The Impact of Arteriovenous Access Placement on Estimated Glomerular Filtration Rate in Diabetic, Non-Diabetic Chronic Kidney Diseases Pre-Dialysis Stage 5

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ABSTRACT

Background: Chronic kidney disease (CKD) represents a significant and often deteriorating condition that can lead to the ultimate need for hemodialysis due to end-stage renal disease. In patients with CKD, creating arteriovenous access (AVA) is a routine surgical procedure.

Objective: This study aimed to explore how AVA surgery affects the estimated glomerular filtration rate (eGFR) in both diabetic and non-diabetic CKD patients at pre-dialysis stage 5, emphasizing the timing and impact on renal functionality.

Patients and Methods: A prospective cohort study was conducted on 100 CKD patients who underwent AVA surgery. These patients were divided into diabetic and non-diabetic groups for comparison. Comprehensive clinical evaluations, lab tests, and subsequent appointments were conducted for thorough analysis.

Results: In the diabetic cohort (Group 1), there was a notable reduction in eGFR, decreasing from 11.05 ± 0.81 mL/min/1.73 m² one month prior to AVA formation to 10.00 ± 0.43 mL/min/1.73 m² three months afterward ($p < 0.001$). There was also an increase in serum creatinine from 6.03 ± 0.96 mg/dL to 6.80 ± 0.99 mg/dL ($p < 0.001$), and urea levels escalated from 211.15 ± 33.6 mg/dL to 237.85 ± 34.78 mg/dL ($p < 0.001$). Conversely, in the non-diabetic cohort (Group 2), a meaningful reduction in eGFR was observed, from 12.07 ± 0.87 mL/min/1.73 m² before AVA formation to 11.84 ± 0.52 mL/min/1.73 m² after three months ($p = 0.004$).

Conclusions: The findings indicated that the insertion of AVA in patients with stage 5 CKD pre-dialysis, especially those with diabetes, significantly decreased eGFR, accompanied by rises in serum creatinine and urea levels.

Keywords: Chronic kidney disease, Arteriovenous access, Estimated glomerular filtration rate, Diabetes, Renal function, Hemodialysis.

INTRODUCTION

Chronic kidney disease (CKD) poses a significant challenge to global health, with an increasing trend in end-stage kidney disease (ESKD) cases, especially noted in the United States and Canada. In 2014, the initiation of hemodialysis accounted for nearly 90% of new ESKD cases in the U.S., while Canada experienced a twofold increase in ESKD rates between 1994 and 2014 [1].

CKD is characterized by either kidney damage or a consistent GFR below 60 mL/min/1.73 m² over a period of at least three months. The progression of nephron damage leads to irreversible sclerosis and a consequent decrease in GFR [2].

The strategic timing for arteriovenous access (AVA) construction is crucial for enhancing patient survival rates and facilitating the onset of dialysis treatment. Effective pre-dialysis AVA planning significantly improves patient outcomes. Yet, identifying the optimal timing for AVA creation is complex due to the potential for delayed AVA maturation, which heightens the necessity of initiating dialysis via a central venous catheter (CVC). On the other hand, premature AVA construction might lead to its underuse [3, 4].

AVA creation impacts various factors, including hormonal, hemodynamic changes, and potential ischemic pre-conditioning. It improves oxygenation, reduces arterial stiffness, blood pressure, and enhances cardiac function. Mechanisms for these benefits include remote ischemic preconditioning (RIPC) and changes in subcutaneous dermal capillaries [5, 6].

Our study investigated the impact of AVA placement on eGFR in diabetic and non-diabetic CKD patients in pre-dialysis stage 5, aiming to understand its timing and effects on kidney function.

PATIENTS AND METHODS

Patients: This prospective cohort study involved 100 patients diagnosed with stage 5 pre-dialysis chronic kidney disease, all of whom received arteriovenous fistula surgery. Participants were enlisted from the Internal Medicine Department, Benha University Hospitals through the period from December 1, 2022, to November 30, 2023.

Inclusion criteria: Patients over 18 years of age with chronic kidney disease stage 5 prior to the initiation of hemodialysis, including both diabetic and non-diabetic individuals.

Exclusion criteria: Advanced peripheral arteriovascular diseases, congestive heart failure with EF less than 30, amputation of extremities, pregnancy, patients with previous renal transplantation, malignancy, and patients with any other hemodialysis vascular access (central venous catheter, arteriovenous graft) 6 months before or during or after arteriovenous fistula creation.

Patients were randomly divided into 2 groups: Group (1) included fifty diabetic patients with chronic kidney diseases predialysis stage 5 (CKD -5) who

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underwent surgery for arteriovenous fistula creation. Group (2) comprised fifty non-diabetic patients with chronic kidney diseases predialysis stage 5 who underwent surgery for arteriovenous fistula creation.

Methods:

All patients were subjected to the following: Detailed history taking with special stress on personal history, comorbidities, history of diabetes (type 1 or type 2) and duration, drug history, and history of surgical operations. Full clinical examination (General and systemic examinations). Laboratory investigations [FBS (mg/dl), HbA1c, 2 hPP, complete blood count (RBCs count, hematocrit & Hb concentration, serum creatinine and blood urea, estimated glomerular filtration rate (eGFR)]. Also, liver function tests[SGOT (ul/L), SGPT (ul/L), S bilirubin (mg/dl), S. albumin (g/dl), serum calcium (mg/dl), serum phosphate (mg/dl), serum sodium (mEq/L), serum potassium (mEq/L), protein creatinine ratio, urine analysis with comment on dysmorphic RBCs., viral markers (HBV s AG- HCV Abs- HIV Abs), immunological markers (ANA – Anti ds DNA – ANCA p, c)), and radiological investigations (Doppler ultrasound on arterial and venous system of upper limb, Abdominal ultrasonography, Echocardiography, Doppler ultrasound and ECG).

Follow up:

Participants were monitored up until the commencement of dialysis, their passing, or 100 days following the operation, depending on which occurred first.

Duration of treatment and follow up: The estimation of the GFR was conducted using the equation provided by the chronic kidney disease epidemiology collaboration (CKD-EPI). The monitoring of patients continued until the initiation of dialysis, their demise, or 100 days after the surgery, whichever happened earliest. Appointments for follow-up were organized on a monthly basis at three, two, and one month prior to the arteriovenous fistula's establishment, at the time of its creation, and then one, two, and three months subsequent to its establishment. During these follow-up sessions, laboratory examinations, including assessments of blood urea, serum creatinine, HbA1c, and other pertinent indicators, were conducted to observe changes in eGFR.

Sample size calculation: Using G power, version 3.1.9.4. for sample size estimation, the effect size in this study was 1.04, considered to be (small) using Cohen's (1988) criteria [7]. With a significant criterion of $\alpha = .05$ and power = .95. The minimum sample size needed with this effect size is N = 42 for (t-test: difference between two independent groups); 21 patients in each group.

Ethical considerations: The study was approved by the Ethics Committee of Faculty of Medicine, Benha University Hospital. Informed consents were signed after getting approval from The Ethics Committee of Benha University. The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring protection of their confidentiality and privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The gathered information underwent review, coding, and organization utilizing the Statistical Package for the Social Sciences (SPSS by IBM Corp., released in 2017, version 25.0, Armonk, NY: IBM Corp.). This included calculating the mean and standard deviation (± SD) for data following a normal distribution and determining the median and range for data that did not distribute normally. For categorical data, frequencies and percentages were computed. The Student's t-test was applied to determine the statistical significance of differences in means between the two groups under study. For non-parametric variables, the Mann-Whitney U test was utilized to evaluate the significance of differences between the two groups. The Chi-square test was employed to investigate the correlations between two categorical variables. Statistical tests were bilateral, with P values of ≤ 0.05 deemed to indicate significant results.

RESULTS

The statistical analysis revealed a significant difference in age between the two groups ($p < 0.001$), with group 1 having a considerably higher proportion of males compared to group 2 ($p = 0.039$). Additionally, the BMI showed a significant difference between the groups ($p = 0.031$). However, the duration of CKD did not show statistical difference between the two groups. In group 1, diabetic nephropathy was identified as the most common cause of kidney disease, with a 100% occurrence rate, and was completely absent in group 2. Vascular kidney disease and glomerular disease were significantly more prevalent in group 1 than in group 2 ($p = 0.033$ and $p = 0.031$ respectively). Tubulointerstitial disease presented a notable difference, affecting 24% of individuals in group 1 compared to only 6% in group 2 ($p = 0.025$). Conversely, obstructive and cystic kidney diseases were significantly more common in group 2 than in group 1 ($p = 0.014$ and $p < 0.001$ respectively). Group 1 also exhibited a significantly higher prevalence of hypertension, IHD, and smoking habits compared to group 2 ($p < 0.05$). On the contrary, group 2 had a significantly higher prevalence of cardiomyopathy and respiratory diseases than group 1 ($p < 0.05$) (Table 1).

Table (1): Demographic data, clinical assessment, causes of chronic kidney disease and comorbidities distribution among studied groups

		Group 1 n (50)	Group 2 n (50)	p
Age (years)		55.4±10.1	46.6±12.4	<0.001*
Age (Groups)	**18 - 44 years**	8(16%)	22(44%)	0.001*
	45 - 59 years	20(40%)	21(42%)	
	>60 years	22(44%)	7(14%)	
Gender	**Female**	14(28%)	24(48%)	0.039*
	Male	36(72%)	26(52%)	
Clinical assessment	**BMI (kg/m2)**	25.7±2.5	24.9±3	0.031*
	Duration of CKD (years)	8.7±2	8.4±2.2	0.496
Causes of chronic kidney disease				
Diabetic nephropathy		50(100%)	Null	-
Vascular kidney disease		13(26%)	4(8%)	0.033*
Glomerular disease		13(26%)	4(8%)	0.031*
Tubulointerstitial		12(24%)	3(6%)	0.025*
Obstructive kidney disease		8(16%)	20(40%)	0.014*
Cystic kidney disease		4(8%)	19(38%)	<0.001*
Comorbidities distribution				
Hypertension		15(30%)	4(8%)	0.011*
IHD		14(28%)	5(10%)	0.041*
Cardiomyopathy		2(4%)	17(34%)	<0.001*
Respiratory diseases		3(6%)	18(36%)	<0.001*
Smoking		16(32%)	6(12%)	0.029*

* For significance (p<0.05), IHD: Ischemic heart disease.

According to diabetic work up in the studied groups, a significant higher FBS, 2 hpp and HBA1c in group 1 compared to group 2 (p<0.001). Haemoglobin, TLC, PLT, ALT, AST, and albumin did not show statistically significant differences between the two groups. There were no statistically significant differences observed in the electrolyte levels (Sodium, potassium, calcium, and phosphate) between group 1 and group 2 (Table 2).

Table (2): blood glucose HBA1c, laboratory parameters before creation of arteriovenous fistula, electrolytes parameters, follow up outcomes between the two studied groups.

	Group 1 n (50)	Group 2 n (50)	p
FBS (mg/dl)	144.96 ± 37.65	113.33 ± 24.9	<0.001*
2hPP (mg/dl)	238.19 ± 7.32	147.28 ± 36.04	<0.001*
HbA1c (%)	7.28 ± 1.33	6.03 ± 1.11	<0.001*
laboratory parameters			
Hemoglobin (g/dl)	10.31 ± 1.13	10.88 ± 1.69	0.051
TLC (x103/L)	8.72 ± 1.83	7.86 ± 1.99	0.287
PLT (x103/L)	319.95 ± 9.26	351.88 ± 8.95	0.085
ALT (U/L)	28.42 ± 3.56	30.38 ± 1.60	0.439
AST (U/L)	33.09 ± 3.01	28.38 ± 1.9	0.262
Albumin (g/dl)	3.71 ± 0.855	3.65 ± 0.834	0.723
Bilirubin (mg/dl)	0.948 ±0 .554	0.858 ± 0.138	0.369
Electrolytes parameters			
Sodium (mEq/L)	139.61 ± 5.27	138.74 ± 2.56	0.38
Potassium (mEq/L)	4.72 ± 0.643	4.78 ± 0.684	0.652
Calcium (mg/dl)	8.68 ± 1.34	8.93 ± 1.27	0.341
Phosphate (mg/dl)	5.24 ± 1.08	5.13 ± 0.954	0.591
Follow up outcomes			
Dialysis initiation	26 (52%)	29 (58%)	0.547
Kidney transplantation	2 (4%)	4 (8%)	0.399
Death	3 (6%)	1 (2%)	0.309
Remaining subjects (end of the study)	19(38%)	16 (32%)	0.675

*Significant P-value; FBS, Fasting blood sugar; 2hPP, 2 hours Post prandial blood sugar; HbA1c, Hemoglobin A1C, TLC, total leukocyte count; PLT, platelet count; ALT, alanine transaminase; AST, aspartate transaminase.

The statistical analysis indicated that there was a significant worsening in renal parameters over time in group 1 and group 2. (p < 0.001). According to renal function parameters one month before and one month after creation of AV fistula

in group 1 and group 2, GFR was significantly higher one month before than 1 month after AV creation (p<0.001). Serum creatinine and urea were significantly lower one month before than 1 month after AV creation (p<0.001) (Table 3).

Table (3): Renal function parameters before creation of arteriovenous fistula among group 1, and among group 2, renal function parameters one month before and one month after creation of arteriovenous fistula in group 1 and among group 2

	3 months before	2 months before	1 month before	p
GFR (mL/min/1.73m2)	12.25±0.87	11.54±0.79	11.05±0.81	<0.001*
Creatinine (mg/dl)	5.45±0.91	5.89±0.94	6.03±0.96	<0.001*
Urea (mg/dl)	190.79±31.91	206.07±32.74	211.15±33.6	<0.001*
Renal function parameters before creation of arteriovenous fistula among group 2				
GFR (mL/min/1.73m2)	13.02±0.91	12.56±0.83	12.07±0.87	<0.001*
Creatinine (mg/dl)	5.03±0.97	5.28±1.02	5.5±1.1	<0.001*
Urea (mg/dl)	176±34.04	184.7±35.65	192.62±38.54	<0.001*
Renal function parameters one month before and one month after creation of arteriovenous fistula in group 1				
	1 month before	**1 month after**	**P**	
GFR (mL/min/1.73m2)	11.05±0.81	10.68±0.47	<0.001*	
Creatinine (mg/dl)	6.03±0.96	6.34±0.87	<0.001*	
Urea (mg/dl)	211.15±33.6	221.8±30.49	<0.001*	
Renal function parameters one month before and one month after creation of arteriovenous fistula in group 2				
GFR (mL/min/1.73m2)	12.07±0.87	12.14±0.43	<0.001*	
Creatinine (mg/dl)	5.5±1.1	5.64±0.96	<0.001*	
Urea (mg/dl)	192.62±38.54	197.51±33.58	<0.001*	

*Significant P-value; * for significant p value (<0.05); GFR: glomerular filtration rate.

According to renal function parameters one month before and two months after creation of AV fistula in group 1 and in Group 2, GFR was significantly higher one month before than 2 months after AV creation (p<0.001, p=0.04 respectively). Serum creatinine and urea were significantly lower one month before than 2 months after AV creation (p<0.001, p=0.021 respectively). Regarding renal function parameters one month before and three months after creation of AV fistula in group 1 and in group 2, GFR was significantly higher one month before than 3 months after AV creation (p<0.001 p=0.04 respectively). Serum creatinine and urea were significantly lower one month before than 3 months after AV creation (p<0.001) (Table 4).

Table (4): Renal function parameters one month before and two months after creation of arteriovenous fistula in group 1 and in group 2 and renal function parameters one month before and three months after creation of arteriovenous fistula in group 1

	One month before AV creation	2 months after AV creation	P
GFR (mL/min/1.73m2)	11.05±0.81	10.2±0.41	<0.001*
Creatinine (mg/dl)	6.03±0.96	6.58±0.97	<0.001*
Urea (mg/dl)	211.15±33.6	230.45±33.94	<0.001*
in Group 2			
GFR (mL/min/1.73m2)	12.07±0.87	11.83±0.41	0.04*
Creatinine (mg/dl)	5.5±1.1	5.69±1.1	0.021*
Urea (mg/dl)	192.62±38.54	199.13±38.65	0.021*
	One month before AV creation	**3 months after AV creation**	**P**
GFR (mL/min/1.73m2)	11.05±0.81	10±0.43	<0.001*
Creatinine (mg/dl)	6.03±0.96	6.8±0.99	<0.001*
Urea (mg/dl)	211.15±33.6	237.85±34.78	<0.001*
in Group 2			
GFR (mL/min/1.73m2)	12.07±0.87	11.84±0.52	0.04*
Creatinine (mg/dl)	5.5±1.1	5.76±0.98	<0.001*
Urea (mg/dl)	192.62±38.54	201.69±34.16	<0.001*

* for significant p value (<0.05); GFR, Glomerular filtration rate

According to renal function parameters one month before and after creation of arteriovenous fistula in group 1, a progressive decline in the glomerular filtration rate (GFR), which decreased over the three-months period, accompanied by a highly significant p-value of less than 0.001. In parallel, both serum creatinine and urea levels showed a continuous increase, creatinine rose and urea each also yielding a p-value of less than 0.001. According to renal function parameters one month before and after creation of arteriovenous fistula in group 2, GFR decreased by the third month after creation of AV fistula, reaching statistical significance (p = 0.004). In contrast, the changes in serum creatinine and urea levels did not achieve statistical significance (Table 5).

Table (5): Renal function parameters one month before and one, two, three months after creation of arteriovenous fistula in group 1 and group 2

	1 month before	1 months after	2 months after	3 months after	P
GFR (mL/min/1.73m2)	11.05±0.81	10.68±0.47	10.2±0.41	10±0.43	<0.001*
Creatinine (mg/dl)	6.03±0.96	6.34±0.87	6.58±0.97	6.8±0.99	<0.001*
Urea (mg/dl)	211.15±33.6	221.8±30.49	230.45±33.94	237.85±34.78	<0.001*
In group 2					
GFR (mL/min/1.73m2)	12.07±0.87	12.14±0.43	11.83±0.41	11.84±0.52	0.004*
Creatinine (mg/dl)	5.5±1.1	5.54±0.96	5.73±1.1	5.8±0.98	0.086
Urea (mg/dl)	192.62±38.54	190.51±33.58	199.13±38.65	202.69±34.16	0.086

* For significant p value (<0.05); GFR, Glomerular filtration rate.

DISCUSSION

Group 1 had more diabetic nephropathy cases and a higher prevalence of vascular, tubulointerstitial, and glomerular kidney diseases, while group 2 had more cases of obstructive and cystic kidney diseases. In terms of comorbidities, group 1 had more hypertension, IHD, and smokers, while group 2 had more cardiomyopathy and respiratory diseases. **Chen *et al.*** [8] concluded that prevalence of CVD was significantly higher in NDKD group than DKD group (P<0.001).

According to diabetic work up in the studied groups, a significant higher FBS, 2 hpp and HBA1c in group 1 compared to group 2. Consistency with our findings, **Ghazanfari *et al.*** [11] recruited a total number of 604 individuals. They found that FBS and HBA1c were significantly higher in diabetic compared to non-diabetic groups (P<0.001).

According to baseline laboratory investigations among studied groups, hemoglobin, TLC, PLT, ALT, AST, and albumin did not show statistically significant differences between the two groups. This comes in line with **Takahashi *et al.*** [10] who concluded that hemoglobin and serum potassium were insignificantly different between diabetic patients and non-diabetic patient.

In follow-up outcomes, 52% of group 1 and 58% of group 2 participants required dialysis. Kidney transplantation rates were 4% in group 1 and 8% in group 2. Regarding death, 6% in group 1 and 2% in group 2 experienced it. There were no statistically significant differences in follow-up outcomes between the two groups. **Dupuis *et al.*** {12} conducted a study comparing the decline in eGFR among predialysis patients who had an AVF with those slated for PD. Within the AVF cohort, 5% of patients passed away and 39% commenced dialysis, while in the PD cohort, there were no deaths and 79% began dialysis within a span of 12 months.

In group 1, our study revealed a significant deterioration in renal parameters over time, with GFR, creatinine, and urea values showing worsening trends (p < 0.001) both before and after AV access placement. **Lundström *et al.*** [13] observed that the eGFR at the moment of surgical intervention was higher in individuals who were administered an AVA compared to those with a PDC, with eGFRs of 8.1 (AVA) vs 7.0 (PDC) mL/min/1.73 m². Additionally, AVA recipients experienced a slower rate of eGFR decline prior to surgery (−5.6 for AVA vs −6.7 for PDC mL/min/1.73 m²/year). Those who received a CVC witnessed the steepest reduction in eGFR before surgery and had the lowest eGFR at the time of the operation. Post-surgery, patients with AVA and PDC saw a deceleration in the rate of eGFR decline compared to before surgery, with a median slope difference in eGFR decline of 5.3 mL/min/1.73 m². Out of the cohort, only 166 patients (22%) experienced an accelerated decline in eGFR following the surgery for access, with a significant number of these cases involving individuals who received an AVA.

By comparing the renal parameters before and after arteriovenous access placement between the two studied groups. It showed the values of GFR, creatinine, and urea before the access placement and after the placement for both groups. The statistical analysis indicated a significant worsening in renal parameters pre-access than post-access in group 1 compared to group 2 (p<0.001). **Sumida *et al.*** [14] found that, in models not adjusted for confounding factors, the rate of decline in eGFR increased for patients who did not have an arteriovenous fistula or graft (AVF/AVG) both before and after a six-month benchmark date leading up to the start of dialysis. Conversely, for those who had an AVF/AVG, a notable slowing in the rate of eGFR decline was observed after the creation of the AVF/AVG, both before and after its establishment, with statistical significance (P < 0.001). After adjusting for potential confounders, the estimated median eGFR slopes at times before and after this six-month index date still showed significant differences for patients without an AVF/AVG, as well as for those with an AVF/AVG, indicating a significant change in the rate of eGFR decline following AVF/AVG surgery.

In a matched analysis of 61 pairs, the average annual decline in eGFR before the establishment of an AVF was −4.1 ml/min/1.73 m² per year for the AVF

group, compared to −5.3 ml/min/1.73 m² per year for the PD group, which was not statistically significant (P=0.75). However, after the establishment of the AVF, the rate of decline improved to −2.5 ml/min/1.73 m² per year in the AVF group versus −4.5 ml/min/1.73 m² per year in the PD group, showing a significant difference (P=0.02). The anticipated annual decrease in eGFR shifted from −5.1 ml/min/1.73 m² per year before AVF creation to −2.8 ml/min/1.73 m² per year afterwards in the AVF group (P<0.01), while no significant change was observed in the PD group before versus after (−5.5 versus −5.1 ml/min/1.73 m² per year, P=0.41) [12].

LIMITATIONS

This study had limitations as it was carried out over a relatively small sample of population, therefore more multi-center studies with larger sample size are needed.

CONCLUSIONS

Arteriovenous access placement in both diabetic and non-diabetic CKD stage 5 patients exhibited a significant decline in renal function post-surgery. However, diabetic patients displayed a more pronounced deterioration in eGFR compared to non-diabetic counterparts. This revealed a potential interaction between diabetes and the impact of access placement on renal function.

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