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Arterio Venous Access Placement and renal function decline

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ABSTRACT

Background: There is controversial evidence on whether arteriovenous access (AVA) placement may protect renal function and hence should be considered in the timing of access placement. This study aimed to investigate the association between AVA placement and eGFR decline as compared to placement of a peritoneal dialysis catheter (PDC) at a similar time point.

Method: We studied a cohort of 744 predialysis patients in Stockholm, Sweden, who underwent surgery for AVA or PDC between 2006 and 2012. Data on comorbidity, medication and laboratory measures was collected 100 days before and after surgery. Patients were followed until dialysis start, death or 100 days, whichever came first. The primary outcome was difference in eGFR decline after AVA surgery compared to PDC. Decline in eGFR was estimated through linear mixed models with random intercept and slope, before and after surgery.

Results: There were 435 AVA and 309 PDC patients. The AVA patients had higher eGFR (8.1 vs 7.0 ml/min/1.73m^2) and less rapid eGFR decline before surgery (-5.6 compared to -6.7 ml/min/1.73m2/year for PDC). We found no difference in eGFR decline after surgery in AVA patients compared with PDC patients (AVA progressed -1.14 (-2.38; 0.10) ml/min/1.73m^2/year faster after surgery compared to PDC).

Conclusion: There was no significant difference in eGFR decline after placement of an AVA compared to a PDC. Both forms of access were associated to reduced eGFR decline in our population. The need for dialysis remains the main determinant for timing of access surgery.

INTRODUCTION

A central question in clinical nephrology is when to create dialysis access. Timely preparation of an arteriovenous access (AVA) improves patient survival and facilitates hemodialysis initiation.[1] Planning of an AVA is part of the multidisciplinary predialysis care associated with improved clinical outcomes such as less acute dialysis, cardiovascular events and infections.[2] The timing of the AVA placement is challenging, especially in the elderly patient where delayed access maturation can occur. Late AVA placement increases the risk of dialysis start with a central venous catheter (CVC), which is associated with both infections and inferior survival.[3] On the other hand, if the AVA is created very early, there is a higher probability it will never be used.[4] It has been proposed that AVA surgery should take place when eGFR decreases to 15-20 ml/min/1.73m^2.[5] According to guidelines a fistula should be placed at least 6 months before the anticipated start of dialysis.[6] With time, the individual eGFR slope has gained increasing importance over the actual eGFR in the decision of when planning for AVA surgery.[7]

During recent years it has also been discussed whether the placement of an AVA itself could be seen as an intervention which has a possibility to attenuate chronic kidney disease (CKD) progression.[8] This has been supported by several studies suggesting that AVA placement is associated with reduced eGFR decline.[9-11] The physiological reasons for these observations were suggested to be related to cardiovascular and microcirculatory changes.[12,13] However, these previous studies had questionable control groups; one study did not have a control group at all and another used patients who received a CVC. [9,10] Although CVC- patients represent a different patient category with more acute illnesses, late referrals and less predialytic multidisciplinary care, all factors associated with an increased mortality and risk of end-stage renal disease.[14,15]

In this study we investigated whether the creation of an AVA is associated with slower eGFR progression in a contemporary cohort of nephrology-referred patients planned for hemodialysis and compared that to the eGFR decline of patients who received a peritoneal dialysis catheter (PDC). We hypothesized that any specific vascular or hemodynamic alterations occurring after the access surgery would only be present among AVA patients, while both groups benefitted from the advantages of a multidisciplinary follow-up during the pre-dialysis period.

MATERIALS AND METHODS

Study population

Data were obtained from the Swedish Renal Registry (SRR) and the Stockholm CREAtinine Measurements (SCREAM) database to identify residents of Stockholm followed by nephrology out-patient healthcare. These two cohorts have been described in more detail previously.[16,17] In short, SCREAM is a healthcare utilization database of the Stockholm population with linkages to other healthcare sources and SRR is the national renal registry with information on out-patient renal care, start of dialysis and transplantation. In this study we included patients (≥18 years) who were not on dialysis, with a hospital code for dialysis access surgery between March 1, 2006 and September 30, 2012, (for definitions see **Supplement**). We excluded patients who started dialysis on the same day as the surgery as they were judged to be unplanned starts.

Access surgery and study variables

The first date of any primary surgery for a dialysis access within the time period was considered the "index date". We divided the patients into three groups based on the type of

access surgery; CVC, PDC and AVA (either an arteriovenous fistula or graft). Any patient with a code for both CVC and PDC or CVC and AVA on the same date was placed in the CVC group since they were not regarded as planned starts. Information on diabetes and cardiovascular disease on or before the index date was obtained through linkage with hospitalization codes, primary and secondary health care records. Ongoing medication was ascertained by the National Registry for Dispensed drugs which mandatorily register all dispensed prescriptions in Swedish pharmacies.[18] A prescription for an angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), beta-blocker or erythropoiesis stimulating agents (ESA) with on-going dispensations before the index date was considered as being treated. The ICD and ATC codes we used to define comorbidity and medication can be found in the **Supplement**. Clinical variables (primary renal disease, body mass index, (BMI) and systolic blood pressure) were ascertained from the SRR. Furthermore, we extracted information from SCREAM on additional laboratory measures of interest (haemoglobin, potassium, albumin, proteinuria (both dipstick and urinary albumin/creatinine ratio), phosphate, and calcium) during the study period.

Decline in glomerular filtration rate

All serum creatinine values from both in-hospital and out-hospital care were standardized to isotope dilution mass spectrometry standards. Glomerular filtration rate (eGFR) was estimated by the CKD-EPI equation, assuming everyone was white.[19] We hypothesized that the eGFR trajectory immediately prior to surgery was most likely associated with the timing of access placement. Therefore, for our main analysis, we excluded measurements >100 days before the index date. The eGFR closest to the index date was recorded as the eGFR at surgery. After the index date, patients were followed until start of dialysis, death or 100 days post-surgery, whichever came first.

Statistical analysis

The study variables were compared between patients receiving an AVA or a PDC by non-parametric statistics. Mean eGFR over time was visualized graphically using smoothing techniques (**Figure S2**). Our main outcome, eGFR decline (ml/min/1.73m^2 per year), was estimated by linear mixed models with random intercept and slope before and after access surgery. To deal with a slightly skewed distribution of slopes in the PDC group, we studied the difference in progression rate after surgery in a quantile regression model with eGFR slope as the dependent variable, excluding those who first received a CVC. In the main analyses we applied an intention- to- treat approach categorizing the patients into the treatment group they first received. Values were missing in fewer than 10 individuals, except for systolic blood pressure (n=190, 25%), primary renal disease (n=189, 25%), body mass index (n=219, 29%) and albuminuria (n=132, 18%). Missing variables were handled through multiple imputation (chained equations, n=20). The imputation model included the treatment variables, confounders, the outcome and time of follow-up. In the final model we included variables *a priori* considered important for treatment decisions or outcomes, as well as those significantly associated (<0.25) with either treatment or outcome. Model 1 included eGFR slope before surgery and last eGFR prior to surgery. Model 2 additionally adjusted for age (<50, 50-65, 65-75, >75 years), sex, primary renal disease and BMI. Model 3 included the variables from Model 2 + beta blockers, erythropoiesis stimulating agents, plasma albumin and albuminuria. We also computed the odds ratios of a 30% slower decline in eGFR/year after surgery in a logistic regression model adjusting for the same variables as in the regression models. Finally, we performed a propensity-matched analysis investigating the slope difference before and after surgery. To determine the propensity score (restricted only to those with overlapping propensity scores) we used a logistic regression model with AVA as the dependent variable and age, sex, eGFR at surgery, diabetes, cardiovascular disease, and

treatment with ACEi/ ARB as explanatory variables. The command p-score in Stata 12 was used to estimate the propensity scores in blocks, checking that the mean propensity scores were not different for AVA and PDC in each block. The coefficients associated with the variables used to create the propensity scores are presented in **Table S1**. The balancing properties were found to be satisfactory (**Table S2**, **Figure S1**) and we proceeded with the matching procedure using both kernel matching and radius matching (caliper 0.01). Standard errors and 95% confidence interval were obtained through bootstrapping. We performed several sensitivity analyses using different model specifications (full follow-up time, mixed effects models for the eGFR slope post-surgery, and expanding the variables for the propensity score model). We also restricted the analysis by excluding those with poor AVA maturation who received a CVC before dialysis initiation. All analyses were performed in Stata 15 (StataCorp).

RESULTS

We identified 435 non-dialysis patients with an AVA placement and 309 with a PDC as their first dialysis access surgery during the study period. 53 patients received a CVC. The AVA patients were slightly older (64.5 versus 62.6 years), and more often men (63.5% versus 62.5%) (**Table 1**). Compared with PDC patients, those who received an AVA more often had cardiovascular disease and diabetes. At the time of surgery, AVA patients had a lower frequency of erythropoietin stimulating agents and angiotensin converting enzyme inhibitor/ angiotensin receptor blocker use. Laboratory values (plasma albumin, haemoglobin, phosphate, calcium and albuminuria) were similar in PDC as compared with AVA patients. Patients who received a CVC as the first dialysis access were generally older, had more

comorbid diseases, more laboratory abnormalities and were more often men, than those who received an AVA.

Decline in eGFR before and eGFR at surgery

The eGFR at the time of surgery was higher in patients who received an AVA (8.1 [AVA] versus 7.0 [PDC] ml/min/1.73m^2). AVA patients had a less rapid decline before surgery (-5.6 [AVA] compared with -6.7 [PDC] ml/min/1.73m^2/year). Patients who received a CVC had the highest decline in eGFR before surgery and lowest eGFR at the time of surgery (**Table 1**). The follow-up period before surgery was similar in AVA and PDC patients while the follow-up after surgery was slightly longer in AVA patients (**Table 1**). The median number of eGFR measurements after surgery was 5 (interquartile range 4-8), while the median number of measurements before surgery was 6.5.

Decline in eGFR after surgery

Both AVA and PDC patients had slower decline in eGFR after surgery compared with before (median slope difference in eGFR decline 5.3 ml/min/1.73m^2) (Figure 1). Only 166 (22%) patients had a more rapid decline in eGFR after access surgery, most of those receiving an AVA. The median unadjusted decline in eGFR after access surgery was somewhat slower in AVA patients (-1.61 ml/min/1.73m^2 per year) compared with PDC patients (-2.17 ml/min/1.73m^2 per year) (**Table 2**). However, in the fully adjusted model the PDC patients progressed 0.26 ml/min/1.73m slower (95% confidence interval -0.88; 0.35, p=0.40) than the AVA patients. The secondary analyses investigating the probability of a 30% slower decline (**Table S3**) and difference in slope before and after surgery using propensity score matching (**Table 3**) did not demonstrate any significant difference in eGFR decline between the two groups. If anything, the PDC patients progressed slightly slower after access surgery.

Sub analyses and sensitivity analyses

Stratifying the analysis on the eGFR at the time of surgery did not influence the direction or the magnitude of the results (**Table S3**). In those with the most preserved renal function (eGFR >15 ml/min/1.73m^2) the progression rate was higher in AVA patients compared with PDC patients. However, the confidence intervals were wide due to the low number of individuals. Using other model specifications or other regression models did not change the results substantially (**Table S3**). In our main analysis the median time to dialysis start was 59 days and 154 days for PDC and AVA patients respectively. The total number of patients who received an access, but never started dialysis during the entire follow-up (median follow-up 0.5 years (IQR 0.15-1.5 years), was 250 (33.6%), AVA 170 (39%) and PD 80 (26%)). At the end of the follow-up the patients who had not started dialysis had a median eGFR of 8.3ml/min/ 1.73m² (IQR 5.6-12.6) (AVA) and 9.8ml/min/ 1.73m² (IQR 6.4-31.3) (PD). In those who never started dialysis, the decline in eGFR was slower after access surgery in those who received a PDC compared with AVA patients.

DISCUSSION

In this study of nephrologist-referred patients under pre-dialysis care, we found that the eGFR decline was faster before than after the placement of a dialysis access. There was, however, no difference in eGFR decline after access surgery between those who received an AVA compared to those who received a PDC, indicating the lack of a specific effect from AVA creation per se on the progression rate. Our results are consistent with previous studies in the sense that we also detected a slower decline in eGFR after access surgery.[10] The absolute decline in progression rate both before and after AVA placement in our study was comparable to the results of Golper et al..[9] Likewise, in line with what previously have been shown, the

CVC patients were older, had more metabolic complications, faster eGFR decline before and lower eGFR at access surgery.[10] On the other hand, in contrast to earlier studies, we found that when comparing AVA to PDC placement, there was no significant difference in the progression rate between the two access-types.

Several pathophysiological hypotheses have been proposed to explain the apparent reduction of eGFR progression after AVA creation. One is the recruitment of a functional renal reserve in previously under perfused kidneys.[20] AVA creation is associated to changes in hormonal and hemodynamic parameters, stroke volume and vascular resistance,[21] changes in cardiac performance,[22] and possibly ischaemic preconditioning. [23] In addition, reduced arterial stiffness, blood pressure and increased left ventricle ejection fraction have also been suggested.[12] The same group also found remote microcirculatory changes associated to AVA placement.[13]

By including a different control group, we could investigate if patients receiving an AVA indeed would have a larger reduction of eGFR decline post-surgery compared to PDC patients, due to the abovementioned physiological mechanisms. In contrast to previous suggestions in the literature, the observed lack of a difference between the two groups in our study suggests that although physiological mechanisms may be present, they did not influence the clinical eGFR trajectory in our population. If the reduction in eGFR progression after access surgery is less likely to be explained by physiological factors attributed to AVA surgery, it opens up for other explanatory models. In support of our findings, Sumida et al. previously found the progression rate decline to be independent of AVA maturation status[10] and Korsheed et al. noted effects on blood pressure and ejection fraction already two weeks after surgery.[10,12] Compliance to prescribed medication, exercise and adherence to a protein restricted diet may be enhanced by the multidisciplinary nephrology care at a predialysis clinic.[24,25] As dialysis access surgery often is accompanied by more frequent healthcare

contacts and closer monitoring, these measures altogether may also have been involved in reducing the progression rate in both AVA and PDC patients. Another likely or contributing explanation for the slower eGFR progression after surgery may have been the statistical effect known as "regression towards the mean;" the decision of access surgery often occurs after a period of faster progression, statistically more frequently followed by a period of slower decline.[26] It could also be possible that the dialysis access is created at a certain "tipping point" when uremic symptoms become more disabling, resulting in lower dietary intake and reduced muscle mass. Any eGFR based on serum creatinine would then be more likely to overestimate renal function and result in a falsely slower eGFR decline.

Our study has several strengths. One is the complete and prospective inclusion of all patients receiving a dialysis access in a region during a given time period, with no loss to follow-up. Furthermore, Sweden has a tax-financed healthcare system where access to healthcare in general and nephrology is virtually equal for different socio-economic groups. The referral guidelines are applicable to the whole region and there are no private nephrology clinics or dialysis units that were excluded in our material which increases generalizability. Our prospective design with two comparable pre-dialytic groups, (PDC and AVA), reduces confounding from differences in symptoms, access to medication and pre-dialytic healthcare, factors that in addition to access surgery may influence progression rate. In addition, we were able to collect extensive information about comorbidity, drugs and laboratory parameters.

Like all observational studies, our study also has weaknesses. The tradition in Sweden is to create the dialysis access and start dialysis late. Therefore, our patients´ average eGFR at access surgery was lower than previous studies and one could hypothesize that a longer follow-up would have made a difference in AVA compared to PDC patients more likely.[17] Nevertheless, the progression rate before and after access surgery was very similar to previous studies and when we stratified our analysis based on eGFR at surgery, we did not detect any

substantial difference compared to our main results. Furthermore, when we looked at our cohort after a maximum of almost three years, we noted that about 1/3 of the patients who received an access never started dialysis, despite our later access creation. In addition, sensitivity analysis did not reveal any significant difference in our results when we analysed our data “as treated” to account for a proper AVA maturation. Although we used eGFR from serum creatinine, any misclassification due to dietary factors and loss of muscle mass would be similar in the two types of accesses.

In conclusion, access surgery in general is associated with a reduction of the eGFR decline in our population. However, as there was no significant difference in eGFR decline after surgery for an AVA compared to a PDC, our study does not support to the hypothesis of a specific physiological effect of AVA placement on the eGFR decline. Thus, the need for dialysis still remains the main determinant for any decisions regarding the timing of the access placement.

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Table 1. Demographics by dialysis access surgery in a regional, representative cohort of referred patients with chronic kidney disease.

Demographics	**Arteriovenous fistula/graft** (n=435)	**Peritoneal dialysis catheter** (n=309)	**Central venous catheter** (n=53)
Age (Years)	65 (52-73)	63 (50-74)	69 (50-78)
Men	276 (63.5)	193 (62.5)	40 (75.5)
eGFR at surgery ml/min/1.73m^2	8.1 (6.4-10.6)	7.0 (5.3-8.9)	5.6 (4.4-7.1)
Follow-up time before (days)	81 (92-63)	82 (93-63)	79 (92.5-63.5)
Follow-up time after (days)	82 (61-92)	68 (21.5-90)	5 (2-8)
eGFR decline/year prior to surgery (ml/min/1.73m^2)	-5.6 (-10.0- -1.3)	-6.7 (-11.7- -3.7)	-11.2 (-16.9- -6.3)
Comorbidity			
Cardiovascular Disease	176 (41)	108 (35)	23 (43)
Diabetes	172 (40)	111 (36)	29 (55)
Current medication:			
ESA use	249 (57)	219 (71)	26 (49)
ACE/ARB	293 (67)	229 (74)	37 (70)
Beta-blockers	301 (69)	214 (69)	36 (68)
Laboratory data:			
Albumin (g/l)	34 (31-37)	34 (31-37)	30 (25- 34.5)
Calcium (mmol/l)	2.26 (2.14- 2.4)	2.25 (2.07- 2.38)	2.23 (1.99- 2.35)
Phosphate (mmol/l)	1.7 (1.4-2)	1.8 (1.5-2.2)	2.15 (1.6-2.6)
Hemoglobin (g/l)	113 (103-123)	112 (101-121)	102 (90-113)
Potassium (mmol/l)	4.6 (4.1-5.1)	4.6 (4.2-5)	4.6 (4.3-5.0)
ACR (<3 mg/mmol)	17 (4.9)	11 (4.1)	1 (2.0)
(3-30 mg/mmol)	68 (19.7)	37 (13.9)	5 (10.2)
(>30 mg/mmol)	260 (75.4)	219 (82.0)	43 (87.8)
Clinical information:			
Systolic Blood Pressure (mmHg)	145 (131.8-163)	145 (130-160)	142 (124.5-157.5)
BMI (kg/m²)	27.5 (23.1-32.1)	25.2 (21.8-28.3)	25.2 (21-30.8)

All continuous values are expressed as median (IQR), categorical values as number (%). ACE/ARB (angiotensin enzyme converting enzyme inhibitors/angiotensin receptor blockers), ACR (urinary albumin/creatinine ratio), BMI (body mass index), ESA (erythropoetin stimulating agents), eGFR (estimated glomerular filtration rate in ml/min/1.73m^2, estimated by the CKD-EPI equation). To convert Calcium in mmol/l to mg/dL, divide by 0.2495. To convert Phosphate mmol/l to mg/dL, multiply with 3.0974. To convert Hemoglobin in g/l to g/dL, divide by 10. To convert creatinine from micromol/l to mg/dL multiply by 0.0113.

Table 2. Differences in estimated glomerular filtration rate decline in after surgery for AV-fistula/AV-graft compared with PD-catheter

	PD-catheter	**AV-fistula/AV-graft**	**P-value**
Median absolute decline in eGFR after surgery	-2.17 (-2.85; -1.75)	-1.61 (-2.12; -0.79)	0.07
Unadjusted	Ref.	0.56 (-0.58; 0.47)	0.22
Model 1*	Ref.	-0.05 (-2.18; 0.34)	0.84
Model 2**	Ref.	-0.09 (-0.68; 0.51)	0.78
Model 3#	Ref.	-0.26 (-0.88; 0.35)	0.40

Values are given as the difference in median decline ($eGFR_{CKD\text{-}EPI}$ (ml/min/1.73m^2/year); 95% confidence interval) for those who received a PD-catheter compared with AV-fistula. A negative difference indicates faster decline compared to the reference. A positive difference indicates a slower decline compared to the reference. A confidence interval including 0.0 indicates no difference between the two groups.

*Model 1: Adjusted for slope before surgery (cubic) and eGFR at surgery; **Model 2: Model 1+ age, sex, primary renal disease and body mass index; #Model 3: Model 2+ ESA treatment, beta blocker treatment, plasma albumin, and albuminuria

AV (arteriovenous), CVD (cardiovascular), eGFR (estimated glomerular filtration rate), ESA (erythropoiesis stimulating agents), PD (peritoneal dialysis)

Table 3. Difference in eGFR decline before and after access surgery in AVAs compared to PDC

	Number of patients with AVA versus PDC	**Difference in eGFR decline after surgery for AVA compared to PDC**	**95% Confidence interval***
Kernel matching	435/305	-4.17	-0.64; -8.79
Kernel matching model 2	268/212	-1.65	0.67; -1.65
Radius matching (0.01)	421/305	-2.33	1.46; -8.45
Radius matching (0.01) model2	255/210	-0.43	1.83; -2.69

*standard errors and confidence intervals estimated through bootstrapping (100 reps)AVA (arteriovenous access), (PDC) peritoneal dialysis catheter, (eGFR) estimated glomerular filtration rate.

FIGURE LEGENDS:

Figure 1. Estimated glomerular filtration rate before and after access surgery

Figure 1 subheading: Values are presented as unadjusted median decline in estimated glomerular filtration rate (95% confidence interval). *denotes a statistical significant difference ($p<0.01$) compared with pre-access surgery slope. Arteriovenous access (AVA), Peritoneal dialysis catheter (PDC)