

Evolution of the upper and lower landing site after endovascular aortic aneurysm repair

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Background: The evolution and correlation between the aortic neck and distally located iliac necks after endovascular treatment of abdominal aortic aneurysms (AAAs) was studied.

Methods: Of 179 patients who had undergone AAA repair between 2003 and 2007, 61 received the same radiologic follow-up and were included in this retrospective study. Data for 61 aortic necks and 115 iliac arteries were analyzed using the preoperative scan, 1-month visit, and final follow-up, with a minimum mean follow-up of 24 ± 15.2 months. Three measurements were taken of the aortic neck: subrenal (D1a), 15 mm below the lowest renal artery (D1b), and at the origin of the aneurysm (D1c). Three measurements were taken at the level of the iliac arteries: origin (Da), middle (Db), and the iliac bifurcation (Dc). These measurements were analyzed using analysis of variance and Spearman correlation coefficient. The results were evaluated for subsequent endoleaks, migrations, and reinterventions. All diameters were compared between patients with a regression of $>10\%$ in the greatest diameter of AAA at last follow-up (group A, $n = 35$) and those without (group B, $n = 26$).

Results: All diameters (in mm) increased significantly over time at the level of the proximal neck (D1a = 3.7 ± 2.8 , $P = .018$; D1b = 4.4 ± 2.5 , $P = .016$; D1c = 4.3 ± 3.1 , $P = .036$) and iliac arteries (Da = 2.1 ± 0.2 , $P = .0006$; Db = 2.5 ± 0.5 , $P = .0006$; Dc = 3 ± 0.7 , $P = .007$). The increase in diameters at the proximal neck and iliac arteries evolved independently (insignificant correlation), with the exception of D1b and Dc ($P = .006$), which showed a weak correlation ($r = 0.363$). The group A patients presented increases in all diameters, although to a less significant extent ($P < .05$) than group B patients. During follow-up, a proximal endoleak and a distal endoleak occurred, both requiring reintervention.

Conclusions: Our results show a trend toward dilatation of the aortic neck and iliac arteries, with no correlation between the two levels, even in patients with a regression of the aneurysm sac during follow-up. Although this study found no correlation with the occurrence of endoleaks, our results suggest the need for a longer follow-up, especially on the landing sites. (J Vasc Surg 2012;55:24-32.)

The long-term results of endovascular treatment (EVAR) of abdominal aortic aneurysms (AAAs) for morbidity and mortality are well-known.^{1,2} However, certain complications are directly related to the presence of an endoprosthesis in the native arteries. One such complication is the dilatation of the aortic neck, which may be responsible for proximal leaks and even endoprosthesis migration, requiring reintervention. This dilatation may relate to the oversizing and radial force of the endoprosthesis, especially during the early months.³ Dilatation in the long-term may be due to the progression of artery wall degeneration.⁴

At the level of the distal iliac necks, there appears to be a dilatation, yet only a few studies have investigated the subject.⁵ We do not know, however, if the dilatations

develop in parallel (ie, affecting the proximal and distal necks in the same proportions) or if they have two distinct evolutions. In addition, we do not know whether the dilatation concerns only the anchor zone, based on which the endoprosthesis diameter was chosen, or if it encompasses the adjacent vascular segments covered by the endoprosthesis. The aim of our study was to examine the correlation between the diameter increases at the proximal and distal necks, while investigating the anchor zones and adjacent vascular segments as well as observing clinical events such as endoleaks.

METHODS

Of 179 patients having undergone AAA repair using EVAR in our clinic between 2003 and 2007, 61 (57 men, four women) with the same follow-up protocol and scan analysis undertaken in the radiology department of our center were included in this retrospective study. Patients had a mean \pm standard deviation follow-up of 39 ± 15.2 months (range, 24-84 months; median, 36 months). AAA repair was considered provided that the maximum aneurysmal diameter >50 mm, the patient suffered from pain, or the annual growth was >10 mm. During the study period, endovascular treatment was considered whenever the patient was not eligible for open surgery in accordance with the criteria⁶ of the French National Agency of Health Accreditation and Evaluation. The analysis excluded patients who had un-

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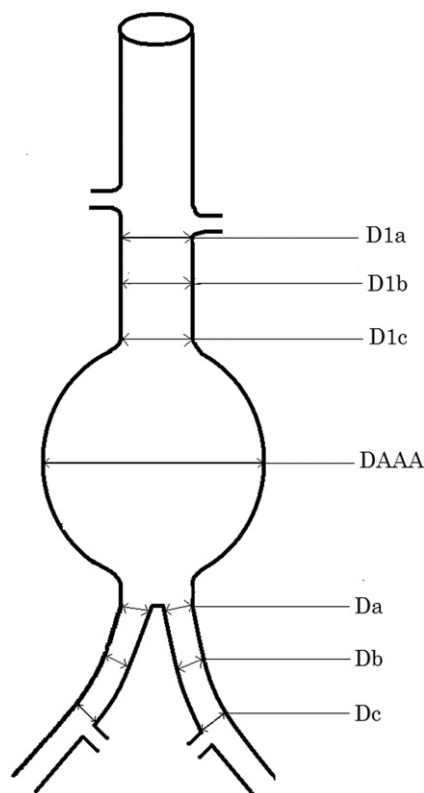


Fig 1. Aortoiliac measurements. DAAA, Greatest diameter of the abdominal aortic aneurysm.

dergone emergency surgery, those who had isolated iliac aneurysm, or those with branched or fenestrated endoprostheses.

Preoperative medical imaging. All patients were evaluated using spiral computed tomography angiography (CTA) before EVAR. All imaging examinations were performed on a multislice LightSpeed16 CT scanner (General Electric Medical Systems, Milwaukee, Wisc). Parameters for the acquisitions were 1.25-mm slice thickness, 120 kVp, and 215 to 360 mA tube current. Imaging was initiated after administering 120 mL of low-osmolar iodinated contrast agent (Hexabrix; Guerbet LLC, Bloomington, Ind), with an iodine concentration of 320 mg/mL. Soft tissue window settings with a width of 400 HU and a center of 40 HU were applied.

At the aortic neck, diameters were measured at the subrenal aorta (D1a), 15 mm below the lowest renal artery (D1b), the origin of the aneurysm (D1c), as well as the greatest diameter of the AAA (Fig 1). At the iliac artery level, the diameters were taken at the origin (Da), middle (Db), and bifurcation (Dc). When the end of the endograft did not correspond with the iliac bifurcation, a landmark was positioned and then recorded on the preoperative CT to ensure that the diameter Dc would be measured at exactly the same position.

Intervention. The diameters of the implanted prosthesis conformed to the manufacturers' instructions, with

$16\% \pm 9\%$ oversizing at the aortic neck and $8\% \pm 7\%$ at the iliac arteries. An aortobiliac endoprosthesis was implanted in 54 patients when the diameter of the aortic bifurcation permitted; in the remaining seven patients, an aortouniliac device with a femorofemoral crossover bypass was used. The proximal extremity of the endoprosthesis was implanted close to the renal arteries, and its distal extremity as close to the iliac bifurcation as possible. Different endoprostheses were used: 31 (51%) Talent Medtronic (World Medical/Medtronic, Sunrise, Fla), 23 (38%) Zenith Cook (William Cook Europe, Bjaeverskov, Denmark), six (10%) Excluder (W. L. Gore and Associates, Flagstaff, Ariz), and one (1%) Anaconda (Sulzer-Vascutek, Edinburgh, United Kingdom).

Follow-up. This study analyzed the CT scans taken before the intervention, at 1 month, and at the last follow-up. The control scans followed the same procedure as the preoperative scans, but in addition to the acquisition at the arterial phase, another at 60 seconds was obtained to visualize late-phase, low-flow endoleaks. For the control scans, all preoperative diameters were taken again, and where applicable, endoleaks noted and migration length measured. The study analyzed 61 proximal necks and 115 iliac arteries.

CT analysis. All preoperative and postoperative imaging was analyzed using the dedicated program, Endosize (Therenva, Rennes, France), which had previously been validated by our department (Fig 2).⁷ All diameters were measured perpendicularly to the central line, from adventitia to adventitia, by the same person.

Statistical analysis. Statistical analysis was performed with SAS 9.2 software (SAS Institute, Cary, NC). Data are presented as means \pm standard deviation for quantitative variables, unless otherwise noted, and as numbers with corresponding percentages for qualitative variables. Evolution with time of mean aortoiliac measures was analyzed by use of a one-way analysis of variance (ANOVA) with the measurements from the preoperative CT scan taken as baseline values. Separate analyses according to the type of endoprostheses were also performed. Correlations between growths of different aortic and iliac measurements, and between growth of aortic neck and baseline characteristics, were calculated by use of the Spearman correlation coefficient. Subgroup analyses were performed between patients with aortic aneurysm regression $>10\%$ (group A) and those without (group B). Comparisons of the evolution with time of mean aortoiliac measures between the two subgroups were performed by use of a two-way (time, group) ANOVA. For each of the endoprostheses, the evolution of each diameter was analyzed using the Kruskal-Wallis and the Mann-Whitney test. The cumulative proportion of patients with a proximal neck evolution $>20\%$ was assessed by means of a Kaplan-Meier analysis. For all analyses, a value of $P < .05$ was considered to be significant.

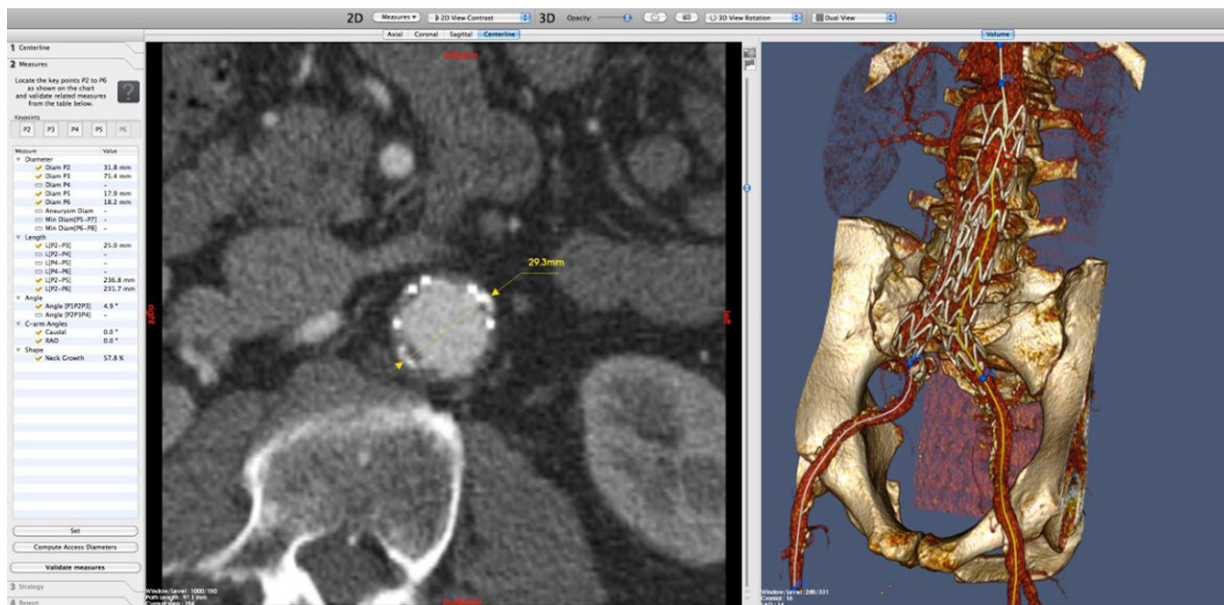


Fig 2. Computed tomography angiography analysis using the Endosize software. Outer-to-outer diameters were measured perpendicularly to the centerline.

Table I. Demographic and clinical characteristics of the patients

Variables*	Mean ± SD or No. (%)
Patient total	61 (100)
Age, years	74.6 ± 8.3
Obesity (BMI > 30 kg/m ²)	8 (13.1)
Coronary artery lesions	26 (42.6)
Coronary artery bypass graft	10 (16.4)
Aortic valve replacement	3 (4.9)
Critical limb ischemia	2 (3.3)
Severe respiratory insufficiency	2 (3.3)
End-stage renal failure	1 (1.6)
Poorly controlled	
Dyslipidemia	13 (21.3)
Arterial hypertension	5 (8.2)
Active smoker	8 (13.1)
Diabetes	5 (8.2)

BMI, Body mass index; SD, standard deviation.

RESULTS

Demographics. The general characteristics of the patients included in the study are reported in Table I. The main risk factor in our patients was the coronary risk.

Type I endoleaks and secondary interventions. One patient (1.6%) with a distal endoleak was treated using iliac extension because he had presented with a 5-mm progression of the anchor zone with a secondary retraction at the bifurcation level, with a commune iliac artery measuring 16 mm before the intervention without associated iliac aneurysm. Another patient (1.6%) with a proximal endoleak was treated using an aortic cuff because he had presented with a 10-mm migration (of the Talent endoprosthesis) with a

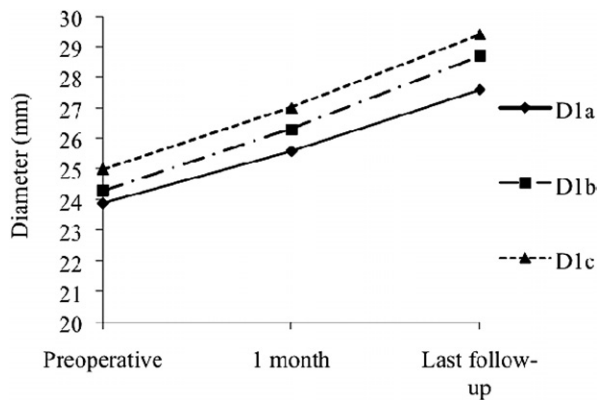


Fig 3. Evolution of diameters of the proximal aortic neck.

moderate neck dilatation (3 mm) but aneurysmal growth of 5 mm.

Aortic neck. The three diameters taken at the proximal neck increased over time (Fig 3; Table II), with a mean increase (in mm) of 3.7 ± 2.8 for D1a, 4.4 ± 2.5 for D1b, and 4.4 ± 3.1 for D1c. This increase was homogeneous across the three levels because there was a significant correlation between D1a and D1b (P = .001) D1a and D1c (P < .0001), and D1b and D1c (P < .0001; Fig 4). The increase in the proximal neck appeared to be more marked at the level closest to the aneurysm than at the level of the renal arteries (Table II).

When 1 month after the implant, a CT scan was taken as a reference, and the observed dilatation of the aortic neck was also significant: D1a increased by 8.0% ± 7.8% (P < .0001), D1b by 10% ± 8.7% (P < .0001), and D1c by 10% ±

Table II. Aortic measures^a

Levels	No.	Diameters				P
		Preoperative	1 month	Last follow-up	Growth	
D1a	61	23.9 ± 3.3 (17 to 26)	25.6 ± 4 (19 to 43)	27.6 ± 4.6 (20 to 48)	3.7 ± 2.8 (-2 to 12)	.018
D1b	56	24.3 ± 3.9 (18 to 38)	26.3 ± 4.1 (20 to 43)	28.7 ± 4.3 (22 to 44)	4.4 ± 2.5 (-1 to 12)	.0156
D1c	61	25 ± 4 (18 to 35)	27 ± 4.4 (20 to 46)	29.4 ± 4.3 (21 to 41)	4.4 ± 3.1 (-3 to 12)	.0358
Da	115	16.4 ± 3.6 (11 to 30)	18 ± 4 (13 to 39)	18.5 ± 3.3 (11 to 33)	2.1 ± 0.2 (2 to 3)	.0006
Db	115	16.9 ± 5.2 (11 to 48)	18.8 ± 5 (12 to 51)	19.4 ± 4.8 (10 to 53)	2.5 ± 0.5 (1 to 3)	.0005
Dc	115	16.2 ± 4.2 (9 to 48)	18.5 ± 4.6 (12 to 53)	19.2 ± 3.6 (11 to 32)	3 ± 0.7 (1 to 4)	.0007
DAAA	61	55 ± 7.7 (42 to 83)	54.5 ± 7 (40 to 74)	49 ± 12.6 (20 to 83)	-6 ± 11 (-34 to 14)	

DAAA, Greatest abdominal aortic aneurysm diameter.

^aData are presented as mean ± standard deviation (range) and P values were derived from analysis of variance.

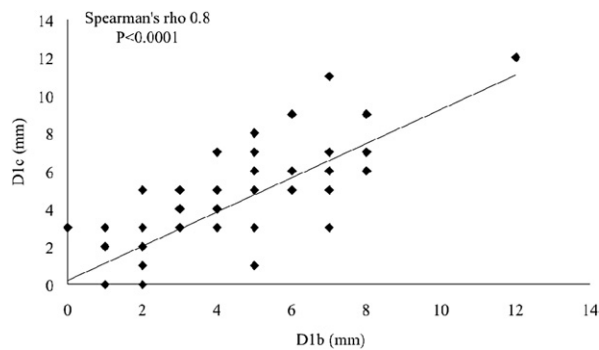


Fig 4. Correlation between growth of D1b and D1c (aortic neck).

8.9% ($P < .0001$). The percentage of patients with an increase in aortic neck diameter $>20\%$ was 11.5% for D1a, 13.1% for D1b, and 14.8% for D1c (Fig 5). No baseline risk factor was correlated with an aortic neck evolution $>20\%$.

Iliac arteries. The three iliac artery diameters significantly increased over time (Fig 6; Table II), with a mean increase (in mm) of 2.1 ± 0.2 for Da, 2.5 ± 0.5 for Db, and 3 ± 0.7 for Dc. Similarly, the dilatation homogeneously affected the iliac artery, because significant correlations were found between Da and Db ($P < .0001$; Fig 7), Da and Dc ($P = .004$), and Db and Dc ($P = .001$). The increase at the level of the iliac arteries was distally more marked than at its origin (Table II). When the first month postimplant CT scan was taken as a reference, the observed dilatation of the iliac artery was still significant for all diameters: Da increased by $6\% \pm 10\%$ ($P < .0001$), Db by $8\% \pm 11\%$ ($P < .0001$), and Dc by $12\% \pm 13\%$ ($P < .0001$). The percentage of patients with an increase in iliac artery diameter $>20\%$ was 11.4% for D1a, 17.2% for D1b, and 19.0% for D1c.

Correlation between aortic neck and iliac arteries.

The increase in the three measurements at the proximal neck was compared with that observed at the iliac artery level (Fig 8, Table III). No significant correlation was found between the diameter increase at the proximal level and that at the iliac artery level, with the exception of D1b and Dc ($P = .006$), which showed a weak correlation ($r = .363$).

Correlation between neck dilatation and baseline characteristics. Only D1a and Dc diameters, on which the choice of endoprosthesis diameter was based, were correlated with the oversizing. A significant but weak correlation was observed between the progression of D1a and the oversizing ($r = 0.296$; $P = .023$) and between the evolution of Dc and the oversizing ($r = 0.279$; $P = .004$). No correlation was found between the evolution of D1a and the preoperative neck diameter ($P = .242$) or the preoperative AAA sac size ($P = .71$).

Subgroups analysis. In group A ($n = 35$), a significant increase ($P < .001$) in all diameters was observed over time at the proximal neck and iliac artery necks (Figs 9 and 10), which was also the case for group B ($n = 26$; $P < .001$). When the two groups were compared, the increase was statistically more marked in group B for all diameters, with the exception of the iliac bifurcation diameter. Separate analysis of each type of endoprosthesis showed a significant difference at the aortic neck (Fig 11) for the three diameters (D1a, $P = .023$; D1b, $P = .021$; and D1c, $P = .004$). Although no difference was noted between the Talent and Zenith devices ($P = .164$), there was a moderate difference between the Talent and Excluder devices ($P = .022$) and between the Zenith and Excluder devices ($P = .042$). At the iliac artery, no difference was noted between the endoprostheses (Da, $P = .15$; Db, $P = .917$; Dc, $P = .319$).

DISCUSSION

Currently, scarce data are available for the long-term progression of distal necks after EVAR, whereas proximal necks have been extensively investigated in a number of studies.^{3,4,8,9} Most studies conducted to date used different methodologies, however, and differing results were observed. Badran et al⁴ took the measurements 7.5 mm below the lowest renal artery using axial slices; therefore, in cases of iliac tortuosity, the diameter measured from the image was smaller. We believe that this measuring method is not accurate because of an obvious parallax error that cannot just be corrected by taking into account the smallest diameter. For this reason, we measured all diameters perpendicular to the central line, which is a reproducible¹⁰ and well-accepted method. In the study of Badran et al,⁴ neck

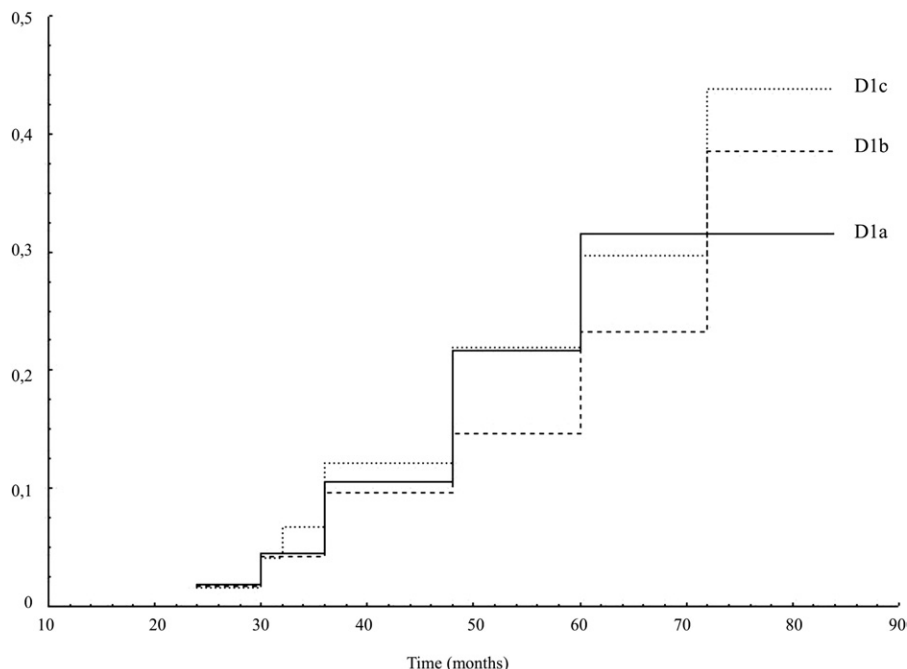


Fig 5. Cumulative proportion of patients with a proximal neck evolution >20%.

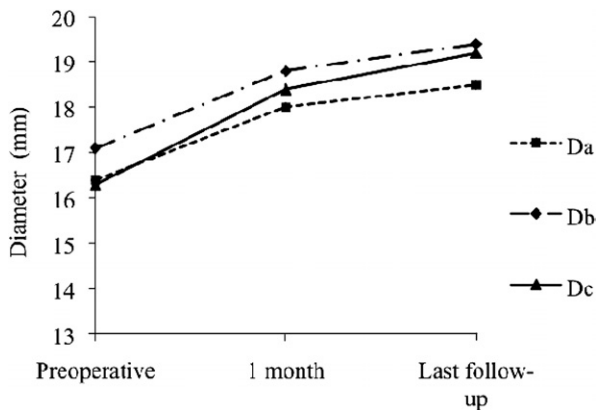


Fig 6. Evolution of distal landing site diameters.

dilatation during the first 2 years of follow-up was possibly linked to oversizing, after which, in their opinion, further progression of parietal wall degeneration may come into play.

Napoli et al⁸ found no correlation between the suprarenal and infrarenal necks but showed that neck dilatation affected only 33% of the patients after EVAR. In contrast to this, our results indicate that dilatation affects all patients, which is in line with the observation of Monahan et al.¹¹ Soberon et al³ considered that dilatation due to oversizing occurred mainly at 6 months. Cao et al¹² identified the following factors predictive of neck dilatation: presence of circumferential thrombus, preoperative neck diameter, and maximal AAA diameter. With respect to this last parameter,

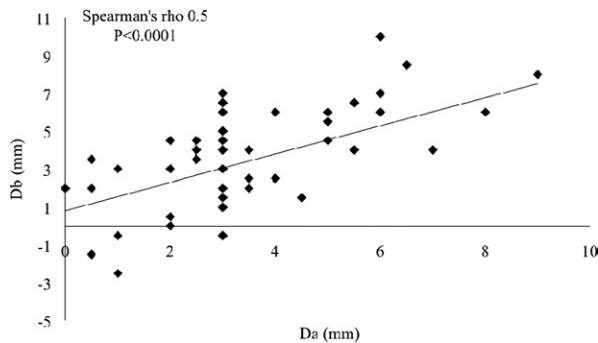


Fig 7. Correlation between growth of Da and Db (iliac arteries).

the study by Dillavou et al⁹ showed that the dilatation of the neck was just as marked as the preoperative diameter was small (cutoff of 25 mm).

In our study, the dilatation of the proximal neck seemed to homogeneously affect the entire area rather than just the zone immediately below the renal arteries. This is, in theory, the reference diameter used to calculate the implemented prosthesis, and thus oversizing. Thus, the progression of diameters D1b and D1c cannot be accounted for by oversizing. The heterogeneity of the nature of various aneurysm neck dilatation (AND) studies has been widely highlighted by Diehm et al,¹³ who explain the origin of the highly variable results reported for AND.

To harmonize the clinical and morphologic outcomes after EVAR, the Society for Vascular Surgery and the International Society for Vascular Surgery have published

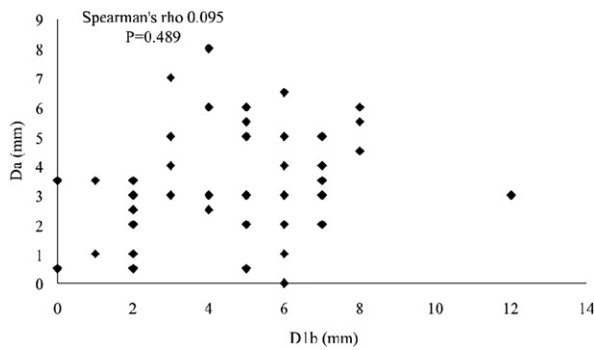


Fig 8. Correlation between growth of D1b and Da.

Table III. Correlation between proximal aortic neck growth and iliac growth

Diameters	D1a	D1b	D1c
Da			
<i>r</i>	0.086	0.095	0.221
<i>P</i>	.515	.489	.09
Db			
<i>r</i>	0.051	0.231	0.237
<i>P</i>	.699	.09	.068
Dc			
<i>r</i>	0.213	0.363	0.214
<i>P</i>	.102	.006	.101

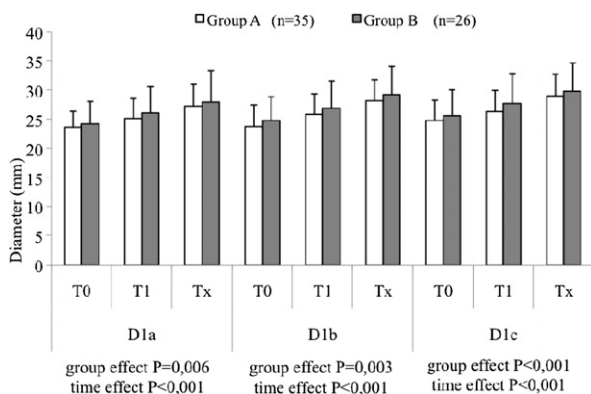


Fig 9. Proximal neck data at each time point (*T0*, preoperative; *T1*, 1 month; *Tx*, last follow-up) for group A and group B. The *P* value for the variables “group” and “time” is derived from two-way analysis of variance. Mean data are presented with the standard deviation (*error bars*).

reporting standards¹⁴ that recommend using the first set of postoperative images. We thus compared the first and last CT scan measurements, in addition to the ANOVA analysis. The dilatation of the necks was significant in both cases. To characterize AND, assessment of the full proximal landing zone is necessary.¹³ Using the AAA neck volumetry for the assessment of AND is therefore recommended.¹⁵

Although the Endosize software has not been designed to perform volumetric analyses of AAA, its algorithm could

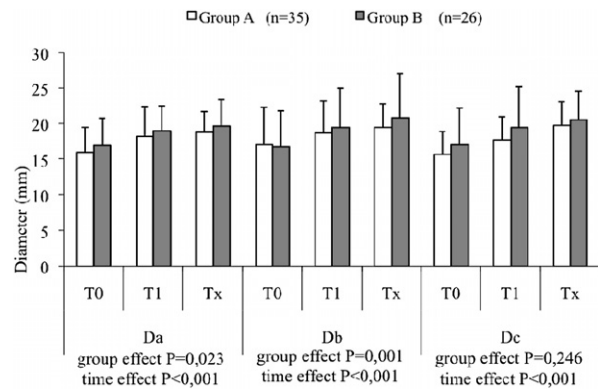


Fig 10. Iliac arteries at each time point (*T0*, preoperative; *T1*, 1 month; *Tx*, last follow-up) for group A and group B. The *P* value for the variables “group” and “time” is derived from two-way analysis of variance. Mean data are presented with the standard deviation (*error bars*).

be used for this purpose. We thus measured three different diameters along the full proximal neck and the iliac artery. These diameters increased significantly over time, the increase being more marked in the proximal zones of the aneurysm, as shown in Fig 5. From a physiologic point of view, this kind of progression may point to a gradual extension of the aneurysmal disease. This hypothesis was partially demonstrated by Diehm et al,¹⁶ by means of a histologic and biochemical analysis. They determined in “seemingly nondiseased infrarenal AAA neck” a number of histologic signs of destruction and biochemical disorders, which could explain the appearance of AND. This explanation would also apply to patients presenting an aneurysm growth over time.

Nevertheless, the results of subgroup analyses showed dilatation of the proximal neck also affected patients exhibiting aneurysmal regressions. Therefore, although the difference between both groups was significant, more relevant was that in patients with aneurysm retraction on imaging, neck dilatation could still be evidenced at all levels, suggesting that EVAR settles the mechanical¹⁷ but not the biologic aspects of AAA. Our series did not have enough patients with proximal endoleaks to draw any conclusions about a potential correlation between both parameters, especially because migrations may also lead to endoleaks, independently from the dilatation of the proximal neck, as shown in our own series. In line with this observation, Monahan et al¹¹ concluded that the dilatation of the proximal neck was not correlated to type I endoleaks or migrations.

Scientific literature on distal necks is rather scarce. For conventional AAA surgery, the question has already been raised about whether associated ectatic iliac arteries should be treated simultaneously. In their retrospective study, Sala et al¹⁸ proposed to treat routinely all patients with ectatic common iliac arteries >18 mm and a life expectancy of at least 7 to 8 years. Several studies investigating EVAR treatment have attempted to demonstrate that patients with

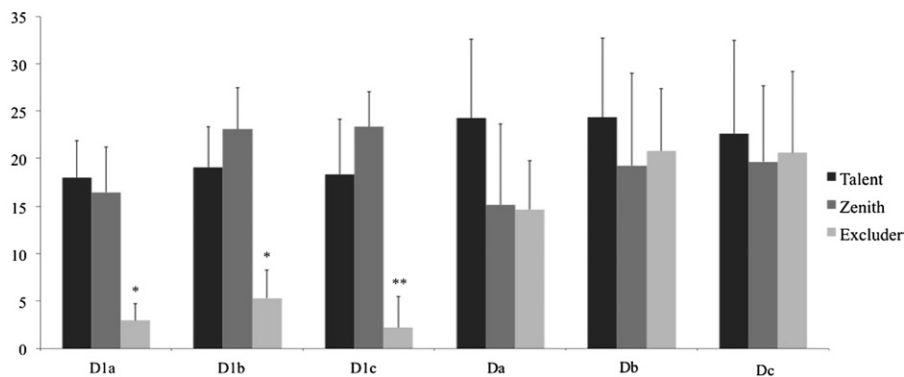


Fig 11. Evolution (percentage) of diameters with respect to each endoprosthesis used. Mean data are presented with the standard deviation (*error bars*). * $P < .05$. ** $P < .005$.

ectatic iliac arteries at the distal anchor zone could be treated efficiently without further postoperative complications by using the bell bottom¹⁹ or standard endoprosthesis,²⁰ without loss of the hypogastric artery.²¹ However, Mc Donnell et al²² found a 7% rate of distal endoleaks in patients with iliac arteries >16 mm in their medium-term follow-up.

Only a few articles have reported exclusively the evolution of normal and pathologic iliac arteries over time. Falkensammer et al⁵ showed that dilatation of the distal anchor zone, although present in all patients, was more marked in patients with concomitant iliac aneurysm, but was not associated with an increased rate of endoleaks or reinterventions,^{23,24} which contradicts the findings of other studies.^{25,26} In addition, Adiseshiah et al²⁷ highlighted that long-term follow-up of these areas was critical, because aneurysmal evolution was more likely to occur later in time in distal necks than in proximal necks.

Our study yielded similar results, showing a significant increase over time in iliac artery measurements at the three levels. Similarly to the proximal neck, all iliac artery diameters appear to progress in patients presenting aneurysmal regression. This trend, however, has to be put into perspective, because even if the analysis revealed a statistically significant progression, a clinical correlation could not be established due to the insufficient number of distal endoleaks. It may be assumed that the parietal degeneration process of the proximal neck is likely to extend to the iliac arteries progressively. However, the correlation analysis revealed that diameter progressions of the distal and proximal necks were an independent phenomenon and that the increase at the level of the iliac arteries was distally more marked than at its origin.

A tentative explanation of these findings is based on alterations in parietal hemodynamic constraints due to the endoprosthesis. In fact, the increase in pressure was more marked at the level of the iliac bifurcation than at the proximal neck,^{28,29} and this difference was more pronounced when the vessels were long and tortuous.³⁰ Likewise, wall shear stress was shown to be more relevant at areas of overlap,²⁸ as well as in the kinking zones of the

endoprosthesis. It seems likely that the presence of the endoprosthesis, in addition to decreasing pressure in the aneurysmal sac, also alters the constraints at the level of the iliac arteries with a more significant stress and pressure compared with the preoperative period. However, this hemodynamic modification alone is not sufficient to explain the results we observed with respect to iliac artery dilatation.

The evolution with each endoprosthesis appears to be similar in our study. There was a difference at the aortic neck only with the Excluder device, suggesting that AND is related to suprarenal or infrarenal fixation.³¹ Nevertheless, the number of patients treated with the Excluder device in our study was too small to draw any conclusions on the effects of suprarenal or infrarenal fixation. No difference was found between the Talent and Zenith devices, and in both cases, there was a dilatation at the aortic neck, in agreement with the findings of Badger et al.³²

Overall, our results show a trend toward a neck dilatation incidence rate that is greater than that observed by other authors. The observed differences in the accuracy of the measurements, which are only slightly greater, sometimes by only 1 or 2 mm compared with the aortic diameters (range, 10–30 mm), are sufficient to affect the results of a statistical test. Although we used three-dimensional reconstructions derived from spiral CT images, intraobserver or interobserver variabilities could lead to difficulties, especially with measurements requiring an accuracy of 1 mm.

Because most of the studies investigating AND or iliac evolution do not use software with an automated centerline extraction, we expected that this type of variability would be reduced by using the Endosize software. To reduce the measurement errors related to image quality, we included only those patients for whom high-quality images had been recorded in our hospital. This was important, because the same acquisition parameters, in particular the slice thickness, are not always used in other institutions. Moreover, Wever et al³³ also showed that the proximal neck demonstrates continued dilatation during follow-up for all patients, with a median increase of 15.5% (cross-sectional area) at 12 months.

CONCLUSIONS

Our study was directly focused on the final status of necks without taking into account intermediary scans, except for the immediate postoperative scan. Our aim was not to investigate the kinetics of progression but rather the potential correlations between the progressions in the different anchor zones of the endoprosthesis. Despite the retrospective nature of the study design, this trend toward dilatation, which was even observed in successfully treated patients, is a new finding that must be taken into account because it raises the question about the modifications of native arteries caused by the endoprosthesis itself. Presently, not enough time has passed and too few clinical events have occurred to allow us to understand whether there is an implication on the occurrence of distal endoleaks and aneurysms on the landing zones. This highlights the need for a sufficiently long follow-up for recovered patients (young patients). To confirm these results, further long-term studies are needed in this patient population.

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AUTHOR CONTRIBUTIONS

Conception and design: AK, AC, AL
Analysis and interpretation: AK, AC, BL, JH, GP
Data collection: AK, GP, JH
Writing the article: AK, AC, BL
Critical revision of the article: AK, AC, BL, AL
Final approval of the article: AC
Statistical analysis: AK, BL
Obtained funding: Not applicable
Overall responsibility: AC

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