REVIEW

Review of Prevalence and Outcome of Vascular Disease in Patients with Diabetes Mellitus

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Objectives. Review the literature to determine the prevalence and outcome in patients with diabetes that undergo surgery to correct carotid artery stenosis, lower extremity arterial disease, and abdominal aortic aneurysm (AAA).

Design and materials. Studies were obtained from searches over the past 15 years on the National Library of Medicine’s online search engine.

Results. The review demonstrated an equivalent prevalence of carotid artery stenosis requiring surgery in patients with diabetes, it favored no increase risk of post-CEA stroke, and it was split on perioperative morbidity and mortality risk. There was an increase prevalence of lower extremity arterial disease requiring surgery in patients with diabetes, it favored equivalent patency and limb salvage rates, and it was split on the morbidity and mortality risk. The review demonstrated a decrease in AAA prevalence among patients with diabetes, it found an increase in the morbidity risk, and equivalent mortality risk.

Conclusions. Stroke, graft patency, and limb salvage rates in patients with diabetes after surgery are similar to patients without diabetes; however, their risk of complications is increased after surgery and the mortality risk may be higher after CEA.

Keywords: Diabetes; Carotid artery stenosis; Abdominal aortic aneurysm; Lower extremity arterial disease.

Introduction

Diabetes mellitus affects approximately 7.8% of the European population and afflicts 19% of all persons 60 years of age or older.1 There exists a 1.5 to 4.5-fold increase in risk of myocardial infarction and a two-fold increase in the risk of death in patients with diabetes.2 In fact, a patient with diabetes in his/her middle-age can expect a 5–10 years reduction in lifespan.3 Cardiovascular disease is responsible for the majority of this decrease in survival and accounts for over half of all causes of death in diabetes.2 Surgical intervention on various vascular conditions from atherosclerosis is instituted on both the patient with and without diabetes. Comparison of the operative outcomes between these groups will allow us insight into the clinical behavior of atherosclerosis in patients with diabetes. The link between diabetes and atherosclerosis has been well studied, but the manifestation of their pathogenesis is still not completely understood. This paper will analyze carotid artery stenosis, lower extremity arterial disease, and abdominal aortic aneurysms (AAA) in patients with diabetes undergoing surgical correction to determine their prevalence as well as outcomes after surgery.

Methods

The literature review was performed using the National Library of Medicine’s search engine, PubMed (www.ncbi.nlm.nih.gov). Using a date range of January 1, 1990 to January 1, 2005, the limiting variables of English-language, trials, and human studies were used. The key words for the carotid artery stenosis review were: carotid and diabetes, CEA and diabetes, carotid artery endarterectomy and diabetes, diabetes and
stroke, and carotid artery endarterectomy and risk factors. Additionally, a search of all randomized controlled trials using the key words carotid artery endarterectomy was performed. The key words for the lower extremity arterial disease review were: infrainguinal vascular disease and diabetes, infrageniculate vascular disease and diabetes, extremity vascular disease and diabetes, lower extremity bypass and diabetes, and lower extremity bypass. The key words for AAA review were: AAA and diabetes. The resulting abstracts were manually screened for applicability and at the minimum objectively analyzed diabetes with respect to at least one of our chosen outcome measures. The outcome measures for the carotid artery stenosis analysis included post-CEA stroke, morbidity, and mortality; for the lower extremity arterial disease analysis it included postoperative graft patency, limb salvage rates, morbidity, and mortality; and for the AAA analysis it included prevalence, post-AAA repair morbidity, and mortality. Additionally, the references for each of the eligible studies in all sections were scanned for relevant studies.

The eligible studies were formatted in tables for comparison. Due to the heterogeneity of the endpoint definitions, combining study numbers was deemed inappropriate and not performed. Endovascular studies were intentionally excluded from our review; their relatively recent entry into the literature provided insufficient data to analyze diabetes as a separate group. Statistical significance was defined as $p < .05$.

## Results

### Carotid artery stenosis

Fourteen papers were identified that examined CEA against our chosen outcome measures (Table 1). Three studies compared diabetes patients against all three chosen outcomes; stroke, morbidity, and mortality. The proportion of CEAs performed on patients with diabetes ranged from 11 to 40%. All studies analyzed stroke risk of patients with diabetes against those without diabetes, except Ref. [7]. In five studies, the stroke rate was combined with the mortality rate and therefore, separate analysis on strict stroke rate was not published. The time-frame was indicated as up to 30 days in all studies except in Refs. [16,17], in which the time-frame of perioperative was used. Thirteen studies analyzed stroke rate, 10 of these studies found that there was no increase in the stroke rate for patients with diabetes undergoing CEA.

#### Table 1. Prevalence and outcome of patients with diabetes and carotid artery stenosis after CEA

<table>
<thead>
<tr>
<th>Study</th>
<th>CEA (N)</th>
<th>DM (%)</th>
<th>Stroke</th>
<th>Morbidity</th>
<th>Mortality (30 days)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kragsterman, 4 2004</td>
<td>1518</td>
<td>13.8</td>
<td>NS</td>
<td>NR</td>
<td>$\dagger$</td>
<td>RR 2.03, $p &lt; 0.002$</td>
</tr>
<tr>
<td>LaMuraglia, 5   2004</td>
<td>2236</td>
<td>24.5</td>
<td>NS</td>
<td>NR</td>
<td>$\dagger$</td>
<td>$1.356, p &lt; 0.011, 5.9$ years (mean)</td>
</tr>
<tr>
<td>Tu, 6 2003</td>
<td>6038</td>
<td>23.1</td>
<td>NS'</td>
<td>NR</td>
<td>$\dagger$</td>
<td>Combined death/stroke OR 1.28, $p &lt; 0.0435$; OR 2.13, $p &lt; 0.0005$</td>
</tr>
<tr>
<td>Axelrod, 7 2002</td>
<td>5522</td>
<td>40</td>
<td>NR</td>
<td>$\dagger$</td>
<td>NS</td>
<td>Nonfatal cardiac events, 3.4 vs. 2.3%, $p = 0.017$</td>
</tr>
<tr>
<td>Bond, 8 2002</td>
<td>1729</td>
<td>11.4</td>
<td>NS'</td>
<td>NR</td>
<td>NS'</td>
<td>No $\dagger$ in combined stroke and death rates in DM pts 3.1 vs. 0.8%, $p &lt; 0.02$ in combined nonfatal cardiac and neurologic events</td>
</tr>
<tr>
<td>Pitoless, 9 2001</td>
<td>781</td>
<td>24.7</td>
<td>NS</td>
<td>$\dagger$</td>
<td>NS</td>
<td>Combined stroke and death rates, 9.8 vs. 3.2%; RR 2.7, $p = 0.027$, univariate only</td>
</tr>
<tr>
<td>Kuhar, 10 2001</td>
<td>741</td>
<td>11</td>
<td>$\dagger$</td>
<td>NS</td>
<td>$\dagger$</td>
<td>Combined stroke and death rates, adjusted RR 1.5, but NS (NASCET data)</td>
</tr>
<tr>
<td>Ballotta, 11 2000</td>
<td>547</td>
<td>36.4</td>
<td>NS</td>
<td>$\dagger$</td>
<td>NS</td>
<td>Cardiac-related deaths 6 vs. 1.7%, $p = 0.02$, 44 months (mean)</td>
</tr>
<tr>
<td>Ahari, 12 1999</td>
<td>2622</td>
<td>13</td>
<td>NS</td>
<td>$\dagger$</td>
<td>NS'</td>
<td>30 days: 3.2 vs. 1.4%, $p = 0.02$; 1 year: 7.9 vs. 4.4%, $p = 0.008$</td>
</tr>
<tr>
<td>Ferguson, 13 1999</td>
<td>1415</td>
<td>NR</td>
<td>NS'</td>
<td>NR</td>
<td>NS'</td>
<td>Combined stroke and death rates, adjusted RR 1.5, but NS (NASCET data)</td>
</tr>
<tr>
<td>Barnett, 15 1998</td>
<td>1087</td>
<td>23</td>
<td>$\dagger$</td>
<td>NR</td>
<td>$\dagger$</td>
<td>Combined stroke and death rates with RR 2.0, but only on univariate analysis (NASCET data)</td>
</tr>
<tr>
<td>Akbari, 16 1997</td>
<td>732</td>
<td>39</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>20 vs. 8.2%, $p &lt; 0.04$</td>
</tr>
<tr>
<td>Reies, 17 1994</td>
<td>3062</td>
<td>20</td>
<td>NS</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Salenius, 18 1990</td>
<td>331</td>
<td>12.1</td>
<td>$\dagger$</td>
<td>NR</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

CEA, carotid endarterectomy; NR, not reported; NS, not statistically significant; RR, risk ratio; HR, hazard ratio; OR, odds ratio; DM, diabetes mellitus.
The three studies that found an increase included a study from Salenius, et al.,\textsuperscript{18} who found that patients with diabetes had a 20\% perioperative stroke rate vs. an 8.2\% risk in patients without diabetes. The other two were not designed to look at stroke separately and therefore, a combined death and stroke rate was published.\textsuperscript{10,15} These rates were increased, but they only provided a univariate analysis. Morbidity was reported in four papers\textsuperscript{7,9,11,16} and was defined as the combination of nonfatal neurologic (TIA or stroke) and cardiac (MI or CHF) complications within 30 days of surgery. Two studies failed to demonstrate a difference in complications between patients with and without diabetes;\textsuperscript{11,16} however, both Refs. [7,9] found that patients with diabetes had a statistically significant increase in complications. Early mortality was studied in 12 papers\textsuperscript{4,6–13,15,16,18} and late mortality was studied in three.\textsuperscript{5,11,12} Seven of these twelve papers failed to show an increase in the mortality rates of patients with diabetes undergoing CEA,\textsuperscript{7,9,11,13,16,18} however, five papers\textsuperscript{4,6,10,12,15} did show that patients with diabetes were at an increased risk of early mortality. The three papers that looked at late death all agreed that patients with diabetes had higher late mortality. These papers had mean follow-up ranging from 1 to 5.9 years.

**Lower extremity arterial disease**

Eleven papers were identified that examined lower extremity arterial disease against our chosen outcome measures (Table 2). Six papers evaluated all four of our chosen outcomes; patency, limb salvage, morbidity, and mortality.\textsuperscript{19,21–23,26,27} The proportion of lower extremity bypasses performed on patients with diabetes ranged from 36.1 to 82.6\%. Eight papers\textsuperscript{19–24,26,27} examined patency on bypass grafts with time-frames ranging from 30 days to 5 years. Six studies found no difference on patency when comparing patients with and without diabetes.\textsuperscript{19,20,22,24,26,27} The other two\textsuperscript{21,23} found increased patency among patients with diabetes, one study examined early patency (30 days)\textsuperscript{21} and the other late patency (5 years).\textsuperscript{23} Limb salvage was examined by all studies except Ref. [7]. The time-frames studied varied from 30 days to 5 years, one study failed to indicate the time endpoint.\textsuperscript{28} Seven papers found equivalent limb salvage rates among patients with diabetes when compared those without diabetes.\textsuperscript{19,20,22,24–26,27} Three studies showed decreased limb salvage rates among patients with diabetes when compared those without diabetes.\textsuperscript{19,20,22,24–26,27} One of these studies\textsuperscript{21} had the largest number of patients and the shortest endpoint (30 days). Seven studies examined morbidity,\textsuperscript{19,21–23,26,27} these studies differed in their definition of morbidity, but all included nonfatal cardiac causes. Three studies found no difference,\textsuperscript{22,26,27} the other four\textsuperscript{19,21,23} demonstrated increased morbidity in patients with diabetes, primarily due to infection and nonfatal cardiac events. All but one study\textsuperscript{28} analyzed mortality. Six of the ten examined early mortality (<30 days).\textsuperscript{1,9,19,21,24,26,27} Five of these six showed no differences in mortality, the outlier was Ref. [27]. Of the remaining four

**Table 2. Prevalence and outcome of patients with diabetes and lower extremity arterial disease after bypass**

<table>
<thead>
<tr>
<th>Study</th>
<th>BPG (N)</th>
<th>DM (%)</th>
<th>Patency</th>
<th>Limb salvage</th>
<th>Morbidity</th>
<th>Mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AhChong,\textsuperscript{19} 2004</td>
<td>265</td>
<td>66.4</td>
<td>NS</td>
<td>NS</td>
<td>†</td>
<td>†</td>
<td>20 vs. 9% repeat debridements, $p&lt;0.04$; 8 vs. 1% &gt;30 days inpt mortality $p=0.04$</td>
</tr>
<tr>
<td>Grego,\textsuperscript{20} 2004</td>
<td>71</td>
<td>77.4</td>
<td>NS</td>
<td>NS</td>
<td>†</td>
<td>†</td>
<td>50 vs. 5 % at 1 year, $p=0.0004$</td>
</tr>
<tr>
<td>Virkkunen,\textsuperscript{21} 2004</td>
<td>5709</td>
<td>44</td>
<td>NS</td>
<td>NS</td>
<td>†</td>
<td>†</td>
<td>20 vs. 9% repeat debridements, $p&lt;0.04$; 8 vs. 1% &gt;30 days inpt mortality $p=0.04$</td>
</tr>
<tr>
<td>Wölfle,\textsuperscript{22} 2003</td>
<td>211</td>
<td>44.5</td>
<td>NS</td>
<td>NS</td>
<td>†</td>
<td>†</td>
<td>20 vs. 9% repeat debridements, $p&lt;0.04$; 8 vs. 1% &gt;30 days inpt mortality $p=0.04$</td>
</tr>
<tr>
<td>Axelrod,\textsuperscript{23} 2002</td>
<td>3838</td>
<td>55</td>
<td>NR</td>
<td>NR</td>
<td>†</td>
<td>†</td>
<td>20 vs. 9% repeat debridements, $p&lt;0.04$; 8 vs. 1% &gt;30 days inpt mortality $p=0.04$</td>
</tr>
<tr>
<td>Calle-Pascual,\textsuperscript{24} 2001</td>
<td>481</td>
<td>36.2</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>20 vs. 9% repeat debridements, $p&lt;0.04$; 8 vs. 1% &gt;30 days inpt mortality $p=0.04$</td>
</tr>
<tr>
<td>Akbari,\textsuperscript{25} 2004</td>
<td>962</td>
<td>82.6</td>
<td>NS</td>
<td>NS</td>
<td>†</td>
<td>†</td>
<td>20 vs. 9% repeat debridements, $p&lt;0.04$; 8 vs. 1% &gt;30 days inpt mortality $p=0.04$</td>
</tr>
<tr>
<td>Bertolé,\textsuperscript{26} 1999</td>
<td>1560</td>
<td>39.4</td>
<td>NR</td>
<td>NS</td>
<td>†</td>
<td>†</td>
<td>20 vs. 9% repeat debridements, $p&lt;0.04$; 8 vs. 1% &gt;30 days inpt mortality $p=0.04$</td>
</tr>
<tr>
<td>Gahtan,\textsuperscript{27} 1998</td>
<td>170</td>
<td>55.3</td>
<td>NS</td>
<td>NS</td>
<td>†</td>
<td>†</td>
<td>20 vs. 9% repeat debridements, $p&lt;0.04$; 8 vs. 1% &gt;30 days inpt mortality $p=0.04$</td>
</tr>
<tr>
<td>Karacagil,\textsuperscript{28} 1995</td>
<td>332</td>
<td>36.1</td>
<td>NS</td>
<td>NS</td>
<td>†</td>
<td>†</td>
<td>20 vs. 9% repeat debridements, $p&lt;0.04$; 8 vs. 1% &gt;30 days inpt mortality $p=0.04$</td>
</tr>
<tr>
<td>Dietzek,\textsuperscript{29} 1990</td>
<td>987</td>
<td>62.9</td>
<td>NR</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>20 vs. 9% repeat debridements, $p&lt;0.04$; 8 vs. 1% &gt;30 days inpt mortality $p=0.04$</td>
</tr>
</tbody>
</table>

BPG, bypass graft; NR, not reported; NS, not statistically significant; RR, risk ratio; OR, odds ratio; DM, diabetes mellitus.
studies, the time-frame analyzed varied from 6 months to 5 years. Three of these four demonstrated increased mortality in patients with diabetes, the outlier was Ref.[20] which had the smallest number of patients and longest follow-up.

Abdominal aortic aneurysm

Fifteen papers were identified that examined abdominal aortic aneurysms against our chosen outcome measures (Table 3). No study evaluated all our chosen outcomes; prevalence, morbidity, and mortality. The proportion of AAA repaired in patients with diabetes ranged from 2.3 to 14.1%, this range includes Ref.[33] that screened patients based on the presence of carotid artery stenosis. Eleven studies analyzed the prevalence of AAA in patients with diabetes. Six papers found a lower prevalence of AAA in patients with diabetes and five papers found no difference in the prevalence. The two largest studies found a lower prevalence, but they shared data from the Veteran Affairs’ Aneurysm Detection and Management trial. Of the studies that did not show a difference in prevalence, Ref. [30] did not provide statistical evidence and Ref. [40] had the smallest number of patients. Only two studies examined the inpatient morbidity following AAA repair in patients with diabetes. Both studies found through subset analysis that these patients had increased risk for certain complications. Ref.[41] included a subset of aortic occlusive disease patients in their analysis, but found increased myocardial infarction and infection rates, and analysis included subset of aortic occlusive disease patients.

Discussion

The aim of this review was to illustrate the differences in the pathophysiology of atherosclerosis by summarizing the prevalence and clinical outcomes of vascular disease in patients with diabetes against patients without diabetes. The results of all sections were scored based on the direction of outcome, but also on the merit and weight of the study (Table 4).
On a fully adjusted model, they found the odds ratio to be over double that of patients without diabetes for the development of lower extremity arterial disease.

Equally as convincing, but trending in the opposite direction is the prevalence of AAA in patients with diabetes. Our analysis demonstrates the prevalence range of AAA to be much lower than the overall prevalence of diabetes. Even though our data favored a lower prevalence of AAA in patients with diabetes, all studies were not in agreement with this conclusion, however, no study showed an increase in prevalence. The finding of a lower prevalence of AAA in patients with diabetes is perhaps the most intriguing in our review and is in agreement with the current theories on the pathogenesis of AAA on a cellular level, which is distinct from atherogenesis. Some investigators hypothesize that there is an increase in wall stiffness in patients with diabetes, which could explain in part the lower prevalence of AAA. Furthermore, up-regulation of matrix metalloproteinases (MMP) has been implicated in the pathogenesis behind AAA formation. Researchers have studied matrix metalloproteinases in diabetic arteries and found down-regulation in the expression of extracellular matrix inducer proteins with a two-fold reduction of total MMP activity. Decreases in MMP activity could contribute to increased collagen deposition which would lead to remodeling and extracellular matrix deposition in the diabetic vasculature. This could also explain the decrease in prevalence of AAA in patients with diabetes that we have demonstrated and underscores the counter-theory that AAA formation is not directly causally linked to atherosclerosis.

### Morbidity

When examining the morbidity of these vascular procedures, we found consistent increases in diabetes patients. This parameter had the greatest heterogeneity between studies and was often least reported. Nonfatal cardiac events and infection were the most frequent subcategories that reached statistical significance. The morbidity in CEA favored equivalency between patient with and without diabetes, only Refs. [7,9] found an increase in combined nonfatal MI and neurologic events. The lower extremity arterial disease bypass studies were evenly split between groups. When differences existed, infection and nonfatal MI accounted for the majority of morbidity. Finally, when examining AAA, both studies that examined morbidity found an increase in infectious complications.
It is not surprising that as the complexity of the type of operation increased, a consensus on morbidity was observed. A subcutaneous operation often performed under local anesthesia, such as a CEA, may not pose enough stress to consistently show differences in morbidity. The advances in pre-operative work-up and perioperative management have decreased the number of cardiac events, so it is not unexpected that infection was the leading cause of morbidity in patients with diabetes.55 Cruse, et al.56 examined surgical wound infections of 23,649 patients undergoing various procedures and found the unadjusted clean wound infection rates were 10.7 and 1.8% in patients with diabetes and those without, respectively. The increased wound infection rates were best illustrated in the lower extremity arterial disease studies. In all three studies that indicated a higher infection rate, patient with diabetes presented with a higher percentage of tissue loss.

Mortality

Population studies have shown that the risk of death in a patient with diabetes is twice that of age-matched and co-morbidity adjusted patient without diabetes;7 70% of these deaths are caused from cardiovascular disease. This paper primarily examined surgical mortality. Studies in our review that did examine late mortality consistently found higher mortality in patients with diabetes.5,11,12,19,20,22,23,26,27 In lower extremity arterial disease bypass and AAA repair patients, mortality appears equivalent between groups. This suggests that the atherosclerotic process driving the development of clinical disease may override the effect of diabetes. Patients with diabetes undergoing surgery for lower extremity arterial disease may have comparable cardiac atherosclerotic burden as patients without diabetes and therefore similar risks; this may also be true for both groups undergoing AAA repair. Patients with diabetes undergoing CEA were found to have an increased mortality risk in almost half of the studies. At first glance, it seems counter-intuitive that an operation posing the least stress would cause the most mortality; however, it has been shown that patients with diabetes have worse outcome with stroke than patients without diabetes.57,58 Patients with diabetes have impaired autoregulation of cerebral blood flow along with rheological changes in erthyrocytes.57 The increase in mortality is also thought to be associated with hyperglycemia from anaerobic glycolysis of excess glucose.59 Fatal strokes could account for some of the increased mortality, but it could also be that patients with diabetes undergoing CEA have more extensive coronary artery disease than patients without diabetes. Increased carotid artery intima and media thickness (IMT), a potential surrogate measurement of coronary atherosclerosis, has been shown to be a risk factor for myocardial infarction.60 Diabetes patients have been found to have higher internal carotid artery IMT measurements, both at baseline and with progression.61,62 Total carotid plaque burden (TPB), which measures intimal thickness only, is also higher in patients with diabetes.63 This non-invasive study correlates with the finding of longer ICA plaques during CEA in patients with diabetes.5 Both IMT and TPB correlate with higher stroke and myocardial infarction rates, patients with the highest measurement groups have nearly three times the relative risk.60,63 Other studies have found diabetes to be closely associated with TPB, but not carotid artery stenosis.64 Taken together, findings support our observation that the prevalence of carotid artery stenosis is not increased in patients with diabetes undergoing correction. Additionally, it could explain some of the increased cardiac risk of patients with diabetes, since their carotid artery stenosis may be a more aggressive form of atherosclerosis than patients without diabetes. This conclusion, is supported by a study that found diabetes patients with carotid artery stenosis had the highest hazard ratio of all risk factors tested for severe MI or death.65

Conclusion

Through, this review of the literature we demonstrate the differences and similarities in prevalence and outcome of patients with diabetes as compared to patients without diabetes undergoing common vascular procedures. Our subjective conclusions are summarized concisely in Table 4. With regards to prevalence, we conclude that it is equivalent in carotid artery stenosis, increased in lower extremity arterial disease, and decreased in AAA in patients with diabetes. Stroke, graft patency, and limb salvage rates in patients with diabetes after surgery are similar to patients without diabetes, but perioperative complication risks were increased in all surgical groups. The perioperative mortality risk may be higher after CEA, this risk may be related to the specific effects of diabetes on the cardiac vasculature. We have also observed biological differences of the atherosclerosis phenotype in patients with diabetes. It is these differences that could account for the discord in outcome when comparing two similar diseases in two dissimilar patient groups. Further study into
the phenotype of diabetic atherosclerosis may help to elucidate its natural history and provide guidance on when and how to intervene.

References
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