0.12–0.88)

Table 1 (*continued*)

Author	Study type	Subjects	Results
Kang et al., 1999[15]	Population-based screening study Boston	(1) >50% carotid stenosis ($n = 374$) (2) <50% carotid stenosis ($n = 139$) (3) ADAM study ($n = 2477$)	Relative risk of AAA is 2–3 times more in carotid stenosis rather than in the general screened population (18% group 1 *vs.* 7%) Prevalence AAA ≥3 cm in carotid stenosis 22% no-DM *vs.* 9% DM (OR 0.58; $p = 0.002$) Prevalence AAA ≥4 cm in carotid stenosis 10% no-DM *vs.* 3% DM (OR 0.32; $p = 0.002$) Thus only patients who are *not* diabetic account for increased prevalence
Shteinberg et al., 2000[17]	Prospective study (over 4 years) Israel	(1) Patients with AAA ($n = 82$) (2) Patients with AOD ($n = 73$)	Decreased prevalence of DM in AAA *vs.* AOD (6% *vs.* 36%, $p < 0.001$)
Jamrozik et al., 2000[18]			
Le et al., 2007[19]	Population-based screening study (over 3 years) Australia	$n = 12,203$ Age 65–83 Men only	Significantly lower rate of DM in AAA compared to no-AAA (OR = 0.79, 95% CI 0.63–0.98) Inverse correlation between fasting glucose and aortic diameter in non-diabetic men (correlation coefficient − 0.0024, $p = 0.0027$)
Lederle et al., 2008[20]	Prospective observational cohort study (over 7.8 years)	$N = 161,808$ Post-menopausal women	Decreased rate of diabetes in women who had AAA events (OR = 0.29, 95% CI 0.13–0.68)

control group (patients with aorto-occlusive disease[17]), or because they only looked at a particular subgroup (patients with carotid stenosis[15] or women suffering AAA-related events[20]). Pooled analysis of the remaining seven papers demonstrated reduced odds of diabetes in patients with AAA (OR = 0.65, 0.60–0.70, $p < 0.001$).[8–10,12–14,18] If analysis was restricted to the five population-based screening studies, pooled analysis still showed a reduced odds of diabetes in AAA (OR = 0.64, 0.59–0.69, $p < 0.001$).[8,9,12,13,18] The two studies reported by Lederle et al. provided results from a multivariate analysis and separated results according to size of aneurysm (3–4 cm *vs.* ≥4 cm).[12,13] When these were removed from the analysis, the remaining three studies still suggested a reduced prevalence of diabetes in patients with AAA (OR = 0.81, 0.66–0.99, $p = 0.038$).[8,9,18]

Potential Mechanisms for the Protective Effect of Diabetes

The predominant risk factors for AAA are male sex, increasing age, smoking, hyperlipidaemia, hypertension and a family history.[12,21] Because atherosclerosis shares similar risk factors it has traditionally been thought of as the underlying pathogenesis in AAA.[22] The evidence above portraying a decreased prevalence of AAA in diabetics suggests that atherosclerosis is an associated feature, rather than

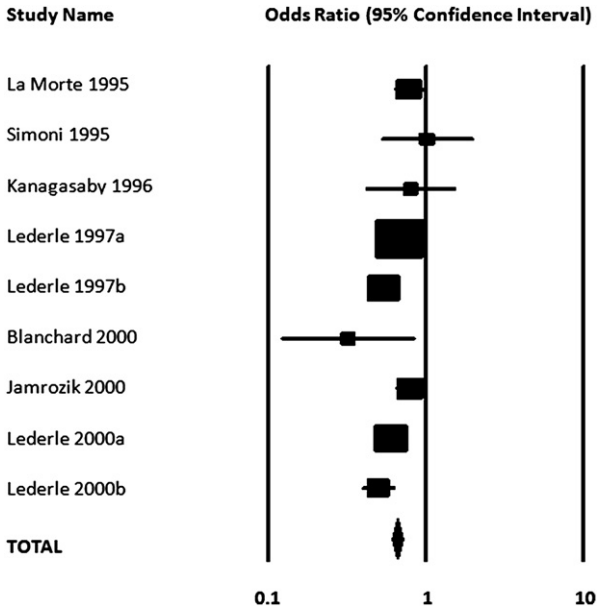

Figure 1 Pooled analysis of the studies reporting prevalence rates of diabetes amongst patients with AAA. Note the studies by Lederle et al. reported separate odds ratios in patients with aneurysms between 3 and 4 cm (denoted by the suffix 'a') and those with aneurysms above 4 cm (denoted by suffix 'b').

a causative factor, of aneurysmal disease. The biological processes underlying this relationship are as yet undetermined, but can be distinguished as changes in the aortic wall and characteristics of the mural thrombus within it.

Biology of the wall

Research *in vitro* and *in vivo* has described potential mechanisms involving the aortic wall that result in aneurysmal disease. This has been the subject of a recent review by Norman et al.,[23] and we present an updated summary. The walls of AAA show evidence of increased proteolytic activity with resulting collagen and elastin depletion.[24] Matrix metalloproteinases (MMPs) are a group of proteolytic enzymes which exhibit an increased activity in human aneurysmal tissue.[25] Of these, smooth muscle cell MMP-2 and macrophage-derived MMP-9 have been shown to be principally involved in the breakdown of matrix proteins, including elastin, and degradation of the vessel wall in aneurysmal disease. Elevated concentrations of both MMP-2 and MMP-9 have been found in patients with AAA,[26,27] and mice deficient in either MMP-2 or MMP-9 fail to develop aortic dilatation compared to wild-type mice.[28] Whilst little is known about the factors that initiate the biological process of matrix destruction, there are a number of mechanistic possibilities.[29]

This review suggests that individuals with diabetes exhibit a lower prevalence of AAA.[13] Furthermore, studies have found the expansion rate of small AAA to be slower in diabetes compared with non-diabetic subjects.[30,31] Diabetes is characterised by an increased synthesis and reduced degradation of the matrix, resulting in enhanced matrix volume.[23] *In vitro* studies have demonstrated that hyperglycaemia results in increased collagen synthesis.[32] Furthermore, abdominal aorta thickness has been found to be greater in people with diabetes.[33] A human study found that MMP-2 and MMP-9 concentrations were reduced in the coronary arteries of diabetic patients.[34] A similar reduction in the activity of MMPs in the aorta of diabetic patients may decelerate the matrix loss necessary for the pathogenesis of AAA.

The high ambient glucose concentrations in diabetes result in glycation of the extracellular matrix (ECM), with a subsequently elevated formation of advanced glycation end products (AGEs).[30] AGEs form covalent cross-links between proteins, including elastin and collagen in the vessel wall,[35] and promote smooth muscle cell proliferation.[36] This may result in a stiffened wall which is resistant to proteolysis.[23] In contrast, earlier study suggested that the stimulation of AGE receptors resulted in upregulation of inflammatory cytokines and MMPs, contributing to aneurysmal formation.[37,38] In support of this, a recent study found that serum concentrations of the AGE carboxymethyllysine were lower in patients with AAA.[39] Glycation of the aortic media inhibits MMP secretion (in contrast to glycation of atherosclerotic intima which stimulates MMP secretion[23,30]).

In our own recent study, clear morphological diversity was observed between vascular SMC cultured from patients with and without type 2 diabetes that persisted *in vitro*.[40] Vinculin is a focal adhesion protein that couples the extracellular matrix to the actin cytoskeleton. Importantly, we noted increased vinculin-positive focal adhesions and disparate α-actin organisation in SMC from patients with type 2 diabetes mellitus, observations that may explain the generalised increased tissue stiffness reported in these subjects.[41] Such observations provide evidence of 'metabolic memory',[42] the long-term molecular and cellular

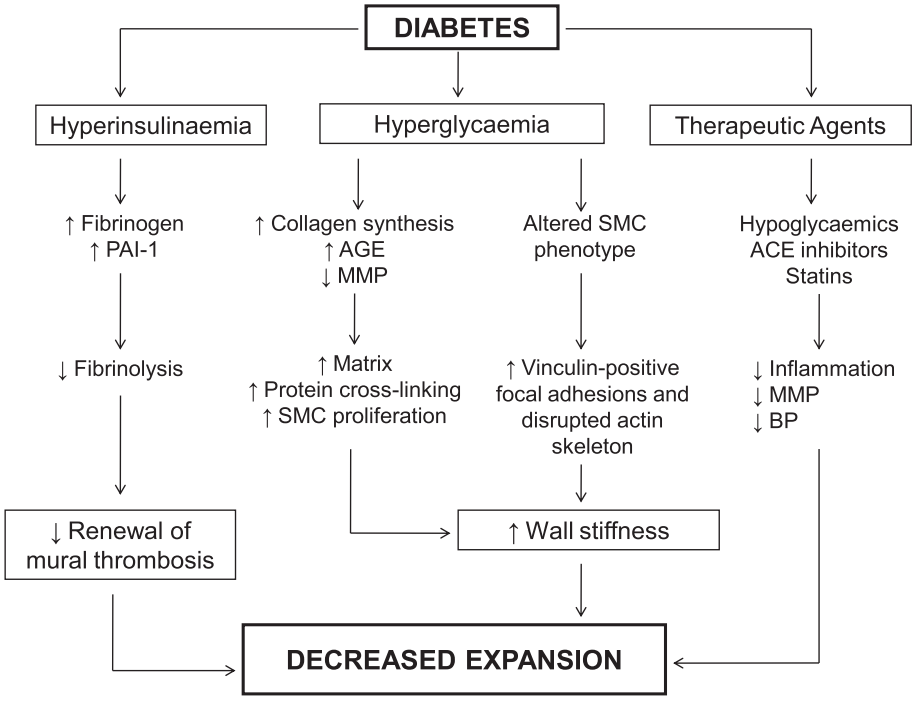

Figure 2 The potential influences of diabetes on pathogenesis of abdominal aortic aneurysms.

changes that occur as a consequence of hyperglycaemia. It is therefore possible to speculate that the metabolic milieu of diabetes may impart a degree of resistance to aneurysmal disease by creating a stiffened aortic wall less prone to degeneration.

Additional explanation may be related to the medical treatment of individuals with diabetes. Angiotensin-converting enzyme (ACE) inhibitors, aside from their effects on blood pressure, reduce vascular inflammation, increase elastin deposition and inhibit MMPs.[43] ACE inhibitors prevent aortic expansion and rupture in animal models,[44] and a population-based case—control study found that use of ACE inhibitors had a protective effect on AAA rupture.[45] Simvastatin use has been shown to decrease MMP expression in the human AAA wall.[46] Metformin decreases MMP-2 and smooth muscle cell proliferation in human aortic cells *in vitro*.[47] Rosiglitazone has been shown to reduce the development and rupture of aortic aneurysms in a murine model[48] and decrease expression of MMP-9 in patients with diabetes.[49] Because of the association of hypertension, atherosclerosis and renal impairment, diabetics are increasingly likely to be taking ACE inhibitors, statins and hypoglycaemic agents. The use of such medication may contribute to the apparent protective effect of diabetes in aneurysmal disease seen in the above studies.[50] None of the studies reported have explicitly commented on the drug histories of recruited subjects.

Biology of the clot

The fibrinolytic system may play a role in the pathogenesis of AAA. Abdominal aortic aneurysms are associated with an intraluminal thrombus (ILT)[51] and the rate of expansion of large AAA correlates with ILT growth.[52] ILT is reported to contain high concentrations of MMP-9[53,54] and signs of collagenolytic activity.[55] Consequently, aneurysmal wall covered by ILT is thinner, has fewer smooth muscle cells and is less resistant to stress.[56,57] A recent study found that the fibrin clot in type 2 diabetics is altered; being denser, less porous and more resistant to fibrinolysis.[58] On one hand, one may subsequently expect increased ILT-mediated expansion and rupture of larger AAA in diabetic patients. However, the renewal of intraluminal thrombus by fibrinolysis releases components that are implicated in aneurysmal expansion, such as MMP-9,[59,60] so the more degradation-resistant clot in diabetes may slow the rate of expansion caused by such mediators.

Plasminogen activator inhibitor-1 (PAI-1) inhibits the conversion of plasminogen to plasmin, thus suppresses fibrinolysis and reduces renewal of the intraluminal thrombus. Plasmin in turn converts pro-MMP to the active form.[61] PAI-1 therefore decreases MMP production. PAI-1 has been shown to prevent formation of aneurysms in animal studies.[62] Furthermore, individuals with the PAI-1 5G5G genotype, who have decreased circulating levels of PAI-1s, are at risk of developing rapidly expanding AAA.[63] Elevated levels of PAI-1 have been reported in diabetes secondary to insulinaemia, and this could aid aneurysmal wall stabilisation and reduce clot degredation and renewal.[64]

Fig. 2 summarises the potential influences of diabetes on abdominal aneurysm pathogenesis.

Conclusions

Diabetes is known to predispose to cardiovascular disease and therefore the negative association with abdominal aortic aneurysms, documented by a number of studies, is seemingly paradoxical. The aim of this review was to analyse the link between AAA and diabetes from the evidence published thus far. Early population and case—control studies appear to demonstrate an overall protective role for diabetes against the development of AAA, although further work into prevalence associations and biological mechanisms is clearly required, with specific attention to the type and duration of diabetes, as well as hypoglycaemic management and concurrent medications.

Whilst the evidence that diabetes has an inverse relationship with aortic diameter may not aid the immediate management of AAA, it may help to identify high-risk groups for screening. Additionally, this observation may help demonstrate the differing cellular mechanisms behind aneurysmal and atherosclerotic disease, and in turn rationalise the search for pharmacological interventions of small AAA.

Conflict of Interest/Funding

None.

References

1 Forouhi NG, Merrick D, Goyder E, Ferguson BA, Abbas J, Lachowycz K, et al. Diabetes prevalence in England, 2001 — estimates from an epidemiological model. *Diabet Med* 2006; **23**(2):189—97.
2 Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;**27**(5):1047—53.
3 Ubink-Veltmaat LJ, Bilo HJ, Groenier KH, Houweling ST, Rischen RO, Meyboom-de Jong B. Prevalence, incidence and mortality of type 2 diabetes mellitus revisited: a prospective population-based study in The Netherlands (ZODIAC-1). *Eur J Epidemiol* 2003;**18**(8):793—800.
4 Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, et al. Diabetes trends in the U.S.: 1990—1998. *Diabet Care* 2000;**23**(9):1278—83.
5 Sorensen TI. The changing lifestyle in the world. Body weight and what else? *Diabet Care* 2000;**23**(Suppl. 2):B1—4.
6 Bengtsson H, Bergqvist D, Sternby NH. Increasing prevalence of abdominal aortic aneurysms. A necropsy study. *Eur J Surg* 1992; **158**(1):19—23.
7 Silverberg E, Boring CC, Squires TS. Cancer statistics, 1990. *CA Cancer J Clin* 1990;**40**(1):9—26.
8 Simoni G, Pastorino C, Perrone R, Ardia A, Gianrossi R, Decian F, et al. Screening for abdominal aortic aneurysms and associated risk factors in a general population. *Eur J Vasc Endovasc Surg* 1995;**10**(2):207—10.
9 Kanagasabay R, Gajraj H, Pointon L, Scott RA. Co-morbidity in patients with abdominal aortic aneurysm. *J Med Screen* 1996; **3**(4):208—10.
10 LaMorte WW, Scott TE, Menzoian JO. Racial differences in the incidence of femoral bypass and abdominal aortic aneurysmectomy in Massachusetts: relationship to cardiovascular risk factors. *J Vasc Surg* 1995;**21**(3):422—31.
11 Mattes E, Davis TM, Yang D, Ridley D, Lund H, Norman PE. Prevalence of abdominal aortic aneurysms in men with diabetes. *Med J Aust* 1997;**166**(12):630—3.

12 Lederle FA, Johnson GR, Wilson SE, Chute EP, Littooy FN, Bandyk D, et al. Prevalence and associations of abdominal aortic aneurysm detected through screening. Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study Group. *Ann Intern Med* 1997;**126**(6):441–9.
13 Lederle FA, Johnson GR, Wilson SE, Chute EP, Hye RJ, Makaroun MS, et al. The aneurysm detection and management study screening program: validation cohort and final results. Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. *Arch Intern Med* 2000;**160**(10): 1425–30.
14 Blanchard JF, Armenian HK, Friesen PP. Risk factors for abdominal aortic aneurysm: results of a case–control study. *Am J Epidemiol* 2000;**151**(6):575–83.
15 Kang SS, Littooy FN, Gupta SR, Johnson GR, Fisher SG, Cote WL, et al. Higher prevalence of abdominal aortic aneurysms in patients with carotid stenosis but without diabetes. *Surgery* 1999;**126**(4):687–91. discussion, pp. 682–91.
16 Karanjia PN, Madden KP, Lobner S. Coexistence of abdominal aortic aneurysm in patients with carotid stenosis. *Stroke* 1994; **25**(3):627–30.
17 Shteinberg D, Halak M, Shapiro S, Kinarty A, Sobol E, Lahat N, et al. Abdominal aortic aneurysm and aortic occlusive disease: a comparison of risk factors and inflammatory response. *Eur J Vasc Endovasc Surg* 2000;**20**(5):462–5.
18 Jamrozik K, Norman PE, Spencer CA, Parsons RW, Tuohy R, Lawrence-Brown MM, et al. Screening for abdominal aortic aneurysm: lessons from a population-based study. *Med J Aust* 2000;**173**(7):345–50.
19 Le MT, Jamrozik K, Davis TM, Norman PE. Negative association between infra-renal aortic diameter and glycaemia: the health in men study. *Eur J Vasc Endovasc Surg* 2007;**33**(5):599–604.
20 Lederle FA, Larson JC, Margolis KL, Allison MA, Freiberg MS, Cochrane BB, et al. Abdominal aortic aneurysm events in the women's health initiative: cohort study. *BMJ* 2008;**337**:a1724.
21 Blanchard JF. Epidemiology of abdominal aortic aneurysms. *Epidemiol Rev* 1999;**21**(2):207–21.
22 Patel MI, Hardman DT, Fisher CM, Appleberg M. Current views on the pathogenesis of abdominal aortic aneurysms. *J Am Coll Surg* 1995;**181**(4):371–82.
23 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): 125–31.
24 Sakalihasan N, Heyeres A, Nusgens BV, Limet R, Lapiere CM. Modifications of the extracellular matrix of aneurysmal abdominal aortas as a function of their size. *Eur J Vasc Surg* 1993;**7**(6):633–7.
25 Freestone T, Turner RJ, Coady A, Higman DJ, Greenhalgh RM, Powell JT. Inflammation and matrix metalloproteinases in the enlarging abdominal aortic aneurysm. *Arterioscler Thromb Vasc Biol* 1995;**15**(8):1145–51.
26 Goodall S, Crowther M, Hemingway DM, Bell PR, Thompson MM. Ubiquitous elevation of matrix metalloproteinase-2 expression in the vasculature of patients with abdominal aneurysms. *Circulation* 2001;**104**(3):304–9.
27 McMillan WD, Tamarina NA, Cipollone M, Johnson DA, Parker MA, Pearce WH. Size matters: the relationship between MMP-9 expression and aortic diameter. *Circulation* 1997;**96**(7): 2228–32.
28 Longo GM, Xiong W, Greiner TC, Zhao Y, Fiotti N, Baxter BT. Matrix metalloproteinases 2 and 9 work in concert to produce aortic aneurysms. *J Clin Invest* 2002;**110**(5):625–32.
29 Pearce WH, Shively VP. Abdominal aortic aneurysm as a complex multifactorial disease: interactions of polymorphisms of inflammatory genes, features of autoimmunity, and current status of MMPs. *Ann N Y Acad Sci* 2006;**1085**: 117–32.
30 Golledge J, Karan M, Moran CS, Muller J, Clancy P, Dear AE, 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):665–72.
31 Brady AR, Thompson SG, Fowkes FG, Greenhalgh RM, Powell JT. Abdominal aortic aneurysm expansion: risk factors and time intervals for surveillance. *Circulation* 2004;**110**(1):16–21.
32 Jones SC, Saunders HJ, Pollock CA. High glucose increases growth and collagen synthesis in cultured human tubulointerstitial cells. *Diabet Med* 1999;**16**(11):932–8.
33 Astrand H, Ryden-Ahlgren A, Sundkvist G, Sandgren T, Lanne T. Reduced aortic wall stress in diabetes mellitus. *Eur J Vasc Endovasc Surg* 2007;**33**(5):592–8.
34 Portik-Dobos V, Anstadt MP, Hutchinson J, Bannan M, Ergul A. Evidence for a matrix metalloproteinase induction/activation system in arterial vasculature and decreased synthesis and activity in diabetes. *Diabetes* 2002;**51**(10):3063–8.
35 Aronson D. Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes. *J Hypertens* 2003;**21**(1):3–12.
36 Sakata N, Meng J, Takebayashi S. Effects of advanced glycation end products on the proliferation and fibronectin production of smooth muscle cells. *J Atheroscler Thromb* 2000;**7**(3):169–76.
37 Gao L, Kang L, Chen Q, Chen C, Xu B, Jiang S. Advanced glycation end products inhibit production and activity of matrix metalloproteinase-2 in human umbilical vein endothelial cells. *J Int Med Res* 2007;**35**(5):709–15.
38 Cipollone F, Iezzi A, Fazia M, Zucchelli M, Pini B, Cuccurullo C, et al. The receptor RAGE as a progression factor amplifying arachidonate-dependent inflammatory and proteolytic response in human atherosclerotic plaques: role of glycemic control. *Circulation* 2003;**108**(9):1070–7.
39 Norman PE, Davis WA, Coughlan MT, Forbes JM, Golledge J, Davis TM. Serum carboxymethyllysine concentrations are reduced in diabetic men with abdominal aortic aneurysms: health in men study. *J Vasc Surg* 2009;**50**(3):626–31.
40 Madi HA, Riches K, Warburton P, O'Regan DJ, Turner NA, Porter KE. Inherent differences in morphology, proliferation and migration in saphenous vein smooth muscle cells cultured from non-diabetic and type 2 diabetic patients. *Am J Physiol Cell Physiol*; 2009.
41 van Heerebeek L, Hamdani N, Handoko ML, Falcao-Pires I, Musters RJ, Kupreishvili K, et al. Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension. *Circulation* 2008; **117**(1):43–51.
42 Ceriello A, Ihnat MA, Thorpe JE. Clinical review 2: the ''metabolic memory'': is more than just tight glucose control necessary to prevent diabetic complications? *J Clin Endocrinol Metab* 2009;**94**(2):410–5.
43 Ahimastos AA, Natoli AK, Lawler A, Blombery PA, Kingwell BA. Ramipril reduces large-artery stiffness in peripheral arterial disease and promotes elastogenic remodeling in cell culture. *Hypertension* 2005;**45**(6):1194–9.
44 Liao S, Miralles M, Kelley BJ, Curci JA, Borhani M, Thompson RW. Suppression of experimental abdominal aortic aneurysms in the rat by treatment with angiotensin-converting enzyme inhibitors. *J Vasc Surg* 2001;**33**(5):1057–64.
45 Hackam DG, Thiruchelvam D, Redelmeier DA. Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case–control study. *Lancet* 2006;**368**(9536):659–65.
46 Evans J, Powell JT, Schwalbe E, Loftus IM, Thompson MM. Simvastatin attenuates the activity of matrix metalloprotease-9 in aneurysmal aortic tissue. *Eur J Vasc Endovasc Surg* 2007; **34**(3):302–3.
47 Li L, Mamputu JC, Wiernsperger N, Renier G. Signaling pathways involved in human vascular smooth muscle cell

proliferation and matrix metalloproteinase-2 expression induced by leptin: inhibitory effect of metformin. *Diabetes* 2005;**54**(7):2227—34.
48 Jones A, Deb R, Torsney E, Howe F, Dunkley M, Gnaneswaran Y, et al. Rosiglitazone reduces the development and rupture of experimental aortic aneurysms. *Circulation* 2009;**119**(24): 3125—32.
49 Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. *Circulation* 2002;**106**(6):679—84.
50 Sorice GP, Folli F. A combination of PPAR-gamma agonists and HMG CoA reductase inhibitors (statins) as a new therapy for the conservative treatment of AAS (aortic aneurysm syndromes). *Med Hypotheses* 2009;**73**(4):614—8.
51 Swedenborg J, Eriksson P. The intraluminal thrombus as a source of proteolytic activity. *Ann N Y Acad Sci* 2006;**1085**:133—8.
52 Wolf YG, Thomas WS, Brennan FJ, Goff WG, Sise MJ, Bernstein EF. Computed tomography scanning findings associated with rapid expansion of abdominal aortic aneurysms. *J Vasc Surg* 1994;**20**(4):529—35. discussion, p. 528—35.
53 Sakalihasan N, Delvenne P, Nusgens BV, Limet R, Lapiere CM. Activated forms of MMP2 and MMP9 in abdominal aortic aneurysms. *J Vasc Surg* 1996;**24**(1):127—33.
54 Fontaine V, Jacob MP, Houard X, Rossignol P, Plissonnier D, Angles-Cano E, et al. Involvement of the mural thrombus as a site of protease release and activation in human aortic aneurysms. *Am J Pathol* 2002;**161**(5):1701—10.
55 Panek B, Gacko M, Palka J. Metalloproteinases, insulin-like growth factor-I and its binding proteins in aortic aneurysm. *Int J Exp Pathol* 2004;**85**(3):159—64.
56 Kazi M, Thyberg J, Religa P, Roy J, Eriksson P, Hedin U, et al. Influence of intraluminal thrombus on structural and cellular composition of abdominal aortic aneurysm wall. *J Vasc Surg* 2003;**38**(6):1283—92.
57 Vorp DA, Lee PC, Wang DH, Makaroun MS, Nemoto EM, Ogawa S, et al. Association of intraluminal thrombus in abdominal aortic aneurysm with local hypoxia and wall weakening. *J Vasc Surg* 2001;**34**(2):291—9.
58 Dunn EJ, Ariens RA, Grant PJ. The influence of type 2 diabetes on fibrin structure and function. *Diabetologia* 2005;**48**(6):1198—206.
59 Touat Z, Ollivier V, Dai J, Huisse MG, Bezeaud A, Sebbag U, et al. Renewal of mural thrombus releases plasma markers and is involved in aortic abdominal aneurysm evolution. *Am J Pathol* 2006;**168**(3):1022—30.
60 Houard X, Rouzet F, Touat Z, Philippe M, Dominguez M, Fontaine V, et al. Topology of the fibrinolytic system within the mural thrombus of human abdominal aortic aneurysms. *J Pathol* 2007;**212**(1):20—8.
61 Murphy G, Atkinson S, Ward R, Gavrilovic J, Reynolds JJ. The role of plasminogen activators in the regulation of connective tissue metalloproteinases. *Ann N Y Acad Sci* 1992;**667**:1—12.
62 Allaire E, Hasenstab D, Kenagy RD, Starcher B, Clowes MM, Clowes AW. Prevention of aneurysm development and rupture by local overexpression of plasminogen activator inhibitor-1. *Circulation* 1998;**98**(3):249—55.
63 Rossaak JI, Van Rij AM, Jones GT, Harris EL. Association of the 4G/5G polymorphism in the promoter region of plasminogen activator inhibitor-1 with abdominal aortic aneurysms. *J Vasc Surg* 2000;**31**(5):1026—32.
64 Festa A, D'Agostino Jr R, Mykkanen L, Tracy RP, Zaccaro DJ, Hales CN, et al. Relative contribution of insulin and its precursors to fibrinogen and PAI-1 in a large population with different states of glucose tolerance. The Insulin Resistance Atherosclerosis Study (IRAS). *Arterioscler Thromb Vasc Biol* 1999;**19**(3):562—8.