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Diabetes and Metformin Use Are Associated with Reduced Sac Shrinkage Following EVAR: A Retrospective Cohort Study

Michael Turner[1], Sophia Nguyen[2]*, David Clark[1], Emma Wilson[3]

[1]Department of Clinical Research and Medical Innovation, Faculty of Medicine, University of Glasgow, Glasgow, United Kingdom.
[2]Department of Translational Medical Sciences, National University of Singapore, Singapore.
[3]Department of Clinical Investigation and Biomedical Systems, University of Sydney, Sydney, Australia.

Abstract

To investigate how diabetes mellitus (DM) and the use of metformin affect aneurysm sac changes after endovascular aneurysm repair (EVAR). We conducted a retrospective analysis at a single center of a consecutive series of patients who underwent elective EVAR for infrarenal abdominal aortic aneurysm (AAA) from January 2011 through December 2021. Inter-group comparisons were performed, Kaplan–Meier survival curves were generated for both overall survival and freedom from reintervention, and Cox regression was utilized to detect factors predicting sac shrinkage. The study population consisted of 529 patients, of whom 74 (14.0%) had DM treated with metformin, 26 (4.9%) had DM but did not receive metformin, and 429 (81.1%) had no diabetes. One year after the procedure, patients with diabetes exhibited significantly lower rates of sac shrinkage than those without diabetes (40.0% vs. 52.0%; P = 0.038) and showed a trend toward more frequent stable sac size (52% vs. 42%; P = 0.055). At the latest available follow-up, sac shrinkage was notably lower in the metformin-treated diabetic subgroup compared with non-diabetic patients (48.6% vs. 59.9%; P = 0.047). Sac shrinkage rates did not differ between diabetic patients who were or were not taking metformin. Endoleaks occurred significantly more often in cases with stable sacs or sac expansion. During the nine-year observation period, overall survival was considerably worse in diabetic patients than in non-diabetics (23.5% vs. 37.5%; P < 0.001). This analysis indicates that both diabetes mellitus and metformin therapy are associated with reduced aneurysm sac shrinkage following EVAR. Any endoleak correlated with poorer sac regression at the one-year mark and at final follow-up. Long-term overall survival was significantly inferior among patients with diabetes compared with those without diabetes.

Keywords: Aortic aneurysm, Abdominal, Metformin, Diabetes mellitus, Endovascular aneurysm repair

Corresponding author: Sophia Nguyen
E-mail: sophia.nguyen@gmail.com

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Introduction

For individuals diagnosed with abdominal aortic aneurysm (AAA) whose anatomy is suitable, endovascular aneurysm repair (EVAR) is typically preferred over conventional open surgery. Reduction in aneurysm sac diameter is widely accepted as a sign of technically successful EVAR [1] and is associated with a decreased incidence of complications for up to 5 years postoperatively [2]. The underlying reasons why some aneurysm sacs shrink while others remain unchanged or enlarge after EVAR are not yet well defined. Identified

risk factors for limited sac regression include impaired kidney function, type I and type II endoleaks (ELs), thrombus in the proximal neck before surgery, and aortic wall calcification [1, 3].

Although diabetes mellitus (DM) is a major contributor to cardiovascular disease, several contemporary studies have reported that people with type 2 diabetes actually experience a decreased risk of developing, enlarging, or rupturing an abdominal aortic aneurysm (AAA) [4, 5]. The biological processes responsible for this apparently protective role of DM in AAA remain incompletely elucidated. However, evidence suggests that diabetic arteries tend to have thicker walls and slower extracellular matrix breakdown, which may be related to the accumulation of advanced glycation end products (AGE) and reduced activity of matrix metalloproteases (MMP) [5, 6]. These alterations could account for the lower rates of AAA formation and subsequent growth observed in individuals with diabetes.

Metformin is the standard initial medication prescribed for type 2 diabetes. Various observational studies have found that diabetic patients receiving metformin display slower AAA expansion rates than those managed with other glucose-lowering drugs, and this difference persists after statistical adjustment for additional risk factors [7, 8]. A recent comprehensive systematic review and meta-analysis quantified the average difference in annual AAA diameter growth between metformin users and non-users as 0.73 mm/year [9]. Consistent with these clinical observations, experiments in animal models have shown that metformin can limit both the initiation and advancement of AAA [10, 11]. Our prior laboratory investigation revealed that metformin enhances contractile function and metabolic activity while reducing proliferative, migratory, and inflammatory responses in smooth muscle cells (SMCs) cultured from human AAA tissue [12]. The possible therapeutic role of metformin in slowing AAA progression is currently being tested in several randomized controlled trials (RCTs) [13-16].

This study was designed to assess the influence of diabetes mellitus—both with and without metformin—on post-EVAR aneurysm sac remodeling, irrespective of the endograft device used. Informed by the results of the studies cited earlier, we anticipated that DM and metformin would encourage sac stability and reduce further sac enlargement after EVAR. Whether the same mechanisms also impair sac shrinkage will be addressed by the data presented here.

Materials and Methods

Study design

This retrospective observational cohort analysis examined a consecutive group of patients who underwent planned EVAR for infrarenal abdominal aortic aneurysm (AAA) at a tertiary referral hospital from January 2011 to December 2021. All preoperative, procedural, and surveillance data (recorded at six to eight weeks, one year after EVAR, and every year thereafter) were prospectively collected from electronic health records for the entire AAA population and stored in coded format within Research Manager (Research Manager, Deventer, The Netherlands). Baseline risk factors were identified through the standard anesthesiology evaluation performed before surgery. During this evaluation, the presence of diabetes and current metformin use were explicitly recorded. Ethical approval was waived by the medical ethics committee (2023-16141), and permission to conduct the study was granted by the hospital's board of directors (2023-2183). The institutional opt-out registry was checked to confirm that no patient had opted out of medical research.

Procedures followed the manufacturer's instructions for use and local institutional guidelines. All cases were reviewed during multidisciplinary team discussions, and the choice of endograft was determined by individual anatomy and the operating surgeon's judgment. After the operation, patients generally received statin therapy and a single antiplatelet medication unless they were already on oral anticoagulants for other medical reasons. Following discharge, imaging with computed tomography angiography (CTA) or duplex ultrasound (DUS) was scheduled six to eight weeks later. Further surveillance imaging, either DUS or CTA, was performed at the one-year mark and annually thereafter. Sac diameter measurements were taken from whichever imaging modality was available; when both CTA and DUS had been performed concurrently, preference was given to the CTA measurements.

Definitions

Primary technical success was evaluated on an intention-to-treat basis. It was achieved when the device was successfully introduced and deployed without the need for open surgical conversion, without perioperative death, and without type I or III endoleaks or graft limb blockage. If additional unplanned endovascular or surgical interventions were necessary to secure success, assisted technical success was classified as "yes" when those interventions succeeded and "no" when they did not.

Outcomes

The principal goal was to assess the influence of diabetes mellitus (DM) and metformin treatment on aneurysm sac remodeling after elective EVAR. Sac remodeling was categorized into three groups: sac shrinkage (a decrease of more than 5 mm from baseline), stable sac (a change of 5 mm or less from baseline), and sac growth (an increase of more than 5 mm from baseline). Secondary endpoints

consisted of the occurrence and specific type of endoleak (EL), reintervention-free survival, overall survival, and freedom from aneurysm-related death. These secondary measures were defined in line with established EVAR reporting standards [17-19].

Statistical analysis

Missing values were not imputed, and all percentages were derived directly from the total number of patients in each respective group. The Shapiro–Wilk test was applied to evaluate normality across all study groups. Continuous variables are reported as the mean with standard deviation (SD) when normally distributed, or as the median with interquartile range (IQR) when the distribution is skewed. Categorical variables are shown as counts and corresponding percentages. Group comparisons were performed using independent-samples t-tests, Chi-square tests, or Mann–Whitney U tests, depending on the data type. Bar charts illustrated the relative proportions of sac remodeling categories observed at the one-year visit and at the latest follow-up. Kaplan–Meier curves depicted overall survival and reintervention-free survival, with inter-group differences assessed by the log-rank test. Cox regression modeling was used to explore potential predictors of sac shrinkage. All statistical computations were carried out using IBM SPSS Statistics (version 29.0 for Windows, IBM Corporation, Armonk, NY, USA). Statistical significance was set at a two-sided P-value of 0.050 or lower.

Results and Discussion

The hospital database initially contained records of 1101 patients. Only individuals who had undergone elective repair of an infrarenal abdominal aortic aneurysm were considered for this analysis. After applying the exclusion criteria, 529 patients qualified for inclusion. Among them, 74 (14.0%) were diabetic patients on metformin therapy (DM + MF), 26 (4.9%) were diabetic patients not receiving metformin (DM-MF), and 429 (81.1%) were patients without diabetes (No DM) **(Figure 1)**. The median follow-up time to the most recent imaging was 3.8 years (IQR 1.6–6.6 years), and this duration did not differ significantly among the three groups.

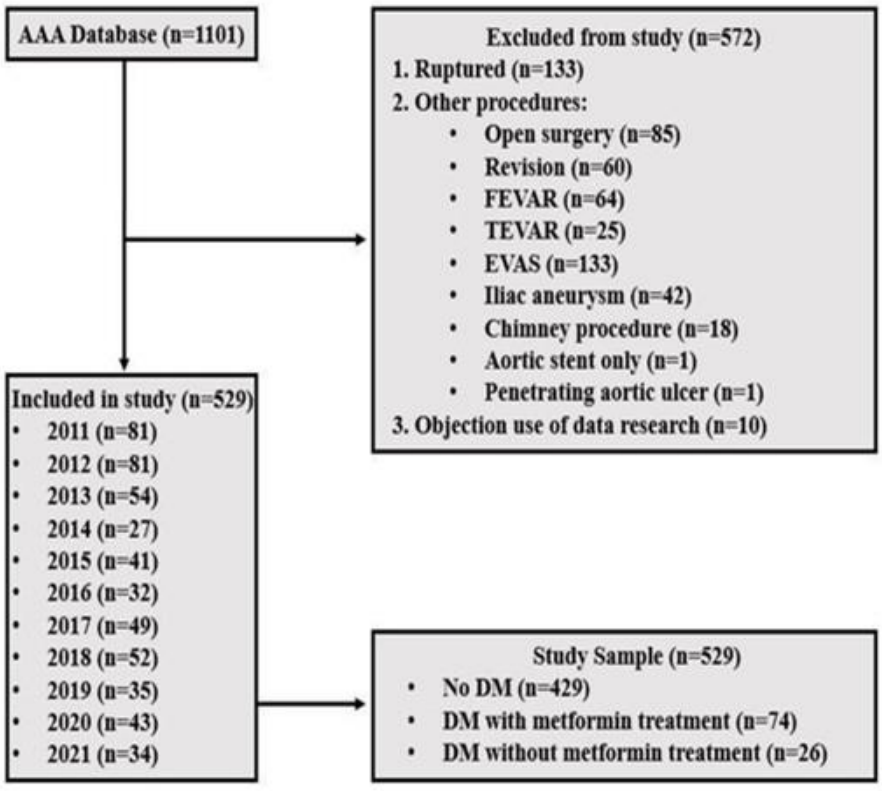


Figure 1. Inclusion flow chart. FEVAR—fenestrated endovascular aneurysm repair. TEVAR—thoracic endovascular aneurysm repair; EVAS—endovascular aneurysm sealing, No DM—patients without diabetes mellitus, DM—diabetes mellitus.

Baseline patient and AAA characteristics

In comparison with patients who did not have diabetes, those in the diabetic cohort presented with markedly elevated body mass index (BMI) ($P < 0.001$), raised glucose concentrations ($P < 0.001$), poorer ASA physical status scores ($P < 0.001$), increased rates of hypertension (HT) ($P = 0.001$), higher occurrence of hyperlipidemia ($P = 0.033$), and a greater proportion with prior cardiac

conditions (P = 0.014) **(Table 1)**. Furthermore, diabetic individuals not receiving metformin exhibited a more frequent history of renal disease (P = 0.037) than their non-diabetic counterparts. Within the metformin-treated diabetic group, 27.0% were managed solely with metformin, 66.2% received supplementary oral antidiabetic drugs, and 37.8% required insulin therapy in combination with oral agents. Among diabetic patients not prescribed metformin, 38.5% were on oral antidiabetic medication alone, while another 38.5% combined oral therapy with insulin.

Table 1. Baseline characteristics according to subgroup.

Variable	Non-DM (n = 429)	DM without Metformin (n = 26)	P-value	DM with Metformin (n = 74)	P-value	Total DM (n = 100)	P-value
Age (years)	72.8 ± 8.1	75.2 ± 9.3	0.164	72.2 ± 7.7	0.551	73.0 ± 0.82	0.852
Male (%)	361 (84.1)	24 (92.3)	0.263	65 (87.8)	0.416	89 (89.0)	0.220
BMI (kg/m²)	25.8 (23.8; 28.4)	27.6 ± 4.5	0.058	27.8 (24.8; 31.0)	< 0.001	27.81 (24.6; 31.0)	< 0.001
Systolic BP (mmHg)	143.0 (127; 156.5)	143.0 (130.0; 156.0)	0.557	143.0 (125.0; 160.0)	0.761	143.06 (127.5; 160.0)	0.596
Diastolic BP (mmHg)	81.0 (74; 89)	82.0 (70.0; 87.0)	0.599	81.0 (74.0; 87.0)	0.410	81.06 (73.0; 87.0)	0.348
Heart rate (bpm)	72.5 (64; 84.5)	78.0 (70.0; 85.0)	0.134	73.0 (66.0; 85.0)	0.471	74 (66.0; 85.0)	0.188
ASA ≤ 2	195 (46.9)	4 (15.4)	0.002	22 (29.7)	0.025	26 (26.0)	< 0.001
ASA ≥ 3	221 (53.1)	22 (84.6)	—	51 (68.9)	—	73 (73.0)	—
Hypertension (%)	293 (69.3)	24 (92.3)	0.012	62 (83.8)	0.011	86 (86.0)	< 0.001
Hyperlipidemia (%)	295 (76.8)	21 (80.8)	0.105	59 (79.7)	0.011	80 (87.0)	0.033
Cardiac history (%)	176 (46.0)	13 (50.0)	0.324	43 (58.1)	0.017	56 (60.2)	0.014
Pulmonary history (%)	79 (21.1)	4 (15.4)	0.602	20 (27.0)	0.115	24 (26.4)	0.279
Renal history (%)	110 (26.3)	11 (42.3)	0.037	23 (31.1)	0.321	34 (35.4)	0.073
Tobacco use (%)	142 (35.0)	9 (34.6)	0.917	27 (36.5)	0.680	36 (37.1)	0.692
Type 2 DM (diet/oral)	—	17 (65.4)	—	60 (81.1)	—	77 (77.0)	—
Type 2 DM (insulin-treated)	—	7 (26.9)	—	14 (18.9)	—	21 (21.0)	—
Type 1 DM	—	2 (7.7)	—	—	—	2 (2.0)	—
Glucose (mmol/L)	5.7 (5.2; 6.3)	8.8 (6.7; 10.4)	< 0.001	9.2 (6.5; 11.4)	< 0.001	9.1 (6.5; 11.0)	< 0.001
Metformin use	—	—	—	74 (100)	< 0.001	74 (76.0)	< 0.001
Other oral antidiabetics	—	10 (38.5)	< 0.001	49 (66.2)	< 0.001	60 (66.7)	< 0.001
Insulin therapy	—	10 (38.5)	< 0.001	28 (37.8)	< 0.001	38 (42.2)	< 0.001
Metformin monotherapy	—	—	—	20 (27.0)	< 0.001	20 (22.2)	< 0.001

No DM—patients without diabetes mellitus, DM-total—patients with diabetes mellitus, DM + MF—patients with diabetes mellitus receiving metformin therapy, DM-MF—patients with diabetes mellitus not receiving metformin therapy, BMI—body mass index; SBP—systolic blood pressure; DBP—diastolic blood pressure; ASA—American Society of Anesthesiologists; DM—diabetes mellitus; AAA—abdominal aortic aneurysm, CIA—common iliac artery, p—p-value in comparison with the no-diabetes group. Values are shown as mean ± SD, frequency (percent), or median (Q1; Q3). [a] Current tobacco use includes those who stopped smoking less than 1 year ago. [b] Type 2 diabetes patients managed exclusively with insulin for glycemic control. [c] Glucose or fasting glucose levels were assessed at baseline. [d] Includes the sulfonylurea agents Gliclazide, Glimepiride, and Tolbutamide. [e] Includes the following insulin preparations: glargine, isophane, detemir, aspart/protamine/novorapid, glulisine, and lispro.

Preoperative maximum aneurysm diameter, aneurysm classification, and selected endograft type showed no notable differences between the diabetic and non-diabetic populations **(Table 1)**. Nevertheless, the subgroup of diabetic patients not on metformin demonstrated a significantly wider infrarenal neck diameter (26.0 mm, IQR 24.0–28.0 mm vs. 23.5 mm, IQR 21.0–25.0 mm; P = 0.004) and a narrower right common iliac artery diameter (14.0 mm, IQR 11.0–18.0 mm vs. 16.0 mm, IQR 13.0–20.0 mm; P = 0.050) when contrasted with the non-diabetic cohort.

Procedure, hospitalization, and 30-day complications

The primary technical success rate was 86.4%, and assisted technical success was achieved in 98.3% of procedures, with comparable outcomes across all groups. Taken together, diabetic patients experienced an extended length of hospital stay (3.0 days, IQR 2.0–5.5 days vs. 3.0 days, IQR 2.0–4.0 days) (P = 0.017), prolonged duration of surgery (100.5 min, IQR 75.5–120.0 min vs. 88.0 min, IQR 71.5–112.0 min) (P = 0.039), and a substantially elevated incidence of complications while hospitalized (38.0% vs. 23.1%) (P = 0.002) relative to non-diabetic patients. Interestingly, the diabetic subgroup not using metformin recorded reduced blood loss during the operation (0.0 mL, IQR 0.0–100.0 mL vs. 100.0 mL, IQR 0.0–300.0) (P = 0.020) compared with the non-diabetic group **(Table 2)**.

Table 2. Hospitalization and 30-day complication data by subgroup.

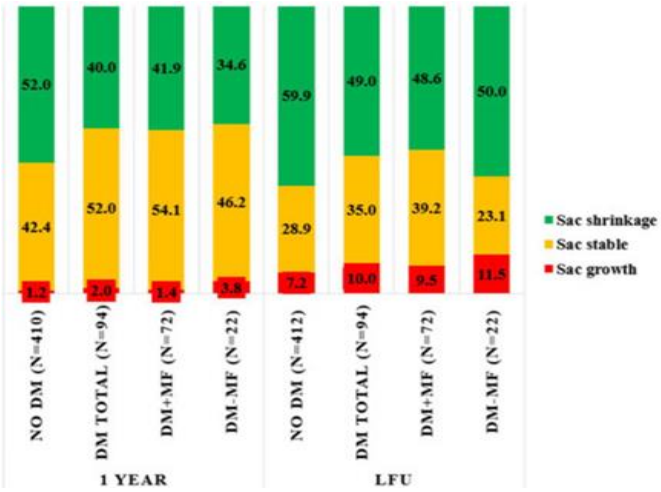
Variable	Non-DM (n = 429)	Total DM (n = 100)	p-value	DM with Metformin (n = 74)	P-value	DM without Metformin (n = 26)	P-value
Length of hospital stay (days)	3.0 (2.0; 4.0)	3.0 (2.0; 5.5)	0.017	4.0 (2.0; 6.0)	0.016	3.0 (2.0; 5.0)	0.425
Intraoperative blood loss (mL)	100.0 (0.0; 300.0)	100.0 (0.0; 250.0)	0.719	150.0 (5.0; 300.0)	0.371	0.0 (0.0; 100.0)	0.020
Overall procedure duration (min)	88.0 (71.5; 112.0)	100.5 (75.5; 120.0)	0.039	98.0 (76.0; 124.0)	0.039	102.5 (75.0; 114.0)	0.474
Primary technical success (%)	369 (86.0)	88 (88.0)	0.602	69 (93.2)	0.087	19 (73.1)	0.071
Assisted technical success (%)	421 (98.1)	99 (99.0)	0.547	74 (100.0)	0.236	25 (96.2)	0.481
Conversion to open surgery (%)	1 (0.2)	1 (3.0)	0.632	1 (1.4)	0.683	0 (0.0)	0.812
In-hospital complications (%)	99 (23.1)	38 (38.0)	0.002	27 (36.5)	0.011	11 (42.3)	0.026
Complication type	Non-DM	DM Total	p-value	DM + MF	p-value	DM − MF	p-value
Systemic complications (%)	31 (31.1)	8 (21.0)	—	4 (14.8)	—	4 (36.4)	—
Urinary tract infection (%)	2 (2.0)	1 (2.6)	—	1 (3.7)	—	—	—
Renal impairment (%)	7 (7.1)	1 (2.6)	—	—	—	1 (9.1)	—
Fever (%)	20 (20.2)	5 (13.2)	—	3 (11.1)	—	2 (18.2)	—
Pulmonary complications (%)	13 (13.5)	5 (13.2)	0.499	4 (14.8)	0.250	1 (9.1)	0.643
Cardiac complications (%)	19 (19.8)	7 (18.4)	0.505	6 (23.1)	0.872	1 (9.1)	0.302
Event	**Non-DM**	**DM Total**		**DM + MF**		**DM − MF**	
Angina (NYHA class)	1 (1.0)	—		—		—	
Myocardial infarction	3 (3.0)	1 (2.6)		—		1 (9.1)	

Coronary artery disease	1 (1.0)	—	—	—
Atrial fibrillation	5 (5.1)	—	—	—
Acute heart failure	2 (2.0)	1 (2.6)	1 (3.7)	—

No DM—individuals without diabetes mellitus; DM-total—individuals with diabetes mellitus; DM + MF—individuals with diabetes mellitus receiving metformin therapy; DM-MF—individuals with diabetes mellitus not receiving metformin therapy. p—p-value versus the non-diabetes group. Values are shown as mean ± SD, frequency (percent), or median (Q1; Q3).

Sac remodeling

In the entire cohort, aneurysm sac shrinkage was noted in 49.7% of cases at the one-year follow-up and rose to 57.8% by the final follow-up assessment. At the one-year mark, only 40.0% of diabetic patients exhibited sac shrinkage, compared with 52.0% among non-diabetic patients (P = 0.038). Diabetic individuals also showed a tendency toward more stable sac dimensions than non-diabetic individuals (52% vs. 42%; P = 0.055). Shrinkage rates remained comparable between diabetic patients receiving metformin and those not receiving it **(Figure 2)**. By the last available follow-up, sac shrinkage reached 49.0% in the diabetic group versus 59.9% in the non-diabetic group (P = 0.067). Notably, diabetic patients treated with metformin showed markedly reduced sac shrinkage relative to non-diabetic patients (48.6% vs. 59.9%; P = 0.047). However, no meaningful differences in sac remodeling patterns emerged between diabetic patients on metformin monotherapy and those not taking metformin, whether evaluated at 1 year or at the latest follow-up.



a)

Group	1 year	P vs No DM	P DM+MF vs DM-MF	LFU	P vs No DM	P DM+MF vs DM-MF
DM total	growth	0.497		growth	0.318	
	stable	0.055		stable	0.179	
	shrinkage	0.038		shrinkage	0.067	
DM+MF	growth	0.905	0.369	growth	0.522	0.602
	stable	0.080	0.934	stable	0.086	0.269
	shrinkage	0.076	0.859	shrinkage	0.047	0.455
DM-MF	growth	0.194		growth	0.299	
	stable	0.351		stable	0.778	
	shrinkage	0.217		shrinkage	0.757	

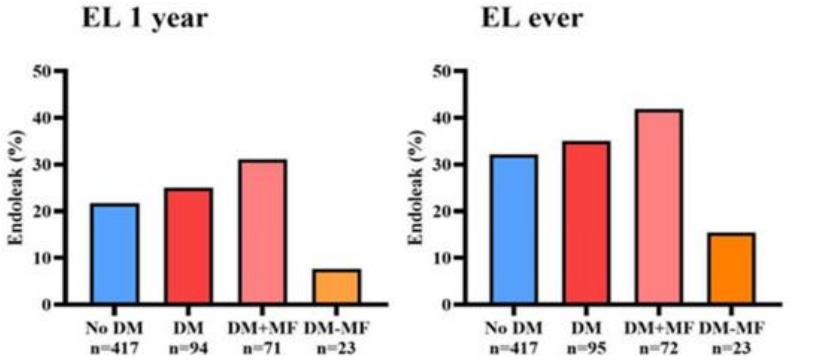
b)

Figure 2. Aneurysm sac remodeling at the 1-year time point and during the latest follow-up assessment. (a) Distribution of aneurysm sac shrinkage, stability, and expansion rates among the different study cohorts at the 1-year follow-up visit, as well as at the final available follow-up. Overall, percentages fall short of 100% due to missing data points. (b) p-values calculated using Pearson Chi-square tests when evaluating aneurysm sac behavior (shrinkage, stability, and expansion) in diabetic versus non-diabetic AAA cases, along with comparisons between diabetic individuals managed with metformin and those managed without metformin. No DM—patients without diabetes mellitus, DM total—patients with diabetes mellitus, DM + MF—patients with diabetes mellitus on metformin treatment, DM-MF—patients with diabetes mellitus without metformin treatment, LFU—last follow-up, P—p-value.

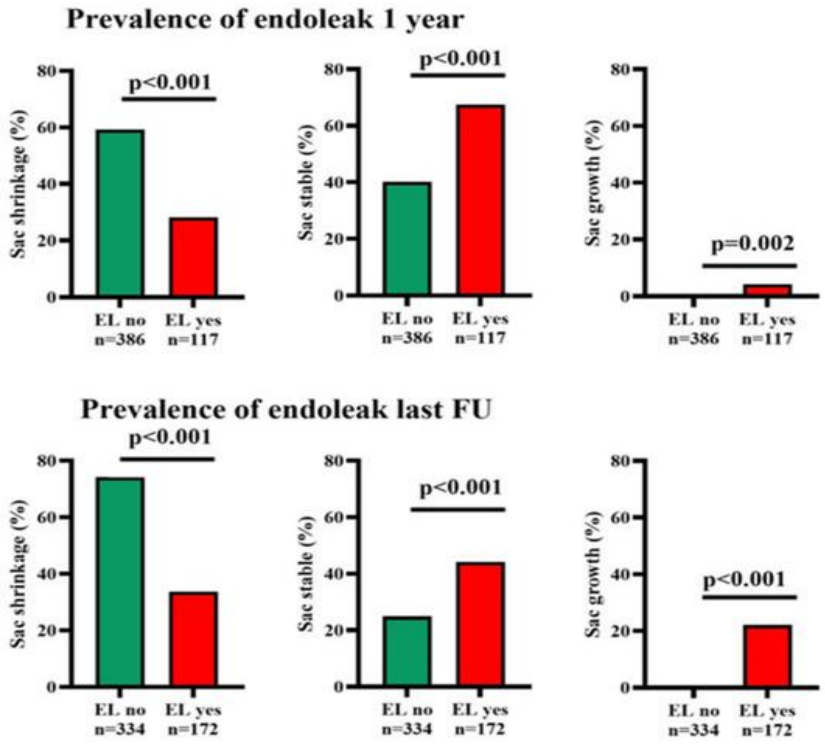
Cox proportional hazards regression evaluating sac shrinkage identified that elevated ASA score, greater patient age, and greater baseline maximum AAA diameter were associated with a higher likelihood of sac shrinkage. On the other hand, hyperlipidemia, documented endoleak throughout the observation period, and the need for reintervention were associated with a reduced likelihood of sac shrinkage. Effect sizes for these associations were modest. The specific type of endoprosthesis used did not affect sac remodeling. Furthermore, no other aneurysm-related features demonstrated a statistically significant relationship with sac shrinkage.

Secondary endpoints

The occurrence of the initial endoleak (any type) detected during surveillance is presented in **Figure 3a** for both the one-year time point and the last available follow-up. Across all patients, endoleak of any type was observed in 22.3% at one year and in 32.7% at the final follow-up. No statistically significant differences were identified across the study groups, although the frequency of endoleaks increased progressively over time in each group, as shown in **Figure 3a**.



a)



b)

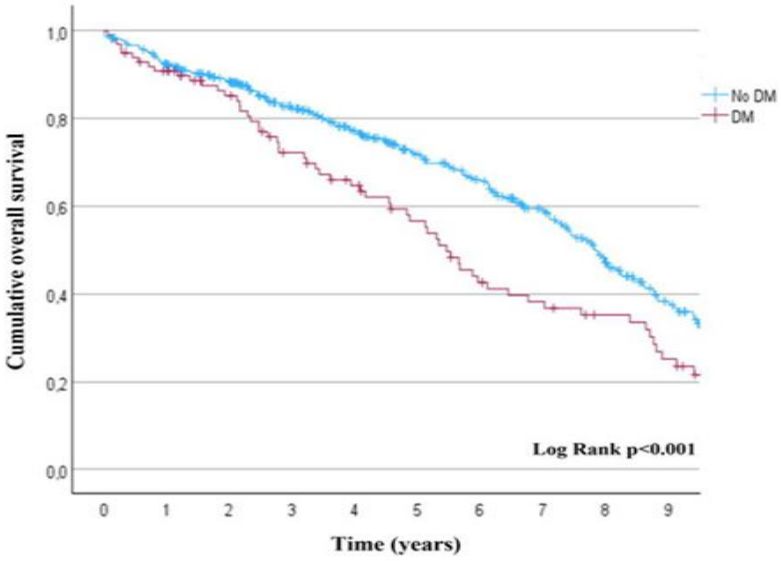
Figure 3. Frequency of endoleaks recorded at the 1-year interval and during the ultimate follow-up evaluation. (a) Distribution of endoleak presence or absence among the different study populations at the 1-year mark and at the most recent follow-up, reported as percentages indicating endoleak occurrence. (b) Distribution of sac remodeling patterns stratified by endoleak presence at the 1-year mark and at the most recent follow-up. Sac remodeling results are presented as percentages for each endoleak category; p-values indicate the statistical significance of differences in sac remodeling patterns between individuals with endoleak and those without, with all comparisons performed using the Pearson Chi-square test. No DM—patients without diabetes mellitus, DM total—patients with diabetes mellitus, DM + MF—patients

with diabetes mellitus on metformin treatment, DM-MF—patients with diabetes mellitus without metformin treatment, LFU—last follow-up, EL = endoleak, P—p-value.

As detailed in **Figure 3b**, sac remodeling results varied markedly depending on the presence or absence of endoleak at both one year and the last follow-up. At each interval, endoleak was substantially more prevalent among patients with stable or enlarged sacs ($P < 0.002$). In comparison, endoleak occurred far less often in patients whose aneurysms had shrunk than in those without endoleak ($P < 0.001$ at both time points).

Analysis of reintervention-free survival was confined to the five-year follow-up window, as the diabetic cohort contained fewer than 10 individuals beyond that interval. At 5 years, reintervention-free survival was 75.7% (95% CI: 5.4–6.5) for diabetic patients and 81.1% (95% CI: 8.5–9.4) for non-diabetic patients ($P = 0.355$). No notable differences were observed among the subgroups. During the entire observation period, 100 patients (18.9%) underwent at least one reintervention, including 38 patients (7.2%) within the initial year, with no significant inter-group variation. 75 patients required only a single reintervention. Some individuals required repeated procedures: 13 patients had 2 reinterventions, 8 had 3, 3 had 4, and 1 patient had 5. The median interval to the first reintervention was 25 months (IQR 2.5–58.7 months). Diabetic patients experienced their first reintervention after a median of 5.3 months (IQR 1.5–50.9 months), whereas non-diabetic patients had a median of 26.5 months (IQR 3.0–61.8 months) ($P = 0.295$).

The one-year overall survival stood at 90.8% (95% CI: 29.1–32.9) in diabetic patients and 92.4% (95% CI: 36.0–37.9) in non-diabetic patients ($P = 0.574$). Kaplan–Meier survival analysis was limited to 9 years of follow-up, as the diabetic cohort had fewer than 10 remaining patients thereafter. At nine years, overall survival had fallen to 23.5% (95% CI: 4.7–6.2) for diabetic patients, in comparison with 37.5% (95% CI: 7.3–8.4) for non-diabetic patients ($P < 0.001$) **(Figure 4)**. After a median follow-up of 3.8 years, 46.7% (n = 247) of the study population had died. Aneurysm-related mortality was limited to five cases in total: four among non-diabetic patients and one in a diabetic patient. In the non-diabetic group, these fatalities occurred on the day of surgery (1 patient), four days postoperatively (2 patients), and five days postoperatively (1 patient). The single aneurysm-related death in the diabetic group took place 50 days after the intervention.



	Years	0	1	2	3	4	5	6	7	8	9
No DM											
	N cumulative events		32	48	70	86	101	116	131	153	167
	N at risk	429	384	339	277	232	183	155	119	80	48
	Overall survival (%)	100.0	92.4	88.4	82.2	77.2	71.8	65.7	59.0	47.2	37.5
	SE		0.013	0.016	0.019	0.022	0.024	0.027	0.029	0.033	0.035
DM											
	N cumulative events	1	9	14	26	31	38	47	51	53	59
	N at risk	99	86	73	58	49	40	29	25	20	14
	Overall survival (%)		90.8	85.2	71.0	64.8	55.2	42.6	36.8	33.6	23.5
	SE		0.029	0.037	0.048	0.052	0.055	0.056	0.056	0.055	0.052

Figure 4. Kaplan–Meier plots illustrating overall survival. Long-term overall survival across a nine-year follow-up interval after endovascular aneurysm repair, contrasting outcomes between non-diabetic individuals and those with diabetes. No DM—patients without diabetes mellitus, DM total—patients with diabetes mellitus, SE—standard error, p

denotes the overall p-value of patients with diabetes with and without metformin treatment compared to patients without diabetes.

This retrospective observational cohort analysis showed that diabetic patients experienced significantly less aneurysm sac shrinkage 1 year after elective endovascular aneurysm repair (EVAR) than their non-diabetic counterparts. However, diabetic patients tended to exhibit more stable sac dimensions. By the latest available follow-up, the difference in shrinkage rates between the two groups remained 10.9 percentage points higher in non-diabetic patients. Still, this gap no longer reached statistical significance. At that final assessment, however, diabetic individuals receiving metformin had a significantly smaller proportion of sac shrinkage compared with the non-diabetic cohort. In addition, endoleaks became more frequent over time and were clearly associated with poorer sac shrinkage at both evaluation points. While overall survival was markedly lower in diabetic patients, no important differences emerged regarding reintervention-free survival or protection from aneurysm-related death across the study groups.

Previous literature has consistently described an inverse relationship between type 2 diabetes and the prevalence, expansion rate, and likelihood of rupture of abdominal aortic aneurysms [4, 5]. Despite this, research examining how diabetes affects clinical results following EVAR has yielded mixed conclusions.

In terms of early postoperative results after EVAR, diabetes was connected to longer hospital admissions, extended operating times, and a greater frequency of complications while patients were still hospitalized. It is widely recognized that insufficiently controlled blood glucose levels worsen perioperative outcomes by raising infection rates, slowing wound recovery, increasing death risk, and extending length of stay [20]. These observations emphasize the vital need for optimal blood sugar control around the time of EVAR procedures.

A large-scale Swedish population-based cohort study involving 748 diabetic and 2630 non-diabetic patients, analyzed using propensity score matching, found no disparity in overall or cardiovascular mortality. Nevertheless, the diabetic group required fewer reinterventions and experienced more acute myocardial infarctions during the four-year observation window. That study, however, did not evaluate sac remodeling aspects such as shrinkage, stability, or growth, nor did it report details on endoleak frequency or subtypes [21]. In a separate study, diabetic patients showed slower sac enlargement over 4 years after EVAR and a suggestion of lower reintervention rates, while mortality and endoleak rates remained similar between diabetic and non-diabetic subjects [22]. Yet another recent analysis examined sac remodeling up to 5 years post-EVAR with Gore Excluder devices and found equivalent sac regression rates in both diabetic and non-diabetic groups. However, 5-year mortality was higher among diabetic patients, even after adjusting for comorbidities [23]. Separately, a meta-analysis examining predictors of sac shrinkage following EVAR found that diabetes was associated with a reduced tendency toward sac shrinkage [1].

Importantly, all of the studies cited above focused solely on the presence of diabetes and did not examine the possible role of metformin treatment. In the current analysis, diabetic patients taking metformin showed even less sac shrinkage at the final follow-up (median 3.8 years) than non-diabetic patients. It is worth noting that the number of diabetic patients not receiving metformin was quite limited. In contrast, one comparable single-center report suggested that metformin therapy had little or no measurable impact on long-term sac remodeling after EVAR [24]. Because existing evidence on the effects of diabetes and metformin on post-EVAR sac behavior and long-term survival remains inconsistent, additional well-designed studies are required to clarify these relationships.

From the studies reviewed, it seems that individuals with diabetes tend to show slower aneurysm sac enlargement over time. Nevertheless, no clear evidence indicates that diabetes mellitus (DM) promotes sac shrinkage after endovascular aneurysm repair (EVAR). Several alterations in the aortic wall among diabetic patients could partly account for this observation. While patients with abdominal aortic aneurysm (AAA) typically exhibit loss of aortic wall matrix components, those with DM frequently demonstrate increased vascular matrix [25]. Moreover, diabetes is associated with increased collagen production, which contributes to greater aortic wall thickness and reduced activity of matrix metalloproteinases (MMPs), which break down the extracellular matrix (ECM).

Additionally, both high blood glucose and elevated insulin levels present in DM lead to elevated formation of advanced glycation end products (AGEs). These AGEs cross-link with collagen and elastin in the aortic wall, stimulating vascular smooth muscle cell (SMC) proliferation and thereby enhancing the wall's overall resistance and tensile strength [26]. As a result, the likelihood of developing AAA decreases. On the other hand, the increased stiffness of the aortic wall may also explain the reduced sac shrinkage and the tendency toward more stable sac dimensions observed in diabetic patients after EVAR, relative to non-diabetic patients.

The rate of hyperlipidemia was greater among diabetic patients than in non-diabetic ones. In the Cox regression

analysis, hyperlipidemia was negatively associated with sac shrinkage, but the effect size remained small. Other initial differences in comorbidities—including hypertension, body mass index, cardiac history, and preoperative glucose levels—did not emerge as meaningful predictors of sac shrinkage when the entire study population was examined. In agreement with these results, a large-scale meta-analysis of patients treated with endovascular aneurysm repair similarly reported no link between various comorbidities such as hypertension, obesity, or coronary artery disease and postoperative sac shrinkage [1]. Interestingly, that same meta-analysis indicated a favorable effect of hypercholesterolemia on sac shrinkage, along with a tendency for statin use to support shrinkage. Consequently, the elevated prevalence of these conditions in the diabetes mellitus cohort does not appear to fully account for the diminished sac shrinkage observed in this group.

Metformin has been proposed as a potential modulator of AAA progression [9], prompting the launch of several randomized controlled trials (RCTs) to examine its influence in individuals with small aneurysms. In preclinical animal models, metformin treatment was associated with reduced AAA development and slower progression, along with better preservation of medial elastin and aortic SMCs, lower infiltration of inflammatory cells, and diminished neovascularization [10, 11]. While these actions may help slow aneurysm expansion, they might not necessarily favor post-EVAR sac shrinkage. At the one-year mark and at final follow-up, sac growth was lower, and the proportion of stable sacs was higher in diabetic patients receiving metformin than in those not receiving it. However, these observed differences did not reach statistical significance. Consistent with this, a recent investigation found that diabetic patients more often displayed stable sac behavior, while non-diabetic patients were more prone to sac regression one year after EVAR [27]. Furthermore, that study noted a reduced rupture risk after EVAR among diabetic individuals managed with non-insulin antidiabetic agents.

In the present study, endoleaks of any type became more frequent over time and were associated with poorer sac shrinkage at both 1 year and the latest follow-up. Moreover, Cox regression confirmed that endoleaks were significantly associated with decreased sac shrinkage. These observations align with findings from an earlier meta-analysis that associated endoleak occurrence with limited sac shrinkage following EVAR [1]. These results emphasize the need for ongoing, careful surveillance and appropriate interventions for endoleaks throughout the follow-up period.

Over a nine-year follow-up, we noted a marked decline in overall survival among diabetic patients—independent of metformin therapy—when compared with non-diabetic patients. This finding aligns with earlier research pairing diabetic and non-diabetic individuals with comparable age and comorbidity profiles [23], a recent extensive observational study spanning 8 years [27], and a meta-analysis encompassing 12 cohort studies involving 20,210 patients who underwent AAA repair [28]. In contrast, other reports found no effect of diabetes on overall mortality [21, 22]; notably, these studies had shorter follow-up periods, and in our own cohort, no survival difference emerged during the initial years after EVAR. Since reintervention-free survival and freedom from aneurysm-related death showed no disparity between the diabetic and non-diabetic groups, these results underline the value of stringent blood glucose control and comprehensive management of additional risk factors, including optimized cardiovascular protection, to enhance long-term survival in diabetic patients.

This investigation has several methodological constraints that should be recognized. First, aortic diameters were assessed using the available imaging techniques, either computed tomography angiography (CTA) or duplex ultrasound (DUS). Measurements obtained with DUS cannot be directly compared with those from CT scans. Nevertheless, the discrepancy in mean aortic diameter measurements among patients with aneurysms is typically less than 5 mm [29]. In accordance with the most recent guidelines, the initial postoperative scan performed 30 days after the procedure was a CTA, and lifelong imaging surveillance is advised for patients who have received EVAR [30]. At our center, DUS served as the primary imaging tool for extended follow-up. As a result, the same imaging modality was used for the majority of scans, beginning 1 year after the operation and continuing through the final follow-up.

In addition, this retrospective analysis relied on a manually maintained database, which carries the risk of data entry errors and incomplete records. The exact time from diabetes diagnosis to the start of metformin treatment before study enrollment remained unknown. These variables could have affected the observed outcomes and merit further investigation in subsequent studies.

Another important limitation concerns the marked imbalance in subgroup sample sizes, especially the relatively small diabetic subgroup that did not receive metformin. The lower number of patients available for analysis during extended follow-up periods affected the assumptions of normality and equal variance. Although non-parametric statistical tests were applied to mitigate this issue, the overall statistical power remained limited. Moreover, the wide variation in individual follow-up durations made time-to-event analysis up to the last follow-up more challenging; however, the length of follow-up did not differ significantly between the study groups. Furthermore, only a small proportion of diabetic patients in the cohort received metformin as monotherapy.

No meaningful differences in sac remodeling were detected between diabetic patients on metformin monotherapy and those not using metformin at either assessment point. Given the small size of the metformin monotherapy subgroup, the analysis focused on comparing diabetic patients on metformin with those not on it. The potential influence of other antidiabetic agents, such as sulfonylurea derivatives and insulin, cannot be ruled out. Nonetheless, when sulfonylurea use was examined as a predictor of sac shrinkage in Cox regression analysis, it did not show statistical significance.

In contrast, earlier observational studies have reported a significant association between metformin and reduced AAA growth [7, 8]. It would have been preferable to include HbA1c values rather than single glucose measurements to reflect long-term glycemic control better. Unfortunately, HbA1c data were accessible for only half of the study population. In addition, several baseline variables differed significantly between groups and influenced both sac remodeling and overall survival. Finally, the study covered a ten-year period, during which accumulating surgical experience may have gradually improved procedural outcomes.

Conclusion

This retrospective analysis demonstrated that diabetes mellitus and metformin use were associated with reduced sac shrinkage after EVAR. Diabetic patients exhibited significantly less sac shrinkage than non-diabetic patients at the one-year follow-up. At the same time point, however, there was a trend toward greater sac stability in the diabetic group. By the last follow-up, only diabetic patients receiving metformin showed lower rates of sac shrinkage than the non-diabetic group. Furthermore, endoleaks became more frequent over time in both non-diabetic and diabetic patients with AAA and were associated with reduced sac shrinkage at both evaluation points. These results highlight the need for diligent surveillance and effective management of endoleaks throughout the follow-up period. Overall survival was markedly lower in diabetic patients than in non-diabetic patients. Importantly, no significant differences were observed between the groups in reintervention-free survival or freedom from aneurysm-related mortality. Given the inconsistent findings in the existing literature, additional prospective, multicenter studies are required to define better the effects of diabetes and metformin on clinical outcomes following EVAR.

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The institute's opt-out registry was consulted to determine whether or not patients objected to participating in scientific research.

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