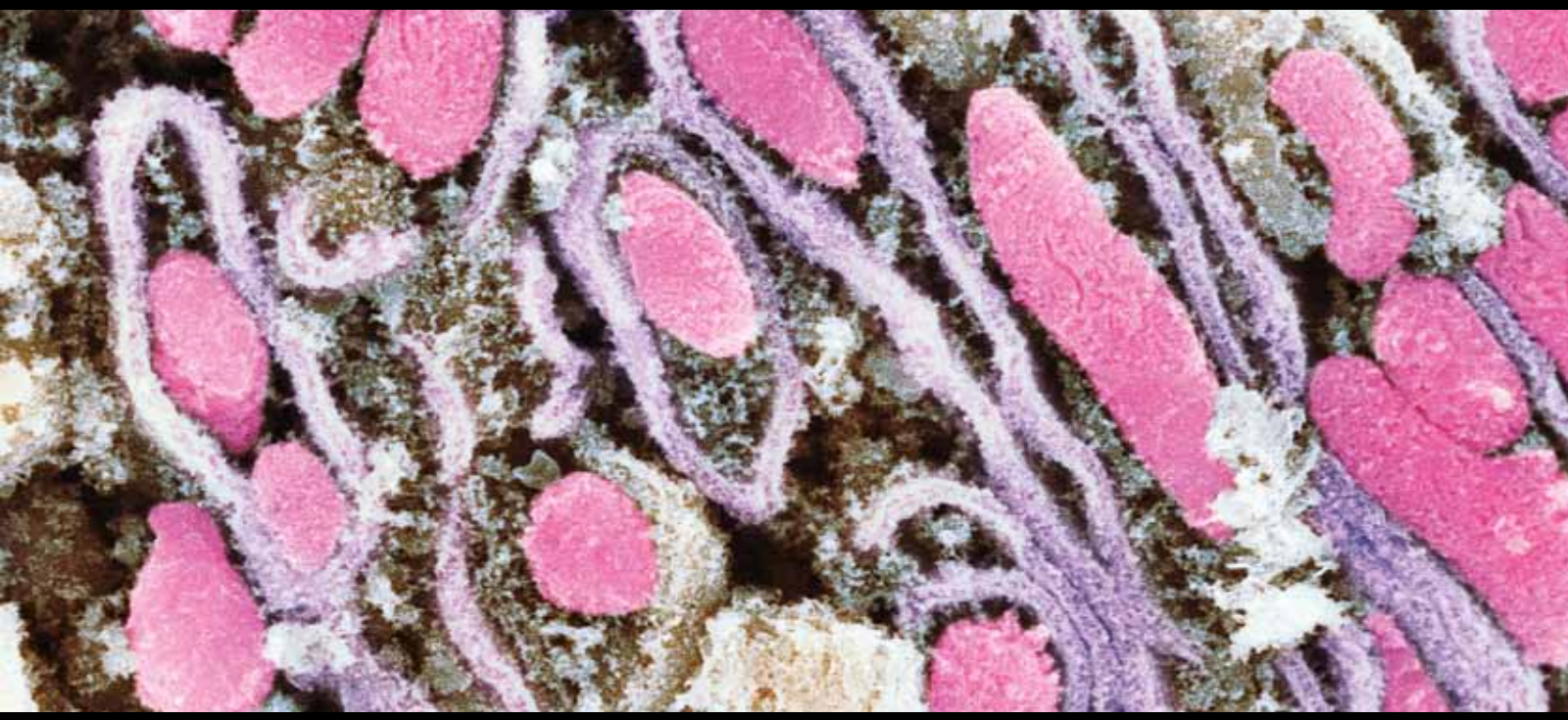
International Journal of Nephrology

Dialysis Access Dysfunction

Guest Editors: Alexander Yevzlin, Arif Asif, and Anil K. Agarwal



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Editorial Board

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Editorial

Dialysis Access Dysfunction

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Vascular access failure (VAF) is the most common reason for hospitalization among hemodialysis (HD) patients. The economic burden of VAF is estimated to be greater than 1 billion dollars per year and continues to grow. The purpose of this special issue is to focus on recent advances in our understanding of dialysis access dysfunction.

Thanks in part to several national initiatives, the rate of arteriovenous fistula (AVF) placement continues to rise in the United States. AVF failure remains a major concern. Although the detection of early stenosis with preemptive correction prior to thrombosis seems to be a plausible option to prevent access failure, there is much debate, on the basis of of surveillance studies, as to whether early surveillance actually improves the longevity of an access system.

Evaluating the available information for surveillance, specifically the data for AVF stenosis and survival, is necessary to determine if surveillance is of any benefit. In an attempt to clarify ambiguities, one of the articles in this issue attempts to review the question: Does regular surveillance improve the long-term survival of arteriovenous fistulas?

Similarly, L. Kumbar et al., have contributed to this special issue with an evaluation of access surveillance outcomes. They state that although different techniques and methods are available for identifying access dysfunction, the scientific evidence for the optimal methodology is lacking. A small number of randomized controlled trials have evaluated the role of different surveillance techniques. The authors conclude that the limited randomized studies especially involving fistulae and small sample size of the published studies with conflicting results highlight the need for a larger multicentered randomized study with hard clinical end points to evaluate the optimal surveillance strategy for both fistulas and grafts.

Another important contribution is made by M. L. Zadeh et al. in this special issue. The authors observe that while native AVF is the recommended vascular access for HD, its failure to mature remains a major problem. The aim of their study was to determine the correlation between diameter and maturation of vessels in radiocephalic AVF. The authors performed a prospective cross-sectional study carried out during 2006-2007 on 96 hemodialysis patients from Hashem-inejad Kidney Center. The maturation of fistula showed correlation with vein diameter, but no correlation was seen with the diameter of the arteries.

Inflammation is a problem for dialysis access as well as for ESRD patients' cardiovascular health. The contribution of the dialysis vascular access type to inflammation, however, remains largely undefined. This special issue contains a paper describing a prospective observational study in an incident HD population. C-reactive protein (CRP), interleukin-6 (IL-6), and interferon-γ-induced protein (IP-10) were measured before and at 6-time points after access placement for 1 year. A mixed effects model was performed to adjust for age, sex, race, coronary artery disease, diabetes mellitus, infections, access thrombosis, initiation of HD, and days after access surgery. In comparison to AVFs, the presence of a tunneled catheter (TC) was associated with significantly higher levels of CRP. Patients who initiate HD with a TC or an AVG have a heightened state of inflammation, which may contribute to the excess 90-day mortality after HD initiation.

These paper and several additional important contributions comprise this special issue on dialysis access. The

guest editors hope that the readership of International Journal of Nephrology finds these contributions useful and enlightening.

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Review Article

Surface-Treated versus Untreated Large-Bore Catheters as Vascular Access in Hemodialysis and Apheresis Treatments

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Background. Catheter-related infections, thrombosis, and stenosis are among the most frequent complications associated with catheters, which are inserted in vessels. Surface treatment processes of the outer surface, such as ion-beam-assisted deposition, can be used to mitigate such complications. *Methods*. This retrospective study (1992–2007) evaluated silver-coated (54 patients) and noncoated (105 patients) implanted large-bore catheters used for extracorporeal detoxification. The catheters were inserted into the internal jugular or subclavian veins. After removal, the catheters were cultured for bacterial colonization using standard microbiologic assays. They also were examined using scanning electron microscope. *Results*. The silver coated catheters showed a tendency towards longer in situ time. The microbiologic examinations of the catheter tips were in both catheter types high positive, but not significant. *Conclusion*. The silver-coated catheters showed no significantly reduction in infection rate by evaluation of all collected data in this retrospective study. There was no association between both catheters in significantly reducing savings in treatment costs and in reducing patient discomfort. Other new developed catheter materials such as the microdomain-structured inner and outer surface are considered more biocompatible because they mimic the structure of natural biological surface.

1. Introduction

Since the introduction of large-bore catheters for acute hemodialysis more than 50 years ago [1, 2], many problems with handling, materials, and contamination of these catheters have arisen. Catheterization of the femoral vessels produces more complications than the catheterization of the superior vena cava (SVC). Cannulation of the SVC versus the subclavian vein is difficult to implement and involves a higher complication rate [2, 3]. Using the infraclavicular catheterization technique, it is often difficult to push the large-bore catheter under the clavicle. Because of the anatomical position of the subclavian vein, perforation is more likely with a rigid, large-bore catheter, apart from the danger of causing a pneumothorax or a hemothorax [3–9].

Despite technical innovations in hemodialysis (HD) and apheresis, the problems of providing temporary or permanent vascular access appear to have found no satisfactory solution. Temporary vascular access, in particular, still presents considerable problems. Therefore, many investigators have inserted large-bore catheters in the superior vena cava rather than in the internal jugular or the subclavian veins [3–9]. Dialysis catheters are used for vascular access in 65% of incident hemodialysis patients, and in 25% of the prevalent HD populations [10]. Complication rates due to infections for venous catheters are reported to be between 34 and 40% and more [11, 12].

Synthetic catheter implants are increasingly used for intensive medical treatment and extracorporeal detoxifications procedures. Correspondingly, typical complications such as infections and thrombosis have also increased. Infections present a particular problem because they can appear at any time, even years after an implantation, and may affect all materials.

Catheter-related bacteremia is a major cause of morbidity among hemodialysis patients. Treatment with systemic

antibiotics alone without removal of the catheter fails to definitively eradicate the infection in most patients [13]. Catheter-related bacteremia can be managed by either catheter removal with delayed placement of a new catheter or exchange of the infected catheter with a new catheter over a guide-wire and additional systemic antibiotic therapy.

The source of catheter-related bacteremia is in most patients a bacterial biofilm, which forms in the catheter lumen. This biofilm, mostly consisting of *Staphylococcus aureus*, cannot be destroyed or eliminated by a systemic antibiotic therapy because of antimicrobial resistance [14].

In 1981, Locci et al. demonstrated that bacterial could most of the time colonize artificial, rough surfaces [15]. The combination of tough surfaces and protein deposits should be an ideal situation for the colonization of bacteria. The bacteria could produce and become covered with a slime layer, in which case antibiotic drugs have no influence on the bacteria. The bacteria under the slime layer use the organic substances of the catheter material for their metabolism. The toxins of the bacteria can penetrate the slime layer and enter the patient blood provoking a catheter infection. Biofilm is a microbial-derived sessile community characterized by cells that are irreversibly attached to a substratum or to interface to each other, embedded in a matrix of extracellular polymeric substances that have produced [16]. Such a biofilm can be the origin of fibrin sheath formations leading to catheter dysfunction due to blood flow reducing and to blood disturbances. The therapy must be to remove the catheter immediately or exchange it over a guide-wire with a new catheter and additional systemic antibiotic therapy.

In addition to infection, biocompatibility of synthetic materials is a major problem. The interaction of blood with a synthetic surface causes coagulation and activation of the complement system. This can lead to the adsorption of various proteins and the formation of a layer of protein on the synthetic surface. Thrombocytes, other cells, and bacteria adhere to this layer of protein so that thrombi may form, which can lead to blood flow disturbances and catheter dysfunction [17]. Because of these problems, surface modification processes that can reduce the rate of infection or thrombogenicity, without adversely affecting basic catheter design and functionality, are of special interest.

The large-bore catheter has been frequently modified over recent years, and all models available are of similar construction with single, double, or triple lumen [18–25]. To influence catheter-related bacteremia, different new developments are available today, like coating of the catheter surface with antibiotic-heparin, cuffs on the outer surface, catheter for tunnelling, installation of an antibiotic-anticoagulant lock into the catheter lumen after the HD, and so forth, [13, 26, 27].

The authors introduced in 1979 the transcutaneous insertion of large-bore catheters through the internal jugular vein [11], and in 1992 they used for the first time available catheters which were coated on the outer surface with silver. In a retrospective study from 1992 to 2007, all catheters with surface treatment of silver versus untreated catheters were investigated after removal using a scanning electron microscope. Also, bacterial colonization and thrombus accumulation and the cuffs of the catheters after fixation were also investigated. In a preliminary study from 2001, the authors found a decline of the infection rate with the surface-treated catheter [28]. To examine these results in a 15-year study is the aim of this paper.

2. Catheter and Material

Most of the available single-, double- or triple-lumen catheters have some deficiencies depending on the material. Not all catheters are radiopaque. No problem is experienced with polyurethane catheters after the incorporation of contrast media; however, the latter material may affect catheter durability when using Teflon. This problem was overcome by making a thicker catheter wall, but this caused endothelial irritation and early thrombus formation. Catheters providing radio contrast are not absolutely necessary, however, because their position can be controlled more simply and gently with an intra-atrial electrocardiogram lead (ia ECG) [29]. The three most important criteria of any catheter material are a good tolerance, a low thrombogenicity, and a low infection rate [30, 31].

Rarely do the material properties perfectly match every requirement in a given application and biomaterials are no exception. For instance, although a candidate orthopedic material may have ideal mechanical properties, it may elicit a deleterious biological response, or a candidate biosensor with good electrical characteristics may corrode readily in the presence of body fluids [32]. Therefore, it often becomes necessary to strike a compromise so that a material has acceptable properties in each pertinent area. This compromise is often made between bulk and surface properties. For example, in a product such as a hemodialysis catheter, which demands both good flexibility and low surface friction, the best candidate may be a slippery, less flexible material rather than a more supple one with unacceptably high friction.

A wide spectrum of biomaterial surface properties, including biological, mechanical, chemical, and other properties that directly influence biocompatibility and functionality, can be modified. Surface engineering is generally considered when a "good" surface is not good enough, when devices would not function without it, or when product differentiation is desired [32].

The importance of surface-engineered biomaterials has been recognized by major medical device companies, because surface modification processes can reduce the rate of infection, thrombogenicity, and other catheter-related complications without adversely affecting the basic design function of catheters.

Although the field is still essentially in its infancy, the range of services currently offered by surface treatment vendors is varied and continually expanding. Examples include conventional coating process such as depending and spraying, vacuum-deposition techniques (e.g., sputtering), and surface modification approaches such as diffusion (nitriding, carburizing), laser and plasma processes, chemical plating, grafting or bonding, and bombardment with energetic particles (as in plasma immersion or ion implantation). Of the

Table 1: Characteristics of 159 patients who received large-bore catheters for dialysis or apheresis.

Parameter	Mean ± SD
Age (30–82 years)	66.5 ± 13.2
Females (n (%))	94 (59%)
Treated surface catheters (silver) (n (%))	54 (34%)
In situ time (days)	217.6 ± 285.8 (Median 123.0, 1–1845)
Treatments (n) (dialysis, apheresis)	76.4 ± 103.4 (Median 44.0, 1–670)

available techniques, those based on ionised particle bombardment have been particularly successful in biomaterial surface modification, primarily because they combine versatility and low-temperature processing with superior process control, reliability, and reproducibility [32].

The ion-beam-based technology used for the treatment of catheters covered herein is ion-beam-assisted deposition (IBAD; Spi-Argent, Spire Corporation, Bedford, MA, USA) [33–35]. The process is typically performed at low temperature under high vacuum. The affected layer in the typical films deposited by the IBAD process is in the order of 1 μm or less, so vacuum-compatible catheter materials may, therefore, be treated without adversely affecting bulk mechanical properties. The IBAD is line-of-sight process. This implies that only the outer surface of the catheters can be treated directly; however, parts with complicated geometries may be manipulated for uniform coverage of all surfaces. The ion-beam-assisted deposition of a silver coating was used [36].

Silver has been indicated as a good prospect for an infection-resistant coating material for catheters. The problem previously preventing the use of silver on catheters has been the inability to deposit adherent films of silver on flexible polymeric substrates. The IBAD process permits the formation of silver coatings at a relatively low temperature with extremely good adhesion that prevents delamination of the film during extended exposure to bodily fluids. The IBAD silver-deposited film has a low coefficient of friction, is highly uniform, and has demonstrated excellent adhesion. Biocompatibility testing consisted of a cytotoxicity test, and the USP Systemic Injection Test. Excellent results were obtained in both tests [32, 36–38].

3. Patients

The authors present the retrospective study from 1992 to 2007; the inclusion criteria were patients >18 years of age who requires a large-bore catheters (in-/outpatient), were free of bacteremia, and provided informed consent. The exclusion criteria were a pregnant or lactating female, a hypersensitivity of silver, and a bacteremia at the time of catheter insertion. An IRB approval was in 1992 not necessary.

In the study, a total of 159 patients (age 66.5 ± 13.2 years, females $n = 94$ (59%) are involved (Table 1)). Large-bore, single lumen catheters were inserted percutaneously in the internal jugular or subclavian veins. The percutaneously catheterisation was necessary in renal failure because of acute kidney injury (AKI) for hemodialysis due to cardiovascular disease, postoperative AKI, and so forth, and in end-stage renal disease (ESRD) because of clotting fistula, septicemia, abscess and catheter thrombosis, and faults in the catheter material ($n = 138$ (86.8%)) (Table 2). Further indications to catheterisation were access problems in patients with familial hypercholesterolemia ($n = 12$ (7.5%)), different indications for plasmapheresis ($n = 7$ (4.4%)), and in 2 patients with carcinoma ($n = 2$ (1.3%)).

In 54 patients (34%), a catheter with a silver coating on the outer surface (Spi-Argent, Spire, Bedford, MA, USA) was inserted, and 105 patients (66%) received untreated catheters. Patients with untreated catheters were younger (62.2 ± 16.2 versus 68.8 ± 10.7, $P = 0.003$), but there were no differences between the groups regarding gender distribution, diagnosis, or extracorporeal detoxification methods. The catheters were placed by nephrologists after the Seldinger technique and/or under fluoroscopic guidance. Before percutaneous insertion, each patient skin was disinfected using a consistent method, and a sterile skin smear was taken for microbiologic examination, and then the catheter was inserted. Before fixing the catheter with a suture, its position (particularly the catheter tip) should be checked with a normal radiological control and/or with an ia ECG [29]. In long-term catheters, a blood smear was taken every 4 weeks to screen for bacteria. Catheters were removed either when other vascular access routes became available or when serious infections developed, or if the catheter was not longer necessary.

Before catheter removal, a skin smear was taken. The catheters were then removed under sterile conditions, and the tip was examined bacteriologically. In the remainder, the catheter was rinsed in a physiological saline solution and fixed in a solution of phosphate buffer containing glutaraldehyde and formaldehyde for histological investigation.

4. Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS 13.0). All continuous data are presented as mean ± standard deviation (SD) or if the data showed no normal distribution, as median and range. Dichotomous data were presented as a number (n) or in percent (%). Univariate, unadjusted analyses were performed with the independent samples t-test, chi-square test, Fisher's exact test for frequencies at or below 5, and the Wilcoxon's rank sum test. Pearson's correlation coefficient was calculated and multivariate analysis was used to evaluate the presence of associated variables. Significance was defined at the 0.05 level.

5. Results

The median in situ period untreated and silver-coated catheters were 138.9 (range, 1–1,845) and 115.0 (range, 4–1,348) days, respectively, ($P = 0.653$). Calculating the in situ times after classification for different age groups, it will be overt,

Table 2: Indications for the insertion of large-bore catheters ($n = 159$).

Indications	(n)	%
Renal failure		
Acute kidney injury (AKI)	40	25.2
Clotting fistula	34	21.4
Septicemia (catheter-related)	29	18.2
Abscess (catheter-related)	8	5.0
Bleeding (catheter-related)	4	2.5
Catheter thrombosis and faults in catheter material	23	14.5
Hypercholesterolemia		
LDL-apheresis	10	6.3
Septicemia	2	1.24
Plasmapheresis		
Different indications	6	3.8
Removal by patient	1	0.62
Carcinoma		
Removal by patient	2	1.24

Table 3: Microbiological examinations of 105 untreated and 54 surface-treated catheters.

Microorganisms	Untreated (n)	%	Treated (n)	%	P value
Negative	47	45	26	48	n.s.
S. aureus	31	29	21	38	n.s.
S. epidermidis	7	7	1	2	n.s.
Pseudomonas	1	1	0	0	n.s.
Enterobacter	1	1	1	2	n.s.
Others	18	17	5	10	n.s.

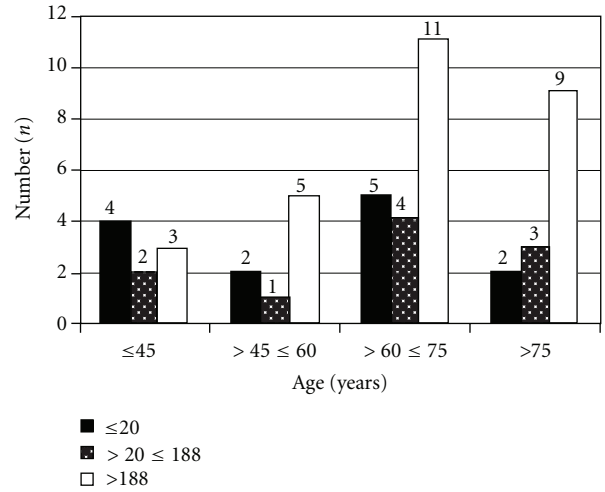

Figure 1: In situ times of treated and untreated catheters in patients after classification and age.

that in patients older than 45 years, in situ times were significantly longer ($P < 0.01$) (Figure 1). Comparing the in situ times of untreated catheters after classification for in situ times, there was a tendency towards longer in situ times for the silver-coated catheters (Figure 2). In the median, catheters were used for 44 (range, 1–670) treatment sessions. Untreated catheters were used for 51 (range, 1–625) treatments, silver-coated catheters for 39.0 (range, 1–670, $P = 0.849$) treatment sessions.

Performing microbiologic examinations, some differences were overt. Of the untreated catheters tips, 55% cultured positive for bacteria. Of the cultures in patients with surface-treated catheters, 52% were positive, not significantly lower. Although untreated catheters showed a lower infection rate with *Staphylococcus aureus*, in treated catheters the infection rate with *Staphylococcus epidermidis*, pseudomonas, and others such as saprophytes were not significantly lower (Table 3).

Performing multivariate analysis, there was a strong association between catheters' in situ period (R-square = 0.96), the number of treatment sessions ($\beta = 0.97$, $P < 0.001$), and patients' age ($\beta = 0.095$, $P = 0.002$). There was no association between the in situ time and silver-coated/untreated catheters, results of the bacteriological examination, and patients diagnosis or outcome. Catheter malfunction or fibrin sheath formation as an outcome of both groups was not investigated.

The decrease of the infection rate in surface-treated catheter in the preliminary study from 2001 cannot be seen in this presented study from 1992 to 2007. An explanation could be that all and more available data are now evaluated. The untreated catheters showed a higher positive culture for bacteria of 55% versus 52% to surface-treated catheters, but without significance. The procedure for both studies was the same.

6. Discussion

Catheter-related bacteremia and thrombosis are the most dangerous complications of large-bore catheter aside from

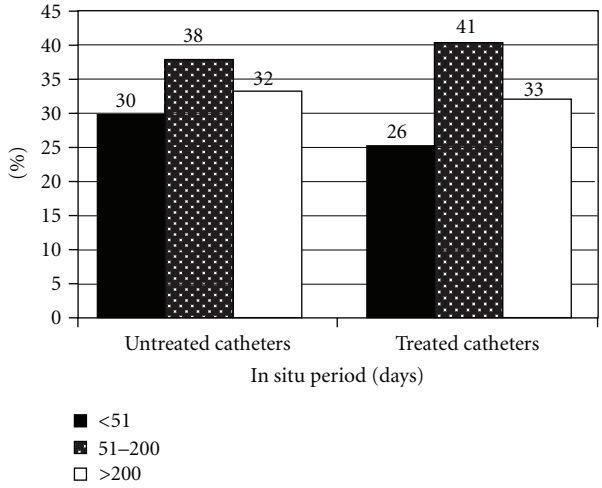

Figure 2: In situ periods of untreated and silver-coated catheters after classification for in situ times.

Table 4: Potential health care cost reductions that could be achieved through the use of surface-treated catheters [45].

Device	Hemodialysis	Average infection (%)
Annual usage (devices)	125,971	
Infection rate (%)	5–20	Rate: 12
Cost ($) of complication (due to infection)	3.517	
Cost ($) of coating	12	
Reduction of infections (%)	10–65	Reduction 40
Market size (1997) ($)	12.6 million	
Price ($) of each device (surface treatment)	120	
Savings ($) per year by using surface-treated devices	17.7 milion	Reduction 40

accidental puncture of an artery. These catheter-related complications are contributing factors to increasing cost medical care. They are responsible for patient discomfort, morbidity, and occasional mortality. In addition to colonization, biocompatibility of a catheter material is an important contributing factor to a successful clinical outcome, particularly in catheters that remain in situ for several weeks or months. Though improved since the use of centrally placed catheters, the incidence of catheter clotting was previously very high.

Infection rates range from 5 to 30% and the most bacteria found is the *Staphylococcus aureus*. These rates do not depend on the route of vascular access [39, 40]. Catheter-related *Staphylococcus aureus* bacteremia is one of the main causes of morbidity and a preventable cause of death in hemodialysis. Patients on dialysis are at a high risk of *Staphylococcus aureus* bacteremia, and they have a four times higher mortality from central venous catheter-related *Staphylococcus aureus* bacteremia than other patients [14, 41, 42]. As such, new surgical techniques, catheter materials, and therapeutic drugs, and sterile handling during the treatments that influence performance and longevity of catheters are of great interest to the medical community [43, 44].

These catheter-related complications are contributing factors to the increasing cost of medical care. They are responsible for patient readmissions and longer hospital stays as well as patients discomfort, morbidity, and occasional mortality. Feldman et al. calculated in 1996, the costs of the morbidity due to catheter infections will soon exceed $1 billion per year [45]. Therefore, he demanded to reduce vascular-access-related morbidity and that strategies must be developed not only to prevent and detect appropriately early synthetic vascular access dysfunction, but to better identify the patients in a whom radial arteriovenous fistula is a viable clinical option. Table 4 shows representative health care cost savings for hemodialysis catheters, given specific infection rates and potential infection rate reductions achieved by treated catheters [35]. The cost analysis was calculated using the literature and the available costs of different companies, which distribute these catheters [46].

To reduce infection rates and thrombogenicity, coated catheters and cuffs were investigated [47–52]. The clinical results of our preliminary investigations showed a significantly reduced infection rate in treated versus untreated catheters, a reduction of more than 75% [28]. With the silver surface treatment, a very smooth metallic surface was obtained, which was responsible for a lower thrombogenicity rate. The activation of coagulation factors at the catheter surfaces was not investigated. Silver ions are bactericidal, therefore, no bacteria growth is possible on the treated catheter surface. The positive association between the in situ time of the catheters and the patients' age maybe because of an alteration of the immune system in elderly patients, especially in hemodialysis patients.

But in our retrospective study of all silver-coated catheters no significant reduction in infection rate, improvement, or life expectancy of silver-coated versus untreated catheters, which were inserted during 1992–2007, was observed. One reason can be that with the IBAD technology, only the outer surface is coated with silver. The postulated penetration of silver ions from the outer to the inner surface cannot be shown with these results. The only outer-surface-treated catheters with silver have no advantage in point of view of reducing infection rate and improvement of patients versus the untreated catheters. The handling of the catheters before, during, and after the extracorporeal treatments cannot prevent the contamination with bacteria, especially the untreated inner side.

Based on these results, new materials must be developed, which should have better biocompatibility to reduce side effects so that they can be left in situ for a long time, because the part of dialysis in patients with vascular problems is increasing in the last decade, because the age of HD patients is permanently growing up. As the requirement for more and more artificial organs and/or organ replacements increases, especially in elderly patients, there will be a definite need for new materials with better biocompatibility and for suitable technologies to solve these infection, thrombosis, and

medical problems to reduce the costs and get a better improvement of patients.

This requirement shows perhaps the new developed catheter material, the microdomain-structured surface (PUR-SMA-coated catheters, Gambro, Germany) [28]. Microdomain surfaces are considered the most biocompatible because they mimic the structure of natural biological surfaces. Microdomain structures are used to match the multiple requirements for improved catheter surfaces, that is reduced thrombogenicity and improved antimicrobial properties. An SMA-modified polyurethane coating consists of hydrophobic and hydrophilic microdomains in range below 50 nm. Up to 50 percent of the SMA molecule is presented to the surface and creates microdomain structures surfaces. If the domains are below a critical dimension of approximately 100 nmm, theoretical considerations indicate that interaction with proteins, blood cells, or even bacteria will be unstable and therefore, not occur as frequently as on non-microdomain structured surfaces.

The new PUR-SMA coating prevents contact of blood components with barium sulfate, possibly leading to leaching as particles or dissolving in the surrounding media. The advantage of the PUR-SMA surface treatment is the coating of the inner and the outer surface in contrast to the ion-beam-based surface treatment technologies in which can be treated only the outer surface of the catheters. The preliminary results with these PUR-SMA-coated catheters showed a good biocompatibility without any blood deposits and a low thrombogenicity and coagulation activity. The microbiological results were low and of those from the Spi-Argent catheters [53].

More new materials must be developed, which should have better biocompatibility to reduce side effects so that they can be left in situ for a long time, because the part of dialysis in patients with vascular problems is increasing in the last decade. As the requirement for more and more artificial organs and/or organ replacements increases, there will be a definite need for new materials with better biocompatibility and for suitable technologies to solve these infection, thrombosis, and medical problems to reduce the costs and get a better improvement of patients. But it appears impossible to create a surface with an absolute "zero" adherence due to thermodynamical reasons and due to the fact that a modified material surface is in vivo rapidly covered by plasma and connective tissue proteins.

Therefore, other concepts of the prevention of implant-associated infections must involve the impregnation of the devices in the inner and outer surface with antibiotics, antimicrobial substances, and/or metals [54]. Another point is to understand the processes leading to the development of catheter-related bacteremia in order to offer effective preventative and therapeutic possibilities [55].

7. Conclusion

In a retrospective study from 1992 to 2007, outer-surface-treated catheters with silver versus untreated catheters in 159 patients, who needed a large-bore catheter, were investigated. The results of a preliminary study from 2001, which showed 75% decline in the infection rate with the surface-treated catheters, cannot be confirmed with the presented study. There was no association between the in situ time and silver-coated/uncoated catheters, results of the bacteriological examination, and patients diagnosis or outcome. One reason maybe that in the surface-treated catheters only the outer surface was coated with silver and another reason is the possibility of contamination by the handling during the extracorporeal treatments. Therefore, new materials and surface treatment technologies are needed to save health care costs for hemoldiaysis catheters, to reduce infection rates and thrombus formations and help to improve the patients outcome.

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Review Article

Minimizing Hemodialysis Catheter Dysfunction: An Ounce of Prevention

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The maintenance of tunneled catheter (TC) patency is critical for the provision of adequate hemodialysis in patients who are TC-dependent. TC dysfunction results in the need for costly and inconvenient interventions, and reduced quality of life. Since the introduction of TCs in the late 1980s, heparin catheter lock has been the standard prophylactic regimen for the prevention of TC dysfunction. More recently, alternative catheter locking agents have emerged, and in some cases have shown to be superior to heparin lock with respect to improving TC patency and reducing TC-associated infections. These include citrate, tissue plasminogen activator, and a novel agent containing sodium citrate, methylene blue, methylparaben, and propylparaben. In addition, prophylaxis using oral anticoagulants/antiplatelet agents, including warfarin, aspirin, ticlodipine, as well as the use of modified heparin-coated catheters have also been studied for the prevention of TC dysfunction with variable results. The use of oral anticoagulants and/or antiplatelet agents as primary or secondary prevention of TC dysfunction must be weighed against their potential adverse effects, and should be individualized for each patient.

1. Introduction

Tunneled catheters (TCs) are frequently used in patients who require both temporary and long-term hemodialysis (HD) but do not have a functioning arteriovenous fistula, graft, or peritoneal dialysis catheter [1]. About 20% of prevalent and 80% of incident HD patients in the United States use a TC and the proportion is even higher in some other countries [2, 3]. TCs have advantages and disadvantages as a vascular access for dialysis [1, 3, 4]. There is no need for a surgical procedure to place a TC or waiting for maturation prior to use. Thus, TCs are immediately available for use, and there are several different options on where to place them in most patients. Unfortunately, TCs have several major problems including frequent TC dysfunction and infections. Patients with TC have more hospitalizations, incur higher costs, and are at increased risk for inadequate dialysis and higher morbidity and mortality [1–6]. The main objective of this paper is to evaluate potential interventions to prevent HD TC dysfunction. According to the NKF Dialysis Outcomes Quality Initiative (KDOQI)-2006, dialysis access dysfunction is defined as an inability to achieve a dialysis blood flow rate of at least 300 mL/min during the first hour of dialysis despite at least one attempt to increase blood flow [1]. Several interventions including instillation of locking solutions and administration of systemic anticoagulation and antiplatelet agents are reviewed. Table 1 is a summary of the most rigorously published clinical trials of interventions to prevent dialysis TC dysfunction [7–27].

Table 1: Studies evaluating therapies for the prevention of HD catheter dysfunction.

	Reference	Study design *N*	Treatment groups			Outcome	Effect	*P*
Catheter locking agents								
Heparin	Thomas, 2007 [7]	*P* *N* = 273	Heparin (1000 U/mL)		Heparin (10 000 U/mL)	Catheter dysfunction (per 1000 HD sessions)	Low H/high H 6.7 versus 7.6	NS
						Thrombolytic therapy (per 1000 HD session)	Low H/high H 26.6 versus 8.2	<0.001
Heparin	Holley, 2007 [8]	*R* *N* = 64	Heparin (1000 U/mL)		Heparin (10 000 U/mL)	Thrombolytic therapy (per 6 months)	Low H/high H 63% versus 31%	<0.001
Citrate (4%)	Buturovic, 1998 [9]	RCT *N* = 30	Citrate 4%	Heparin (1666 U/mL)	Polygeline (3.5%)	Catheter survival (days)	C/H/P 51/23/32	<0.01
Citrate (4%)	Lok, 2007 [10]	*P* *N* = 250	Citrate 4%		Heparin (5000 U/mL)	Thrombolytic rate (per 1000 days)	C/H 3.3 versus 5.5	<0.001
						Catheter removal for poor flow (per 1000 days)	C/H 1.65 versus 2.98	0.042
Citrate (4%)	Grudzinski, 2007 [11]	*R* *N* = 307	Citrate* 4%		Heparin** (10 000 U/mL)	Thrombolytic rate (per 1000 days)	C/H 3.23 versus 4.10	0.07
						Catheter removal for poor flow (per 1000 days)	C/H 1.88 versus 1.81	NS
Citrate (4%)	MacRae, 2008 [12]	RCT *N* = 61	Citrate 4%		Heparin (5000 U/mL)	Thrombolytic therapy (6 months)	C/H 41% versus 45%	NS
Citrate (5%)	Hendrickx, 2001 [13]	RCT *N* = 19	Citrate 5%		Heparin (5000 U/mL)	Thrombolytic therapy (per HD session)	C/H 8% versus 1%	NS
						Aspiration of thrombus (6 months)	C/H 14% versus 7%	<0.001
Citrate (30%)	Stas, 2001 [14]	*P* *N* = 11	Citrate 30%		Heparin (5000 U/mL)	Aspiration of thrombus	C=H	NS
Citrate (30%)	Weijmer, 2005 [15]	RCT *N* = 291	Citrate 30%		Heparin (5000 U/mL)	Thrombolytic Therapy (6 months)	C/H 47% versus 44%	NS
						Catheter removal for poor flow (per 1000 days)	C/H 3.2 versus 3.6	NS
Citrate (47%)	Bayes 1999 [16]	*P* *N* = 10	Citrate, 46.7%		Heparin (5000 U/mL)	Blood flow rate	C=H	NS
Citrate (47%)	Power, 2009 [17]	RCT *N* = 232	Citrate, 46.7%		Heparin (5000 U/mL)	Thrombolytic therapy (per 1000 days)	C/H 8.2 versus 4.3	<0.001

Table 1: Continued.

	Reference	Study design *N*	Treatment groups		Outcome	Effect	*P*
Tissue plasminogen activator	Schenk, 2000 [18]	*P* *N* = 12	r-TPA (1 mg/mL interdialytic lock)	Heparin (1000 U/mL)	Blood flow rate mL/min	TPA/H 237 versus 208	0.001
					Thrombolytic therapy (4 months)	TPA/H 0% versus 20%	—
Tissue plasminogen activator	Gittins, 2007 [19]	*P* *N* = 9	r-TPA (1 mg/mL interdialytic lock)	Heparin (1000 U/mL)	Aspiration of thrombus	H > rTPA: O.R. 2.4	0.001
					Clot volume	H > rTPA: O.R. = 1.9	<0.001
Tissue plasminogen activator	Hemmelgarn, 2011 [20]	RCT *N* = 225	r-TPA (1 mg/mL interdialytic lock midweek heparin 5000 U/Ml in other 2 sessions)	Heparin (5000 U/mL)	Catheter malfunction	rTPA < heparin HR 1.91	0.02
					Catheter-related bacteremia (episodes/1000 catheter days)	rTPA<Heparin 0.40 versus 1.37	0.02
Modified catheters							
Heparin-coated catheters	Clark, 2009 [21]	*R* *N* = 88	Heparin-coated catheter (+ heparin lock 5000 U/mL)	Noncoated catheter (+ heparin lock 5000 U/mL)	Primary patency (at 3 months)	HCC/NCC 82% versus 76%	NS
					Thrombosis rate (per 1000 days)	HCC/NCC 0.8 versus 0.4	NS
Heparin-coated catheters	Jain, 2009 [22]	*R* *N* = 175	Heparin-coated Catheter (+ Hepain lock 5000 U/mL)	Non-coated Catheter (+ Hepain lock 5000 U/mL)	Cumulative catheter survival (at 6 months)	HCC/NCC 48% versus 41%	NS
					Thrombolytic therapy (per 1000 days)	HCC/NCC 1.8 versus 1.8	NS
Oral agents							
Warfarin (mini dose)	Mokrzycki, 2001 [23]	RCT *N* = 85	Warfarin (1 mg)	Placebo	Primary catheter patency (at 1 year)	W/P 58% versus 48%	NS
					Assisted primary catheter patency (at 1 year)	W/P 20% versus, 18%	NS
Warfarin (low intensity)	Wilkieson, 2011 [24]	RCT *N* = 174	Warfarin (INR 1.5–1.9)	Placebo	Primary catheter patency	W/P 46% versus 47%	NS
					Catheter removal for dysfunction	W/P HR = 0.87	NS

Table 1: Continued.

	Reference	Study design *N*	Treatment groups			Outcome	Effect	*P*
Warfarin (low intensity)	Zellweger, 2005 [25]	*P* *N* = 65	Warfarin (INR 1.5–2.0) (high-risk pts)		Controls (low-risk pts)	Primary catheter patency (at 9 months)	Anticoagulation (adequate versus inadequate) 47% versus 8%	0.01
Warfarin (high intensity)	Obialo, 2003 [26]	*P* *N* = 63	Aspirin 325 mg/d	Warfarin (INR 2-3)	Control	Primary catheter patency (number of days)	A/W/C 114/111/68	<0.001
						Catheter survival (at 4 months)	A/W/C 91%/73%/29%	<0.001
Warfarin (medium intensity) and ticlodipine	Coli, 2006 [27]	RCT *N* = 144	Primary prevention Warfarin (INR 1.8–2.5) + ticlodipine 250 mg/day (1°W + T)		Secondary prevention (INR 1.8–2.5) + Ticlodipine 250 mg/day (2°W + T)	Catheter dysfunction (1 year)	1°W + T/2°W + T 12% versus 52%	<0.01
						Catheter dysfunction (events per pt/year)	PWT/RWT 0.16 versus 1.65	<0.001

2. TC Insertion

Several investigators have reviewed the principles of TC insertion [6, 28–30]. TC insertion should be performed with ultrasound guidance to identify the vein and guide the needle puncture [6, 31, 32]. The right internal jugular vein is the preferred site as it offers a more direct route to the right atrium and usually allows a smooth wide curvature to the TC [1, 6, 28, 29]. The use of fluoroscopy is strongly recommended to guide placement of the TC tip in the midatrium [1, 28]. TCs in the left internal jugular vein have a poorer blood flow than in the right internal jugular vein. TC in the subclavian vein can lead to subclavian vein stenosis and prevent future use of the ipsilateral upper extremity for a permanent vascular access [33]. Other sites such as femoral veins are not recommended as sites for TC insertion given the risks of infection and limitations to patient mobility.

3. The Role of Biofilm and Fibrin Sheath Formation in Hemodialysis Catheter Dysfunction

A biofilm is defined as a microbially derived, sessile community, characterized by cells that are attached to a substratum or to each other and are protected by a matrix of extracellular polymeric substances that they have produced [34]. One major complication of biofilms, in addition to infection, is the development of a fibrin sheath, which plays a major role in TC dysfunction.

While the pathophysiology of biofilm production is unclear, it has been hypothesized that biofilm formation occurs after initial contact of free-floating bacteria with a foreign surface, that is, dialysis TC, and can occur as early as 1–14 days after placement [35–40]. The bacteria initially attache and adhere irreversibly to the foreign surface, generate molecular signaling, and proliferate to transform into bacterial microcolonies [35–37]. Subsequently, the bacteria generate a coating of exopolysaccharide from the bacterial products so that their progeny can adhere firmly to the surface covered by a sticky glycocalyx matrix, called the biofilm, which envelopes the community of bacterial microcolonies [35–37]. Biofilms subsequently evolve and mature into a community of bacteria covered by a dense layer of matrix [35–37]. Furthermore, bacteria form biofilms preferentially in very-high-shear environments, similar to conditions that occur within the TC during the dialysis procedure, by enhancing bacterial adhesion [34]. Of note, the mere presence of a biofilm does not necessarily lead to infection and it may grow too slowly to produce clinical symptoms such as fever, chills and bacteremia. However, one important noninfectious complication of biofilm formation is the concurrent development of a fibrin sheath, which plays a major role in TC dysfunction.

Since the pathogenesis of biofilm development to fibrin sheath formation is not well understood, there is debate as to the sequence of fibrin sheath formation, biofilm development, and their interdependency [41]. However, the best evidence supports the hypothesis that a biofilm evolves over days to months into a more complex structure, a fibrin sheath. In addition to fibrin, these sheaths contain multiple other molecular and cellular components, including laminin, fibronectin, collagen, and smooth muscle cells, overlying endothelial cells [35]. These findings demonstrated that the TC-related fibrin sheath is an active response of the components of the vessel wall to the TC (e.g., biofilm formation) and associated thrombosis, as opposed to a mere deposition of acellular material and thrombus [42]. The fibrin sheath initiates at the point of contact between the TC and the vessel wall, advances along the entire length of the TC or device, and can create a one-way valve mechanism, with resultant decrease in the TC flow [42]. Fibrin sheaths play a major role in TC malfunction [35, 43–45]. Although the reported incidence of fibrin sheath can be as high as 100%, this condition may remain subclinical. However, in clinically affected (symptomatic) patients, the fibrin sheath may result in thrombus formation and malfunctioning TCs, in addition to infection [42, 43].

Once biofilms form, they are very resistant to antithrombotic and antimicrobial agents. There have been several recent clinical studies that have focused on investigating prophylactic pharmacologic treatment with antithrombotic and antimicrobial locking solutions and biological characteristics of bacterial TC adherence and biofilm formation showing some promising results [46, 47]. As with the paucity of therapies to prevent biofilm development, there are also few proven therapies to prevent fibrin sheath formation. The current treatment paradigms for management of fibrin sheaths in dysfunctional TCs include thrombolytic therapy, angioplasty with fibrin sheath disruption, and TC exchange [1, 42]. Transfemoral percutaneous fibrin sheath stripping is associated with poor patency. The best management strategy for TC malfunction is its prevention. The most common form of prevention is with the use of anticoagulant locking during the intradialytic period.

4. Heparin Catheter Lock

Heparin lock has been used for decades with relative safety; however, TC dysfunction continues to remain problematic. The rate of TC thrombosis associated with heparin lock in several large series ranges between 4–5.5 episodes/1000 days, and the rate of TC loss due to dysfunction is 1.8–3.6/1000 days [7–12]. The concentration of heparin used as a TC locking solution varies among studies, ranging between 1,000 U/mL and 10,000 U/mL. In a prospective trial comparing a period of high dose (10,000 U/mL) versus a period of low dose (1,000 U/mL) heparin lock, there was no significant difference in TC dysfunction or bleeding complications between heparin lock concentrations, although the need for TPA therapy was 4-fold higher ($P < 0.001$) when low-dose heparin lock was utilized [7]. Similar results were reported in a smaller, retrospective study comparing TPA administration in 2 HD units, one unit using high-dose heparin lock (10,000 U/mL) and the other using low-dose heparin lock (1,000 U/mL) [8]. Low-dose heparin lock was associated with 2-fold increase in TPA administration

($P < 0.001$). Theoretically, the use of high-concentration heparin lock may be advantageous in reducing both TPA-related costs and delay in treatment initiation; however, when Holley and Bailey took into account the differential cost/treatment between low- and high-dose heparin lock ($0.20 versus $2.67), low dose heparin resulted in significant savings despite higher TPA use [8]. Low-dose heparin lock (1000 U/mL) is particularly advantageous in the immediate postinsertion period [21]. In a retrospective analysis comparing heparin lock (5000 U/mL) versus heparin lock (1000 U/mL) or citrate administered immediately after TC insertion, patients receiving high-dose heparin lock (5000 U/mL) had a 9-fold increase in composite bleeding events ($P = 0.01$), and 7.7% experienced a major bleeding event (versus 0% in the low-dose heparin or citrate group) [48]. A significant increase in severe hemorrhage after TC insertion was associated with heparin lock (5,000 U/mL) in a large randomized controlled trial in comparison to citrate 30% lock, (rate of severe hemorrhagic events: heparin 13% versus citrate 4%, $P = 0.005$) [15].

The optimal volume of heparin lock should be individualized according to the patient and catheter characteristics. All dialysis TCs have some degree of locking solution leakage, depending on their design, even when <20% of the TC lock volume is instilled [49]. TC leak begins immediately after instillation and continues over a 30-minute period, and is higher in nontunneled catheters for both periods [50, 51]. The excess leakage volume is 0.16–0.48 mL with <20% TC fill volume, and 0.99–1.43 mL with >20% TC fill volume. TC lock overfill by 20% has been suggested to ensure delivery of heparin to the TC tip and wall and to improve TC patency which may be desirable in TCs with a history of recurrent thrombosis. Overfill by 20%, however, may result in the inadvertent systemic administration of substantial amounts of heparin and may be problematic in the preoperative patient, or in patients with bleeding diatheses [49, 52]. Undesired systemic anticoagulation (increased activated partial thromboplastin time), caused by heparin lock overfill may persist for up to 4 hours [53]. The average rate of major bleeding episodes associated with heparin lock (5,000 U/mL) is approximately 2/1000 TC days [15].

Heparin lock has been traditionally administered in a thrice weekly dosing, with an interdialytic heparin dwell period. The results of a recently published small prospective study reported improved efficacy using a 6-day per week heparin locking regimen. This protocol is not practical in an outpatient HD setting, but may be useful in hospitalized patients with HD TCs. One caveat to this protocol, however, is that more frequent access of the TC lumen has the potential to increase the risk of infectious contamination if not using sterile procedures [54].

5. Trisodium Citrate Lock

In the last decade, trisodium citrate has emerged as an alternative to heparin as a TC locking solution. Seven clinical trials reported citrate lock (4%, 30%, or 46.7%) to be equivalent or superior to heparin lock (5,000–10,000 U/mL) with respect to the thrombolytic therapy rates and number of TCs removed for flow problems (Table 1 [6, 9–12]). In contrast, 2 studies reported unfavorable outcomes with citrate lock. The first was a small study (19 TCs) comparing citrate 5% to heparin (5000 U/mL) [13]. The rate of thrombus aspirated from the TC was doubled with citrate (14% versus 7%, $P < 0.001$); however, the rate of thrombolytic therapy was not significantly different (P = NS). In a larger ($n = 232$) recently published randomized controled trial comparing 46.7% citrate lock versus heparin lock (5,000 U/mL), the need for thrombolytic therapy was greater in the citrate group (8.2 versus 4.3/1000 days, $P < 0.001$) [17]. One advantage of citrate lock is that the bleeding event rate is reported to be significantly lower. In the first study, which included both tunneled ($n = 98$) and nontunneled ($n = 193$) HD catheters in acute and chronic renal failure patients, citrate lock (30%) was associated with a 70% reduction in major bleeding events when compared to heparin lock (5,000 U/mL), ($P = 0.01$) [15]. In the second study of 61 patients with HD TCs, there were significantly fewer systemic bleeding events using 4% citrate lock (7 in 32 patients) versus heparin lock (5,000 U/mL) (21 in 29 patients) ($P = 0.035$) [12].

Citrate and other chelating agents have been shown, in vitro, to inhibit biofilm formation and growth of *Staphylococcus aureus* and *Staphylococcus epidermidis* at concentrations greater than 0.5%. In contrast, heparin stimulated biofilm formation in this study [55]. Clinical trials using 4% citrate lock have not shown to lower TC-related bacteremia (CRB) rates, with the exception of one study [10]. In a prospective, nonrandomized trial, a significant reduction in CRB rates was observed when the TC locking protocol changed from a time period using heparin lock to a period of citrate lock 4% use; however, these findings are confounded by the concurrent initiation of a topical polyantibiotic ointment protocol, applied to the TC exit site, during the study period [10]. In two other studies comparing 4% citrate to heparin, there was no significant difference in CRB rates between locking agents [11, 12]. The ability of citrate to inhibit biofilm formation and bacterial growth is highly concentration dependent. In an in vivo study, Ash et al. observed a reduction in CRB when concentrations of 23% citrate or higher were used as a HD TC locking solution [56]. In a large randomized controlled trial, 30% citrate lock was associated with a significant reduction in the CRB rate (1.1 versus 4.1/1000 TC-days, $P < 0.001$) and fewer admissions for TC-related infections (0.7 versus 2.7 per 1000 TC days) [15]. More recently, a randomized controlled trial by Power et al. using 46.7% citrate lock versus heparin lock (5000 U/mL), failed to show a difference in CRB rates; however, the CRB rate was lower than that reported in other series (0.7/1000 TC days), which may have resulted in underpowering this study [17].

An additional potential advantage of 4% citrate lock is the estimated cost savings calculated in 2 Canadian studies. An 80–85% reduction in costs was calculated using citrate in comparison to heparin [10, 11]. In a 2008 position paper by the American Society of Diagnostic Interventional Nephrologists, the working group recommended that either

heparin lock 1000 U/mL or 4% citrate lock be used in most TCs and that the injected volume not exceed the internal TC volume [57]. There are, however, advantages to citrate lock that make it a more desirable option, including lower bleeding risk, possible reduction in biofilm formation, avoidance of HAAb formation, lack of interference with prothrombin assays, and lower cost. At the present time, 4% citrate is used in the majority of Canadian HD units where it is available as a prefilled syringe (5 mL). (Citralok, MED-XL, Montreal, QC, Canada) In the United States 4% citrate is currently available in larger volume bags (250–500 mls) requiring preparation by the HD unit staff.

5.1. Novel Catheter Locking Solutions. Recently, Maki et al. reported the results of a multicentered, randomized, controlled trial using a novel catheter lock solution containing sodium citrate, methylene blue, methylparaben, and propylparaben (C-MB-P) in comparison to heparin catheter lock for HD TCs. The use of the C-MB-P solution was associated with a lower incidence of TC loss due to patency failure (0 versus 4, $P = 0.04$) and a lower rate of TC-related bacteremia (RR 0.29; CI 0.12–0.70; $P = 0.005$) [58].

6. Thrombolytic Agents as Catheter Locking Solutions

Fibrinolytic agents have been studied as an alternative to heparin for use as a TC locking solution. The potential advantage of these agents is the prevention of TC-related infections and improved TC patency. In a meta-analysis of 5 randomized controlled trials in 991 cancer patients using TCs for chemotherapy, urokinaselock or flush was associated with a significant reduction in TC-related infection (HR 0.77, 95% CI 0.60–0.98, $P = 0.01$) [59]. In vitro, alteplase has been shown to modestly inhibit *Staphylococcus aureus* biofilm formation in concentrations ≥0.5 mg/mL [55]. Prevention of HD TC thrombosis using a tissue plasminogen activator (TPA) interdialytic lock was first evaluated in 2 small clinical studies. In comparison to alteplase lock (1 mg/mL), heparin lock (5000 U/mL) was associated with more frequent thromboses (O.R. 2.4, 95% CI 1.5–4.0; $P = 0.001$). Schenk et al., using a prospective randomized crossover design, evaluated the efficacy of TPA lock versus heparin lock (1000 U/mL) in 12 HD TCs [18]. TPA lock was associated with significantly improved blood flow rates, lower venous pressures, and fewer complications. In contrast, TC thrombosis, requiring fibrinolytic intervention, occurred in 20% of patients during the heparin period. There was no difference in bleeding or infectious events between the groups. The "Pre-CLOT" (Prevention of Catheter Lumen Occlusion with r-TPA versus heparin) randomly assigned 225 patients with a newly inserted TC to heparin (5000 U per milliliter) three times per week or recombinant tissue plasminogen activator (rt-PA) (1 mg in each lumen) substituted for heparin at the midweek session (with heparin used in the other two sessions) [20]. TC malfunction occurred in 40 of the 115 patients assigned to heparin only (34.8%) and 22 of the 110 patients assigned to rt-PA (20.0%) (hazard ratio, 1.91; 95% confidence interval (CI), 1.13 to 3.22; $P = 0.02$). Catheter-related bacteremia occurred in 15 patients (13.0%) assigned to heparin only, as compared with 5 (4.5%) assigned to rt-PA (corresponding to 1.37 and 0.40 episodes per 1000 patient-days in the heparin and rt-PA groups, resp.; $P = 0.02$). The risk of bacteremia from any cause was higher in the heparin group than in the rt-PA group by a factor of 3 (hazard ratio, 3.30; 95% CI, 1.18 to 9.22; $P = 0.02$). The risk of adverse events, including bleeding, was similar in the two groups. The incremental cost of caring for patients with rt-PA as compared with heparin was $1,173 per patient (Canadian dollars).

7. Oral Agents for Prophylaxis to Inhibit Catheter Dysfunction

The use of warfarin alone or in combination with an antiplatelet agent has been evaluated for primary prevention of HD TC dysfunction in 3 randomized controlled trials. The first study was a randomized placebo controlled trial which included 85 HD patients receiving their first TC and compared fixed dose warfarin (1 mg/day) to placebo [23]. This minidose of warfarin was previously shown to be associated with a 75% reduction in TC thrombosis rates in cancer patients [60]. Unfortunately, minidose warfarin was not associated with improvement in primary unassisted patency or assisted TC survival in HD TCs. There was no increase in bleeding events with mini-dose coumadin. Another important finding of this study was that an INR of <1.00 was associated with significantly greater risk of TC loss due to dysfunction (HR = 4.0, 95% C.I. 1.1–14.5; $P = 0.04$) and earlier need for thrombolytic therapy (H.R 2.8, 95% CI 1.3–6.1, $P = 0.009$) [17]. The second study compared low-intensity monitored warfarin (target INR 1.5–1.9) to placebo in HD patients with newly placed TCs [24]. Warfarin was ineffective in preventing TC dysfunction. The third study included 144 newly inserted HD TCs, compared low-intensity warfarin (targeted to an INR of 1.8–2.5) and ticlodipine (250 mg/day) initiated within 12 hours after TC insertion (primary prevention) to a control group (ticlodipine alone) who received warfarin after the first thrombosis (secondary prevention) [27]. There was a significant reduction in TC thrombosis/dysfunction when the combined regimen of warfarin and ticlodipine was used as primary prevention compared to secondary prevention (0.16 versus 1.65 thrombotic events/patient year, $P < 0.001$), improvement in TC flow rates, and fewer TC removals for dysfunction (2.4% versus 17.5%, $P < 0.001$). It should be noted, however, that more patients in the primary prevention group achieved adequate anticoagulation than in the secondary prevention group (92% versus 65%, $P < 0.05$). There were no bleeding events associated with the warfarin/ticlodipine combination.

Warfarin use for secondary prevention was also evaluated by Zellweger et al. in a prospective study of 35 HD patients considered high risk for TC dysfunction given low-intensity warfarin (INR 1.5–2.0) compared to low-risk TC patients [25]. Therapeutic warfarin with adequate anticoagulation was associated with improved dysfunction-free TC survival

at 9 months (47.1%) in comparison to that with inadequate anticoagulation (8.1%) ($P = 0.01$). In an observational study by Obialo et al., 63 HD patients with TCs who were already receiving chronic aspirin ($n = 21$, A, 325 mg/day) or therapeutic warfarin ($n = 11$, W, target INR 2-3) therapy for an underlying cardiovascular indication, and controls ($n = 31$, C) not taking either medication were prospectively monitored [26]. Both aspirin and warfarin were associated with improved primary TC patency at 120 days in comparison controls (C) (A 91%, W 73%, C 29% ($P < 0.001$)). Gastrointestinal bleeding rates were significantly higher in those patients on aspirin and warfarin in comparison to controls (A 24%, W 18%, C 0%, $P < 0.02$), and elderly patients were at highest risk of bleeding (H.R. 1.14, 95% C.I. 1.0–1.3, $P = 0.008$).

In summary, the combination of low-intensity warfarin, to achieve a target INR of 1.5–2.0, with or without ticlodipine, has not been consistently shown to be efficacious in maintaining HD TC patency, particularly when used as primary prevention. Although this therapeutic combination was not associated with an increased bleeding risk in the trial by ColÌ et al., low-intensity warfarin was associated with a significant bleeding risk in HD patients when used for the prevention of TC [24] or arteriovenous graft thrombosis [61]. In this study, by Crowther et al., warfarin was associated with 6 major bleeding events (all patients were also on aspirin), whereas none in the placebo group had major bleeds ($P = 0.03$). Furthermore, warfarin had no effect on arteriovenous graft survival. The use of warfarin should be reserved for high-risk patients with recurrent TC dysfunction, using a low-intensity protocol (target INR of 1.5–2.0).

8. Heparin-Coated Catheters

Heparin-coated HD TCs (HCC) have not been shown to reduce the need for thrombolytic therapy or improve TC survival in 2 retrospective trials [21, 22]. However, in one of the studies, Jain et al. reported a significantly lower TC-associated bacteremia rate in the HCC group (34% HCC versus 60% noncoated HD TCs, $P < 0.001$) [22]. In the second study, Clark et al. found no difference in infection between HCC and noncoated HD TCs; however, the mean observation period was relatively brief; (48–74 days) [21].

9. Conclusion

TCs remain uniquely vital to provide not only short-term renal replacement therapy but also long-term HD to thousands of patients every day. TC malfunction and infections are the two most important complications from TC and are responsible for higher morbidity and mortality in many dialysis patients. Recent studies have elucidated the importance of bacteria in the formation of biofilms and the development of fibrin sheaths that play a major role in the development of TC malfunction and TC-associated infections.

Most efforts to prevent dialysis TC malfunction have focused on the instillation of locking solutions in TCs. Heparin and citrate prevent clot formation in dialysis TCs and are the most commonly used TC lock solutions. Thrombolytic agents have been recently shown to be more effective in reducing TC-related infections and improving TC patency. Systemic administration of oral anticoagulation could be of benefit in selected patients at high risk for recurrent TC dysfunction, but is associated with greater bleeding risk. The role of antiplatelet agents for prevention of TC dysfunction has not been defined.

10. Future Directions

Important areas of future research include development of modified TCs with new designs and thrombosis-resistant properties and novel locking solutions and interventions to prevent or reduce biofilm and fibrin sheath formation. Furthermore, attaining a better understanding of the pathogenesis of biofilm and fibrin sheath development may allow for the development of novel therapies to manage these entities through translational research. Thus, other additional future areas of research could focus on (1) the molecular and genetic basis of biofilm and fibrin sheath development, (2) therapeutic agents that target the biofilm phenotype and community signaling-based agents that prevent the formation, or promote the detachment, of biofilms, and (3) whether a blood-based biomarker could be associated with the conversion from bacteria colonization into infection and fibrin sheath development [35, 47].

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Review Article

Does Regular Surveillance Improve the Long-Term Survival of Arteriovenous Fistulas?

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The rate of arteriovenous fistula (AVF) placement continues to rise and AVF failure is a major complication. The main cause of AVF failure is stenosis leading to thrombosis. Although the detection of early stenosis with preemptive correction prior to thrombosis seems to be a plausible option to prevent access failure, there is much debate, on the basis of studies of surveillance with arteriovenous grafts, as to whether early surveillance actually improves the longevity of AVFs. Evaluating the available information for surveillance, specifically the data for AVF stenosis and survival, is necessary to determine if surveillance is warranted. These trials have shown that vascular access flow (Qa) surveillance is beneficial in revealing subclinical stenosis. Preemptive angioplasty and surgical revision have shown to decrease thrombosis rates. However, at the present time, there is only limited data on whether preemptive treatment equates to improved long-term AVF survival.

1. Introduction

The occurrence of end-stage renal disease (ESRD) and dialysis access placement in the United States continues to increase [1]. Due to the superior long-term patency, lower complications, and decreased mortality rates, arteriovenous fistulas (AVFs) are the access of choice and represent 41.3% of the total hemodialysis accesses in the United States [1, 2]. Even as the rate of fistula placement improves, hemodialysis access failure continues to be a leading cause of hospitalizations and morbidity in the dialysis population [1]. The development of significant stenosis leading to poor flow and thrombosis is a leading cause of AVF revision and failure [2]. Although the detection of early stenosis with preemptive surgical correction or angioplasty prior to thrombosis seems to be a plausible option to prevent access failure, there is much debate as to whether early surveillance actually improves the longevity of AVFs.

There are many noninvasive methods available for the surveillance of stenosis (Table 1). Clinical monitoring is a useful technique that involves physical examination of the access site, excessive bleeding from the AVF venopuncture site, difficult cannulation, or unexplained reduction of urea reduction ratio (URR). Other surveillance methods are available including access recirculation, flow studies, pressure studies and direct visualization by Doppler ultrasonography [3]. These various methods of surveillance have been studied and are all predictive of stenosis [4, 5]. This has led to the guidelines by the National Kidney Foundation Dialysis Outcomes Quality Initiatives (K/DOQI) advocating routine surveillance of AVFs and arteriovenous grafts (AVGs) in dialysis centers [6].

Surveillance of AVGs and AVFs is defined separately by the K/DOQI guidelines and studies have shown different results in these two distinct access groups [6]. In AVGs, there has been considerable debate on the validity of surveillance for thrombosis. Initial observational studies revealed a reduction in graft thrombosis with routine surveillance programs and preemptive angioplasty [7]. However, this was not confirmed by randomized controlled trials, as surveillance and preemptive angioplasty failed to lower thrombosis rates or improve long-term graft survival [7]. Therefore, the recommendation of routine surveillance for AVGs [6] has been questioned [3].

Table 1: Noninvasive methods of surveillance for AV access stenosis.

Clinical monitoring
Access recirculation
Flow studies
Sodium, urea, glucose, differential conductivity, inline dialysance, ultrasound dilution and thermal methods
Pressure studies
Dynamic
Static
Direct visualization
Doppler ultrasonography
Magnetic resonance angiography

Debate also exists surrounding surveillance for AVFs on eventual thrombosis or fistula longevity. Measurement of vascular access flow (Qa) is the recommended method of surveillance for AVFs, and much of this data is based on the observational studies in AVGs [6]. There have been numerous observational studies with historical control groups evaluating the benefit of Qa surveillance in AVFs, and results have been mixed [8–13]. Few of these studies [10–13] showed decreased thrombosis rates, while others [8, 9] showed no improvement [14]. Evaluating the available randomized controlled trials can better assess the question of whether the use of surveillance leads to a significant decrease in the rate of AVF thrombosis and improves long-term survival.

2. Randomized Controlled Trials

To date, there are four randomized trials that evaluated surveillance of AVF for stenosis and two of these evaluated the effect of prophylactic angioplasty on thrombosis rates and long-term outcomes (Table 2). In the most recent study, investigators randomly assigned 137 patients with AVFs to two groups: a group of monthly surveillance with Qa and clinical criteria and a control group with clinical criteria alone [15]. The clinical criteria consisted of an increase in dynamic venous pressures, decrease in blood flow (Qb), excessive bleeding from venopuncture sites or unexplained reduction in URR. The patients in the Qa surveillance arm were referred to angiography if their Qa was <500 mL/min or if it fell by >20% once the access flow was <1,000 mL/min. Each group was referred for any changes in clinical criteria. The primary end point was time to detection of a stenotic lesion that was ≥50%. Although thrombosis rates and AVF longevity were not reported in this study, the patients in the Qa surveillance arm were twice as likely to have stenosis detected compared to the control group.

The more relevant outcome of thrombosis rates were evaluated in a separate trial [16]. This study [16] included 103 patients of whom 68 had AVFs and 35 had AVGs. They were randomized into two major groups: one with monthly surveillance by Qa or static venous pressure and a control group. All patients underwent color flow Doppler ultrasound every 6 months. Patients with Qa < 750 mL/min or static venous pressure ratios ≥0.5 were referred for angiography. Using Doppler ultrasound, AVFs with >50% stenosis, Qa < 600 mL, or greater than 25% decline in Qa were also referred for angiography. If there was evidence of a stenotic lesion ≥50% of the vessel diameter, the patients underwent angioplasty. The primary end point was AVF thrombosis. Access longevity was not studied, but patients with AVFs followed with monthly surveillance by Qa and/or static venous pressure had a lower total thrombosis rate than the control patients (16.8 versus 27.1 per 100 patient years; $P < 0.05$).

These studies revealed that surveillance using Qa detects early stenosis and leads to decreased thrombosis rates, but is there any long-term benefit for early intervention in patients with subclinical stenotic AVFs? This was evaluated in a trial [17] that included 60 patients with a stenotic lesion of >50% by angiogram who were randomized into a treatment group that underwent percutaneous transluminal angioplasty (PTA) or a control group with no intervention. Patients were initially screened with measurements of blood flow (Qb decrease by >30 mL/min on two consecutive hemodialysis sessions), access flow (Qa < 850 mL/min) or urea-based access recirculation. If there was an abnormality, these patients were sent for fistulography, and if >50% stenosis was found, they underwent randomization. All the AVFs with stenotic lesions were considered to be functional if they were providing adequate dialysis. The study end point was thrombosis or surgical revision due to inadequate dialysis. Impressively, the median functional failure-free AVF survival was 84 months (51.8 to 116.2 months) in the PTA group and 21 months (9.8 to 32.2 months) in controls ($P < 0.001$). A total of 6 patients in the PTA group had thrombosis compared to 14 patients in the control group ($P = 0.029$). However, the proportion of patients undergoing elective surgery was comparable. Therefore, early intervention in stenotic AVFs led to decreased time to and rates of thrombosis.

Surveillance of AVFs and early intervention has been shown to be successful in detecting stenosis and preventing thrombosis, but does identifying a significant stenosis lead to an increase in longevity of the access? A follow-up study from the same institution was performed shortly after in 2004 [18]. This study design was similar to the prior study. It included 79 patients with a significantly stenotic lesion who were randomized into treatment (PTA or surgical revision) or control group. The stenotic lesion was identified as in the above study with the only difference now being a Qa < 750 mL/min. One unique variation in the study protocol was that the treatment and control group were further divided into a "functional" (Qa > 350 mL/min) or "failing" (Qa ≤ 350 mL/min) group. The primary end point was primary patency as defined by the interval from stenosis to access failure. The primary patency rates were higher in the treatment groups compared to the control for both functional ($P = 0.021$) and failing subgroups ($P = 0.005$). Access survival rates were significantly higher in the treatment group than the control group ($P = 0.050$). Interestingly, within the treatment group, survival rates

Table 2: Randomized controlled trials of arteriovenous fistula surveillance.

Name	Survey method	Preemptive angioplasty/surgical revison	Control group	Treatment group	Reduce thrombosis	Prolong survival
Polkinghorne et al.[15]	Qa (<550 mL/min) and Clinical criteria versus Clinical criteria alone	No	68	69	*	*
Sands et l. [16]	Qa (<800 mL/min), Static venous pressure and Doppler ultrasound versus Doppler ultrasound alone	No	40	63	Yes	*
Tessitore et al. [17]	Qa (<850 mL/min), Qb, Ru, and Rhd	Yes	30	32	Yes	*
Tessitore et al. [18]	Qa (<750 mL/min), Qb, and Ru	Yes	36	43	Yes	Yes

* Data/values not reported or unavailable.
Qa: vascular access flow, Qb: blood flow, Ru: urea-based access recirculation, and Rhd: ultrasound dilution recirculation.

were also higher in the functional subgroup compared to the failing one ($P = 0.033$). This study showed that early intervention on stenotic AVFs leads to increased longevity. If intervention is delayed until Qa flow is too low, then the AVF was not as salvageable with intervention.

When, then, is the appropriate time to intervene? Should prophylactic correction of subclinical stenosis become universal when a low Qa is detected? The two trials that evaluated preemptive treatment of subclinical stenosis showed decreased thrombosis rates [17, 18]. In both trials, the majority of patients were sent to angiography, because their Qa was <850 mL/min or 750 mL/min, further validating the importance of using a surveillance program. The current guidelines recommend correction only in poorly functioning AVFs that are causing clinical compromise [6]. These trials show that preemptive treatment of stenosis detected by surveillance, prior to clinical consequences, is beneficial and in one trial [18], preemptive treatment was better when the Qa > 350 mL/min. Once the Qa became lower than this threshold, the access was past the point of repair.

One of the major limitations of universally recommending preemptive intervention is that there is a paucity of information on long-term survival, as only one study evaluated this [18]. Even in that study, over a quarter of the treatment group underwent surgical revision as opposed to PTA [19] that may have contributed to these AVFs surviving longer. In fact, one study [16] revealed an increased restenosis rate after PTA.

The key question of whether detection of stenosis and early intervention increases the longevity of AVFs is unfortunately still not answered. Even though thrombosis rates have been lower in all studies, if there is no correlation to longer AVF survival, the beneficial effect may be inconsequential. If there is no benefit of access survival with surveillance, increased studies and interventions only consume more resources and add to cost. The method of repair (PTA or surgical) is also relevant. Although the available information suggests a benefit with surveillance, there needs to be larger, powered randomized trials on the long-term survival of AVF to conclusively settle the issue of the use of surveillance leading to longer AVF survival.

3. Conclusion

Observational studies have shown mixed results for the use of Qa surveillance in preventing AVF thrombosis. Randomized controlled trials, though, have shown that Qa surveillance is beneficial in revealing subclinical stenosis. Preemptive angioplasty and surgical revision have shown to decrease thrombosis rates. Larger, randomized controlled trials need to be done to show whether preemptive treatment equates to improved long-term AVF survival.

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Clinical Study

Relationship between Vessel Diameter and Time to Maturation of Arteriovenous Fistula for Hemodialysis Access

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Introduction. Native arteriovenous fistula (AVF) is the recommended vascular access for HD patients by the Dialysis Outcomes Quality Initiative (DOQI) guidelines. The aim of our study was to determine the correlation between diameter and maturation of vessels in radiocephalic AVF. *Methods.* A prospective cross-sectional study carried out during 2006-2007 on 96 hemodialysis patients from Hasheminejad Kidney Center with non probability selection, all of them with end to side native AVF. *Results*. In this population 62.5% had wrist (distal radial artery) AVF and 37.5% had antecubital (proximal radial artery) AVF. The mean diameter of artery was 2.57 mm (SD = 1.09) and the mean diameter of vein was 2.40 mm (SD = 0.79). The mean of maturation period was 38.60 days (SD = 42.13). There were no relationship between duration of maturation period and diabetes mellitus, sex, age, diameter of vein and artery ($P > 0.05$). Period of maturation showed some correlation with the diameter of vein ($P = 0.04$) in patients with distal radiocephalic fistulae. *Conclusions*. The maturation of fistula shows correlation with vein diameter, but no correlation was seen with diameter of the arteries. There is much discrepancy between times to maturation in various reports. The average time for fistula maturation was 38/6 days in our study.

1. Introduction

Surgery for hemodialysis (HD) access is the most commonly performed vascular surgical operation in the United States, predominantly because of a steady increase in the prevalence of end-stage renal disease (ESRD) [1]. Native arteriovenous fistula (AVF) is the recommended vascular access for HD patients by the Dialysis Outcomes Quality Initiative (DOQI) guidelines.

The current national kidney foundation (DOQI) guidelines endorse this practice and recommend that initial cannulation be delayed for at least four weeks following surgery [2]. A fistula is considered mature when it can achieve a 300 mL/min dialysis blood flow within 1–6 months of its creation. Failure to mature (primary failure) is defined as the inability to meet this goal.

Native AVF composed only 17% of all initial permanent hemodialysis access procedures performed in Medicare patients from 1996 to 1997 [3].

In 2002, the dialysis outcomes and practice patterns study (DOPPS) [2], one of the largest prospective observational studies published on hemodialysis practices and outcome in 309 international dialysis facilities, reported that AVF accounted for 24% of all access procedures in the United States, compared with 80% in Europe [4].

Gold standard for AVF maturation is the clinical definition of a successful maturation. It is an AVF capable of being used for successive occasions of hemodialysis.

Reported AVF maturation rate varies widely, from 30% to 90% [5–7], lower maturation rate may effectively reduce the functional patency of AVF to a level approaching that of prosthetic arteriovenous grafts [8].

Furthermore, AVF requires a longer period of maturation compared with prosthetic arteriovenous grafts. Protracted hemodialysis via percutaneous catheter may be required while awaiting fistula maturation, leading or increasing the risk for infection and compromise central vein patency [9]. The construction of a functional radiocephalic fistula can be challenging and high initial failure rates have been reported in many publications. Estimates of nonmaturation rated vary from just under 10% in brachiocephalic fistula to between 25% and 33% in radiocephalic fistula [10, 11].

The aim of our study was to determine the correlation between diameter and maturation of vessels in radiocephalic AVF.

2. Methods

A prospective cross-sectional study carried out during 2006-2007 on 96 hemodialysis patients from Hasheminejad Kidney Center with nonprobability selection, all of them with end to side native AVF.

A checklist was used for collecting data about each patient's vein and artery diameter and time of fistula maturation according to their hospital records.

Our criteria for AVF maturation was (1) easily palpable superficial vein, (2) vein relatively straight, (3) adequate diameter for easy cannulating needles (3-4 mm), (4) adequate length ($\geq$10 cm, for adequate distance between the cannulating needles), and (5) uniform thrill to palpation and auscultation. We evaluated these criteria by nurses or nephrologists or surgeon.

Data in this study included demographic characteristics such as age, gender, and past medical history, and data about their arterial diameter and time course of maturation were collected from medical records of the enrolled patients and analyzed using the SPSS for windows software, version 16 (SPSS Inc, Chicago, Il, USA). We used descriptive and analytic tests. P value less than 0.05 were considered statistically significant.

3. Results

From the patients of Hasheminejad Kidney Center during 2006-2007, a total of 96 with native AVF with mean age 54.70 (SD = 17.17) years; 58.3% male and 41.7% female enrolled in our study.

In this population, 62.5% had wrist (distal radial artery) AVF, and 37.5% had antecubital (proximal radial artery) AVF. In our study, the mean diameter of artery was 2.57 mm (SD = 1.09), and the mean diameter of vein was 2.40 mm (SD = 0.79). The mean of maturation period was 38.60 days (SD = 42.13).

In antecubital AVF, proximal radial artery diameter was 3.52 mm (SD = 1.08), the mean of vein diameter was 3 mm (SD = 0.69), and maturation period in this patients was 36.05 days (SD = 36.19). In patients with distal radiocephalic fistulae, the mean of artery diameter was 2 mm (SD = 0.6), and the mean of vein diameter was 2.05 mm (SD = 0.62); in this group, the mean of maturation period of AVF was 40.13 days (SD = 45.55).

In our study for radiocephalic fistulae, there were no significant relationships between duration of maturation period and diabetes mellitus, sex, diameter of vein and artery, and age ($P > 0.05$). Meanwhile, in our study, period of maturation showed some correlation with the diameter of vein ($P = 0.04$) in patients with distal radiocephalic fistulae.

4. Discussion

The ideal hemodialysis access fistula should be durable, pose minimal risk for infection, and require few interventions to maintain ongoing functional patency. It is well documented that mature AVF demonstrate superior overall patency, lower revision rate, and cost savings, compared with prosthetic arteriovenous grafts [12].

Despite almost uniform agreement on the need to increase the AVF creation rate, prevalence in the United States has increased only modestly since publication of DOQI clinical practice guideline in 1997. Less than 30% of access sites in the United States are autogenous fistula [3].

Cannulation, 14 days after creation was associated with 2.1-fold increased risk of subsequent fistula failure compared to fistula cannulation more than14 days.

No significant difference in AV fistula failure was seen for fistula cannulation in 15 to 28 days compared with 43 to 48 days [13]. The finding that use of vein with larger stream diameters was associated with greater success rate was consisting with the following studies.

Three studies examined preoperative venous diameter and AVF adequacy for dialysis [6, 14, 15].

Wong et al. [15] found no difference in the average venous diameter at the wrist between failed and adequate AVF but reported that all AVF failed if the diameter was 1.6 mm or less. Mendes et al. [6] reported that 16% of AVF were adequate with a vein diameter of 2 mm or less, compared to 76% of those >2 mm.

There is much discrepancy between time of maturation in various reports. For example, the median time to first fistula cannulation differed between countries, ranging from 28 days in Japan and Italy to 96 and 98 days in transplantation in UK and US, respectively [4]. According to our data, the maturation of fistula is correlated vein diameter with, but no correlation was seen with diameter of the arteries. There is much discrepancy between time of maturation in various reports.

In NKF-K/DOQI guidelines, the average time for fistula maturation is reported to be 1 to 4 months, but in our study, it was 38.6 days. In some other surveys, there was a direct relation between maturation of fistula with both age and gender, but these were not seen in our study. In our data, no correlations were seen between diameter of arteries and age, gender, and diabetes.

Future studies should be performed with more samples to evaluate these factors and also other factors which can decreases the period of fistula maturation.

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Review Article

Surveillance and Monitoring of Dialysis Access

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Vascular access is the lifeline of a hemodialysis patient. Currently arteriovenous fistula and graft are considered the permanent options for vascular access. Monitoring and surveillance of vascular access are an integral part of the care of hemodialysis patient. Although different techniques and methods are available for identifying access dysfunction, the scientific evidence for the optimal methodology is lacking. A small number of randomized controlled trials have been performed evaluating different surveillance techniques. We performed a study of the recent literature published in the PUBMED, to review the scientific evidence on different methodologies currently being used for surveillance and monitoring and their impact on the care of the dialysis access. The limited randomized studies especially involving fistulae and small sample size of the published studies with conflicting results highlight the need for a larger multicentered randomized study with hard clinical end points to evaluate the optimal surveillance strategy for both fistula and graft.

1. Introduction

Vascular access is the lifeline of a hemodialysis patient. The evolution of vascular access has come a long way since the days of Scribner Shunt [1]. Currently arteriovenous fistula (AVF) and arteriovenous graft (AVG) have been recognized as the permanent accesses for a dialysis patient with tunneled cuffed catheter (TCC) being the bridge to obtain a permanent access. Fistula First Breakthrough Initiative with its efforts to highlight the importance of autologous arteriovenous fistula and to educate the nephrologists, vascular surgeons, and patients has yielded a progressive improvement in the number of patients who are currently using the fistula for hemodialysis. In May 2011, the national arteriovenous fistula rate reached 58.6% [2]. Though we have increased the use of the autologous arteriovenous fistula, a number of complications such as thrombosis, infection, stenosis, and access loss have plagued the care of these accesses. Vascular access failure has economic as well as adequacy of dialysis delivery implications. Measures taken for optimization of vascular access consumes about 8% of the Medicare spending on end-stage renal disease (ESRD), yet evidence on how to evaluate and treat the factors which affect the vascular access function is at best suboptimal [3]. Meanwhile, vascular access problems like low blood flow rates and loss of patency are frequently noted in dialysis units. These issues and other complications lead to extended treatment times, underdialysis, and frequent hospitalizations [4].

The Dialysis Outcome Quality Initiative Guidelines (DOQI) published by the National Kidney Foundation has provided a list of techniques which could be applied for monitoring and surveillance of vascular accesses [5]. Center for Medicare and Medicaid Services (CMS) mandates that both monitoring and surveillance be part of the dialysis care being provided to the ESRD patients with an aim of identifying and intervening at an early stage, with the intent of controlling the spiraling costs of access care [6]. Though various techniques are in use for this purpose, no clear consensus has been reached regarding the most optimal surveillance technique which identifies a failing access of all types. We performed a systematic literature review to identify various surveillance techniques and its effects on access function outcomes.

2. Methods and Results

In order to understand the available surveillance techniques and their effects on vascular access outcomes, we performed a PUBMED search through July 2011 of articles in English language, limited to the last 20 years, and available as full

articles. The following MeSH terms used in the search "hemodialysis vascular access" [All Fields] OR "hemodialysis vascular access monitoring" [All Fields] OR "haemodialysis" [All Fields] OR "renal dialysis" [MeSH Terms] OR "renal" [All Fields] AND "dialysis" [All Fields] OR "renal dialysis" [All Fields] OR "hemodialysis" [All Fields] AND "blood vessels" [MeSH Terms] OR "blood" [All Fields] AND "vessels" [All Fields] OR "blood vessels" [All Fields] OR "vascular" [All Fields] AND access [All Fields] AND "epidemiology" [Subheading] OR "epidemiology" [All Fields] OR "surveillance" [All Fields] OR "epidemiology" [MeSH Terms] OR "surveillance" [All Fields] OR transonic [All Fields] AND access [All Fields] AND flow [All Fields] OR differential [All Fields] AND conductivity [All Fields] AND technique [All Fields] OR clinical [All Fields] AND monitoring [All Fields] AND "haemodialysis" [All Fields] OR "renal dialysis" [MeSH Terms] OR "renal" [All Fields] AND "dialysis" [All Fields] OR "renal dialysis" [All Fields] OR "hemodialysis" [All Fields] AND access [All Fields]. This resulted in 4412 publications. We then identified, reviewed, and extracted those studies which evaluated the various surveillance techniques, either comparing different surveillance modalities or were randomized studies. We then focused on those studies in which access outcome was the primary objective. We found only 7 studies with randomization and 17 studies where a cohort of patients was used. All studies were prospective with access outcome as an end point. There were six studies which evaluated only the autologous AVF, eight studies about AVG, and 10 studies where AVF and AVG were combined in the primary analysis. The discussion below summarizes the findings and conclusions from these studies.

3. Discussion

3.1. Monitoring and Surveillance Techniques. Monitoring strategies include physical examination (inspection, palpation, and auscultation) of the vascular access to detect physical signs that suggest the presence of physical pathology [7]. It also includes review of routine laboratory studies regularly obtained in the dialysis unit, dialysis adequacy (urea reduction ratio or Kt/V), and difficulties in cannulation or achieving hemostasis after needle withdrawal, documented recirculation, and other clinical clues. Physical examination of the access by an experienced individual has high sensitivity and specificity [8–10]. Measurement of dynamic venous pressure (DVP) during dialysis is currently considered as a monitoring strategy rather than a surveillance tool. Most of the modern dialysis machine measures the dynamic venous pressure during treatment, but the utility of dynamic venous pressure at flows 150–200 mL/min in detecting stenosis or predicting access thrombosis is very limited [11]. DVP is crucially dependent on the needle gauge and the length of the metallic portion of the dialysis needle. In addition, the length and the thickness of the needle shaft vary among manufacturers. In most dialysis units revalidation of the measurement procedures are usually not done with change of needle type [11, 12].

Surveillance, on the other hand, mandates periodic evaluation of the Vascular Access by means of specifically designed tests that may involve special instrumentation, for which an abnormal test result suggests the presence of pathology. Surveillance tests require additional time and effort from staff and in some circumstances dedicated technicians or nurses to yield consistent results. Access flow measurement [5, 13–15], duplex Doppler ultrasound [16–18], and direct or derived static pressure [19, 20] are the frequently used surveillance tools studied in the literature, flow measurement being the most widely used technique.

Access flow is measured by inducing forced recirculation where the arterial and venous blood lines are reversed. A signal is engendered either by infusion of a substance (saline, glucose), change in ultrafiltration rate (change in hematocrit), or addition of sodium (change in conductance) in the venous return line [14]. Most flow measurements are done at blood pump flows of 200–300 mL/min to avoid the increasing difference between actual blood flow and the blood pump flow at higher prepump pressure. During the interval of measurement, effective dialysis is reduced.

Duplex ultrasound studies (DUSs) can provide an independent accurate measure of blood pump blood flow. DUS measurement can be made in a few minutes producing virtually no effect on Kt/V, but routine use of it may be limited by cost and operator skill. The delta hematocrit method can reduce the effective treatment time for up to 8–10 minutes, whereas the conductivity-based method can take up to 20 minutes or more [15, 21].

Static venous pressure is another well-established technique for detecting physiologically significant stenosis in AVG [19, 22] and is able to reduce graft thrombosis [22, 23]. Its usefulness in predicting thrombosis or access failure in AVF is currently unknown. After initial description of the technique by Besarab et al., measurement of the static intra-access pressure (Pia) has evolved over time. Original method required a pressure transducer between the venous return tubing and the venous needle and connected to a pressure monitor. As intra-access pressure is influenced by mean arterial pressure (MAP), Pia is normalized to MAP as a ratio Pia/MAP. Pia/MAP ratio of 0.5 has a sensitivity of 81% and specificity of 80% in detecting a stenosis >50% by diameter [24]. The same group evolved a computerized method using the dynamic pressure readings taken during any dialysis session and extracting from it the static pressure while factoring out the contributions of chair heights, blood pump flow, and hematocrit [25]. The evolved method achieves the same result in AVF and AVG [19].

The rationale for monitoring and surveillance should be to improve longevity of the vascular access, reduce thrombosis rate and the use of temporary catheters. Understanding the pathophysiological effect of the stenosis is important in interpreting findings of monitoring and surveillance tools. Access dysfunction occurs mostly due to underlying stenosis. Stenosis eventually reduces access flow and alters the pressure profiles and is nearly always a prerequisite for access thrombosis [26, 27]. In reality access flow and pressures vary during and between dialysis sessions. Variation occurs due to cannulation technique, changes in hemodynamic among the dialysis sessions [28–30]. Therefore, a single measurement of either flows or pressure is not helpful in detecting

an evolving stenosis [28]; rather multiple repetitive measurements are required [31–33]. The relationship between blood flow and intra-access pressure in a stenotic access depends on the location of the lesions [34]. One single technique may not be able to detect lesions at various locations that can occur in an access. Frequently multiple lesions are common in the territory of a vascular access, and the physiologic effect produced will depend on whether these are simple lesion at the inflow or outflow of the access or mixed (both inflow and outflow), their time of occurrence, and the progression of the stenosis independently over time or concurrently [31, 35]. In general an outflow stenosis causes an increase in intra-access pressure and overtime decreases access flow [36]. Clinically it can be manifested as prolonged postneedle withdrawal bleeding, aneurismal dilatation, and development of recirculation. This is particularly more evident in AVG than in AVF. In AVF some of the intra-access pressure can be dissipated by the development of collaterals. Determination of the rate of progression of the stenotic lesions is crucial for timing of intervention and to prevent unnecessary intervention. Angioplasty of the subclinical stenosis does not improve access outcome rather could promote stenosis [37]. Therefore, sequential measurement of pressure or flow or both is required to identify accesses at risk which will need intervention. The effect of inflow stenosis differs from outflow lesions. With inflow stenosis intra-access pressure either remains stable or decreases and the access flow may decrease without any change in the prepump pressure setting of the dialysis machine [36]. Surveillance tools based on pressure monitoring may not be able to detect such stenosis. But it can be detected by sequential flow measurement or physical examination [31, 32].

The study conducted by Tessitore et al. [34] indicates that the best test to detect a given stenosis depends on its location. Flow measurement is useful for identifying inflow stenosis, whereas derived static venous pressure is a better tool for outflow lesions. As mentioned before, an access can have multiple lesions involving both inflow and outflow. It is, therefore, imperative to implement a process rather than a single method in detecting stenosis.

Vascular accesses are abandoned in large part due to irreversible thrombosis which in many times is preceded by one or more episodes of reversible thrombosis. This is especially true for AVG. In several observational studies, it was noted that the primary patency of the graft after elective angioplasty (70% to 85%) is superior to angioplasty after thrombectomy (37% to 63%) [38]. This finding favors implementation of a surveillance method to detect graft stenosis prior to thrombosis and preemptive angioplasty to improve graft survival. In search of an optimal surveillance tool, many observational studies have been conducted comparing different surveillance techniques and their ability to identify accesses at risk.

We should keep in mind that an abnormal surveillance data should always be correlated with clinical findings to determine the need for referral for intervention. At present there is little quality assurance for the success of intervention other than anatomical success. At most access center, peri-procedural assessment of intra-access pressure or flow measurements are unavailable to be correlated with prediction of secondary access patency. Several studies, Tessitore et al. [39], Murray et al. [40], and Van der Linden et al. [41], found that higher post intervention Qa was the only variable associated with improved access longevity. Although both DOQI guideline and CMS mandate implementation of surveillance methods, they do not prefer one surveillance technique over another due to lack of sufficient evidence in the literature [5].

3.2. Observational Studies

3.2.1. Intervention before Thrombosis through Surveillance. Four observational studies by May et al. [42], Wang et al. [43], Paulson et al. [44], and McDougal and Agarwal [45] tested the positive predictive value and sensitivity of the access flow in predicting graft thrombosis. In these studies only 25% to 43% of the grafts with baseline flow of <500 to 700 mL/min developed thrombosis over the next 3 months. Neyra et al. tested this hypothesis in a prospective manner. Their study showed only 26% of the AVG with a 25% decrease in access flow thrombosed over the next 3 months [46]. The accuracy of the correlations may be strongly influenced by the accuracy and timing of the access flow measurement. Flow measurements are time dependent and vary during dialysis as well as within dialysis sessions. The study conducted by Polkinghorne et al. [47] measured blood flow multiple times during the dialysis session for 3 consecutive sessions. They noted significant reduction in flow and MAP throughout the dialysis treatment in a progressive manner. Flow can decrease by 10–30.6% during the last hour of dialysis. Similar results were found by Huisman et al. [48] using duplex Doppler ultrasound and Doppler ultrasound studies methods.

Besarab et al. [22] conducted a prospective observational study to test the utility of static venous pressure to detect and correct venous outlet stenosis prior to thrombosis. Observation period was quite long for 7.75 years, and a total of 832 patient-access years of risk was monitored. 65% to 80% of the accesses were prosthetic graft. The result of this study was very promising; static venous pressure/systolic BP was found to provide excellent criteria for angiographic referral and intervention of >50% stenosis using angioplasty or surgical revision. There was marked reduction of the thrombosis rate (70%) and access replacement rate (79%) compared with the historical baseline. Similar observational studies using different surveillance tools also showed promising results. Specifically Sands et al. [49] showed a 6.5-fold reduction in thrombosis rate from 1.25 to 0.19 events per patient year at risk (duplex ultrasound imaging) and Mccarley et al. [50] a 4.4-fold reduction from 0.71 to 0.16 (access flow). Both Hoeben et al. [51] and Glazer et al. [52] achieved a 2-fold reduction in thrombosis events, from 0.32 to 0.17- (using flow methodology).

The utility of combining flow monitoring and static venous pressure was tested by another observational study conducted by Smits et al. [11]; this study fails to show any advantage of combining the 2 surveillance strategies. On the contrary, recent observational study by Plantinga et al. [53] on 363 prospectively followed incident dialysis patients

did not find any advantage of using such surveillance. A similar finding was also observed by Shahin et al. [54].

In the era of automation, Zasuwa et al. have described a novel methodology using an automated noninvasive surveillance algorithm which incorporates the vascular access pressure ratios. They studied the thrombosis rates during a baseline 6-month period to the subsequent 6-month periods when the algorithm was applied. A vascular access pressure ratio of >0.55 was considered significant. No special instruments or clinical staff was required for this automated process which generated a warning list of patients who had abnormal results. After 18 months of implementation, the thrombosis rate decreased from 0.29 to 0.13 events per patient-access-year, an impressive 57% decrease [55].

3.3. Randomized Controlled Trials. Randomized controlled trials are the gold standard for evidence in medicine. Interventional nephrology is a relatively new subspecialty. Very few RCTs have been conducted involving the vascular access. Twelve RCTs have been published; eight of them describing outcomes in AVG and 4 in AVF. There are two additional studies on reanalysis of the published data. Nine studies compared surveillance and intervention versus usual clinical monitoring and intervention in 1363 participants [49, 53, 56–62], including two studies which were prospective cohort studies [53, 61]. Sample size of the individual trials ranged from 51 to 189 with a mean of 151 and a mean duration of 17 months (range of 6–28 months). The other five were trials of patients with abnormal surveillance results who are randomly allocated to intervention (either percutaneous or surgical) or usual clinical monitoring. These 5 trials included 336 participants with a follow-up period of 12–15 months [37, 63–66]. All of the studies have their own limitations concerning sample size, population characteristics, method of surveillance, poor reporting of allocation concealment, blinding, vintage of the access in use, recruitment criteria, and the method of intervention. See Table 1.

Sands et al. [49] studied 103 patients (68 AVF and 35 AVG) in a randomized controlled study to see whether frequent monitoring on a monthly basis rather than 6 monthly evaluations minimize access thrombosis. They also compared the efficacy of the two surveillance techniques, access flow, and static venous pressure. The study populations were randomized into three groups: monthly measurement of access flow (Qa), monthly measurement of static venous pressure (VPS), or no monthly monitoring (control group). Color flow Doppler ultrasound was performed in all patients every 6 months. In the flow group criteria for referral were access flow <800 mL/min in AVG and <600 mL in AVF or a ≥25% decline in flow. In the static pressure monitoring group, static venous pressure ratios >0.5 were referred for angiography and angioplasty of >50% stenosis. Mean follow-up time was 197 days. Their study showed that intervention based on monthly surveillance decreased access thrombosis both in AVF and AVG ($P < 0.01$) compared to no monitoring. In this study, measurement of access flow tends to result in lower thrombosis rates than the static venous pressure. This study has several limitations. In regards to static venous pressure, they used the same intervention criteria for fistula and graft, as we know that fistulae have lower static venous pressure than AVG and remain patent at a low flow state [67]. Moreover, the criteria for intervention were based upon changes in flow rate (≥25% decline in flow rate) but not changes in static pressure readings over time, which may limit the efficacy of pressure monitoring. Lastly accesses in the control group were older than those in the monitoring group (851.7 days versus 542.8 days, $P < 0.05$). This study did not answer whether more frequent monitoring is needed to see beneficial results.

Moist et al. [58] conducted a randomized controlled trial that studied 112 prevalent patients with AV graft comparing monthly Qa plus standard surveillance (dynamic venous pressure and physical examination) to standard surveillance alone. Patients were referred for intervention if flow was <650 mL/min or 20% decrease in flow in the treatment group. This study showed no difference in time to graft loss ($P = 0.890$). In multivariate analysis, only aspirin therapy was associated with an 84% reduction in risk of graft thrombosis (odds ratio 0.14; $P = 0.002$).

The randomized trial published by Ram et al. [62] in 2002 followed 101 patients with AV grafts for up to 24 months. The study population was randomized in three groups: control group, flow (Qa), or stenosis groups. All patients had monthly flow measurement with ultrasound dilution and quarterly percent stenosis by duplex ultrasound. Criteria for referral and preemptive percutaneous transluminal angioplasty (PTA) of >50% stenosis were clinical monitoring for control group, flow <600 mL/min or clinical criteria for flow group, and stenosis >50% or clinical criteria for stenosis group. Flow and stenosis groups had higher preemptive PTA rate (0.34/patient year and 0.65/patient year resp.) compared to the control group (0.22/patient year). The higher PTA rate in the intervention group failed to prolong graft survival (62% in control, 60% in flow, and 64% in stenosis group, $P = 0.89$). There was reduced rate of graft thrombosis seen in the stenosis group (47% in control, 53% flow, and 29% in stenosis group, $P = 0.10$), but it did not reach statistical significance which could have resulted from the small sample size in each group.

Malik et al. [56] conducted a multicenter randomized prospective study to observe the effect of surveillance by classic Doppler ultrasound versus clinical monitoring on patency of AVG. The sample size was 192, mean followup 392 ± 430 days. This study showed longer graft patency by regular Doppler ultrasound screening by early detection of access stenosis and intervention. But the intervention rate was quite high, therefore increasing the cost of care. An overall cost analysis was not performed.

In AVG studies, the surveillance programs have led to increased detection of stenosis and higher angioplasty rates. AVFs are known to have less frequent stenotic rates which may raise the question if surveillance programs lead to increased detection of the stenosis among fistulae. Polkinghorne et al. [59] reported a randomized, double-blind prospective controlled study to evaluate if access flow surveillance of AVF results in increased detection of AVF stenosis. Of a total of 137 patients, 68 patients were assigned to access flow measurements and 67 patients to the control

Table 1: Randomized trials comparing surveillance and intervention versus usual clinical monitoring and intervention.

Name	Total no. of patients	Control	Study patients	Surveillance methods tested	Primary outcome	Result
Mayer et al., 1993 [57]	70	35	35	Ultrasound evaluation of stenosis	Graft survival	Positive
Sands et al., 1999 [49]	103	41	62	Access flow, static venous pressure	Access thrombosis	Positive
Moist et al., 2003 [58]	112	53	59	Access flow, dynamic venous pressure	Access thrombosis, loss	Negative
Ram et al., 2003 [62]	101	34	67	Access flow, stenosis	Access thrombosis, survival	Negative
Roca-Tey et al., 2004 [61]*	159	65	94	Access flow	Access thrombosis	Positive
Malik et al., 2005 [56]	192	92	97	Ultrasound evaluation of stenosis	Cumulative patency	Positive
Plantinga et al., 2006 [53]*	363	185	178	Multiple	Multiple outcomes	Positive
Polkinghorne et al., 2006 [59]	137	67	68	Access flow	>50% stenosis	Negative
Robbin et al., 2006 [60]	126	61	65	Ultrasound evaluation of stenosis	Graft survival	Negative

* Prospective nonrandomized studies.

group. The primary end point was angiographically significant stenosis. Access flow was measured by ultrasound dilution technique (Transonic Inc, USA). The results showed that patients in surveillance group were twice as likely to be detected with an angiographically significant stenosis compared to the controls group (control hazard ratio (HR) confidence interval (CI) (2.27, 95% 0.85–5.98, $P = 0.09$). There was a trend towards earlier detection of stenosis in the surveillance group. When using access flow alone, there was a moderate prediction of (>50%) AVF stenosis (0.78, 95% CI 0.63–0.94, $P < 0.006$). Surveillance does add to earlier recognition of a dysfunctional fistula although how this will translate into hard clinical end points is yet to be determined. This study also highlights that, although there can be difficulty in performing blinded randomized controlled trials in the care of the fistula, it is not impossible.

Robbin et al. [60] studied 126 hemodialysis grafts in prospective randomized clinical trials comparing ultrasound surveillance and clinical monitoring in graft outcomes. 61 were randomized to receive routine clinical monitoring, and 65 were randomized to receive duplex ultrasound surveillance every four months in addition to routine clinical monitoring. The mean followup was about 22 months (21.9 months in ultrasound group and 22.9 months in control group). The ultrasound group had more frequent angioplasty (64% higher) than the control group without any added benefit in terms of graft thrombosis or surgical intervention. The hazard ratio for graft survival in the ultrasound group was 0.93 (95% CI 0.53 to 1.64). A subgroup analysis restricted to patients with virgin grafts revealed no significant difference with respect to time to graft failure ($P = 0.32$) or thrombosis-free survival ($P = 0.72$). One of the major limitations of the study was surveillance frequency which was done every four months; whether more frequent surveillance would improve graft longevity is yet to be determined. Also the spontaneous variation in flow within the access was not assessed. Without such, many accesses may have been prematurely acted upon because of the presence of a lesion which was not hemodynamically significant. Finally, the quality of monitoring which was used in both groups may have been sufficient to detect most stenosis. As stated previously, physical examination of the access by an experienced individual has high sensitivity and specificity [8–10]. Unfortunately such high-skill level is missing in most dialysis centers. See Table 2.

The first randomized control trial that was conducted by Lumsden et al. [37] in 1997 investigated the effect of prophylactic percutaneous transluminal angioplasty (PTA) to prolong the patency of AVG in high-risk predominantly inner-city African-American dialysis patients; almost a third of the population were also diabetic. The grafts studied were not all virgin; the majority had surgical or percutaneous intervention prior to enrolment. The sample size was 64 in 2 dialysis units. Color flow duplex ultrasound was used to detect >50% stenosis, which was subsequently confirmed by angiography. Those who had >50% stenosis were randomized to balloon angioplasty versus observation; follow-up period was 12 months. There was no significant difference in patency in two groups at 6 months and 12 months. Although the demographically study populations were matched, there were more prior interventions and central stenosis in the intervention group than in control group, which may influence the result. Subgroup analysis of the 21 virgin grafts by the same group showed improved long-term patency with surveillance [68].

In 1999, Martin et al. [64] conducted a subset analysis of the above study. In the study population 21 patients had virgin grafts that had never undergone surgery, PTA, or thrombolysis. Among the virgin grafts, eight patients were randomized to the treatment group and 13 to the control group. The virgin groups were well matched as to age, sex, and risk factors. Stenosis of more than 50% were treated with PTA 27 times (average, 3.4 per patient) in the virgin treatment group. This study showed positive result with PTA in the virgin graft, graft patency was significantly increased ($P > 0.0001$), and the graft thrombosis significantly decreased ($P = 0.0151$) in the eight-patient virgin subset when compared with the 24-patient nonvirgin subset of the treatment group. There was a trend towards prolonged graft patency ($P = 0.0349$) and a reduction of thromboses, 0.10 versus 0.44 thromboses per patient-dialysis year, in the virgin-treatment group compared to the virgin-control

Table 2: Randomized trials with abnormal surveillance results and comparing intervention versus observation.

Name	Total no. of patients	Intervention	Conservative	Surveillance methods used	Primary outcome	Result
Lumsden et al., 1997 [37]	64	32	32	Color flow duplex scan	Cumulative patency	Negative
Martin et al., 1999 [64]	21	8	13	Color flow duplex scan	Virgin graft patency	Positive
Dember et al., 2004 [63]	64	32	32	Static venous pressure/systolic blood pressure ratio	Access survival	Negative
Tessitore et al., 2004 [65]	79	43	36	Access flow	Access survival, thrombosis	Positive
Scaffaro et al., 2009 [66]	108	53	58	Duplex scan	Thrombosis	Negative

group. This study has a major limitation due to very small sample size.

In a more recent study by Dember et al. [63] in 2004, 64 high-risk patients with AVG with elevated static venous pressure (≥ 0.4) detected by monthly measurement of static venous pressure/systolic BP ratio (SVPR) were randomized to observation and intervention groups. The intervention group received angiography and repair of the identified stenosis, whereas the observation group had stenosis repair in the event of thrombosis or clinical evidence of access dysfunction. The grafts enrolled in the study were both virgin and nonvirgin grafts with a mean age of 321 days in the intervention group and 350 in the observation group and around one-third had previous intervention across both groups. The follow-up period was 3.5 years. Although the proportion of patients with a thrombotic event was greater in the observation group (72%) than in the intervention group (44%) ($P = 0.04$), time to access abandonment did not differ significantly between the groups (hazard ratio 1.75, 95% CI 0.80–3.82, $P = 0.16$). One of the interesting findings was that access loss from infection was higher in the intervention group than in the observation group. This was noted only in nonvirgin grafts. Most of the infections occurred weeks or months after the procedure excluding the idea of direct bacterial contamination but raises the possibility that angioplasty may predispose to graft infection in the setting of occult bacteremia.

The studies on AVF and AVG have different study end points, and the major limitation has been identifying a hard end point for the interventions performed on dysfunctional access. There has been growing perception that, with increased emphasis on fistula use, the prevalence of catheter use is on the rise. In a study by Scaffaro [66], one of the end points was increased need for central venous catheters when an access fails. This does bring a new end point to the interventions being introduced for dysfunctional access. In this study, 108 patients were randomized to control and intervention groups. The control group received clinical and hemodynamic monitoring on a weekly basis; on detection of dysfunction, patient was referred to a vascular surgeon. In the intervention arm, the patients received, along with clinical and hemodynamic monitoring, a quarterly color flow duplex ultrasound study for access flow followed by angiography when access flow was under 500 mL/min. 58 patients were randomized to the control group and 53 to the intervention group. The end points were the thrombosis of the fistula and need for central venous catheters. The outcomes were evaluated at the end of 11 months. There was significant reduction in the need for central venous catheters (CVCs) in the interventional group (25.9% versus 7.5% for control and interventional group $P = 0.021$). Though there was no significant difference in the thrombosis (24.1% versus 17.0%; $P = 0.487$), the composite end point of AVF thrombosis or CVC need was reduced by the interventional strategy (44.8% versus 20.8%; $P = 0.033$). Considering that the fistula thrombosis rate is lower compared to the AVG, a followup of 11 months may have been shorter and the results may have been different with a longer followup. Since the cost of CVC placement is seldom considered in cost analyses, this study emphasizes the need for a global vascular access economic analysis.

The prospective trials involving arteriovenous fistulae are fewer compared to the AV grafts. Among the few which have been performed, Tessitore et al. [39] conducted probably the first prospective controlled open trial in 2003 to evaluate the effect of prophylactic PTA of stenosis with no known access dysfunction on survival of native virgin forearm radiocephalic AVF. Sixty-two functioning fistulas with stenosis were randomized to intervention versus controlled groups (32 versus 30, resp.). The end points were either fistula thrombosis or surgical revision due to dysfunction, but it is not clear if repeat angioplasty for access dysfunction was an end point or if not how many of the accesses had repeat angioplasty. The result showed fourfold increase in median survival and a 2.87-fold decrease in risk of failure. PTA was also associated with a significant decrease risk of hospitalization, central venous catheterization, and thrombectomy. Subsequently the same group conducted a 5-year randomized controlled trial [65] on 79 mature forearm AVF to evaluate the effect of blood flow surveillance and preemptive repair of stenosis on fistula longevity. Surveillance program included ultrasound dilution measurement of access flow on a quarterly basis, ability to maintain the prescribed blood flow rate, and urea-based access recirculation. Forty-three patients were allocated to preemptive angioplasty and 36 to the control group. Primary patency rate was improved in the intervention group (RR 3.35 with 95% CI 1.44–7.78, $P = 0.003$) and a trend towards improved secondary patency rate (RR 2.66 with 95% CI 0.98–6.85, $P = 0.055$). The study analysis also identified that higher baseline access flow (Qa)

as well as higher postintervention Qa are major determinants of longer failure free interval and AVF useful life. The results suggest that the quality of the intervention is a major factor in improving patency duration.

All the studies conducted so far have small sample size, much lower than what is required to see a significant difference, and the quality of the studies reported was moderate to poor. In 2008 Tonelli et al. [69] conducted a meta-analysis of the 12 RCTs, 8 involving AVG and four trials on AVF. In fistula trials, access blood flow or ultrasound-based screening significantly decreased the access thrombosis (RR 0.47, 95% CI 0.28–0.77; 360 participants; $I^2 = 8\%$) but not the risk of fistula loss (RR 0.65; 95% CI 0.28–1.51; $I^2 = 0\%$) or resource use. In case of grafts there was no decrease in risk of thrombosis (RR 0.94; 95% CI 0.77–1.16; 446 participants; $I^2 = 0\%$) or access loss (RR 1.08; 95% 0.83–1.40; $I^2 = 0\%$). In the same year, another meta-analysis conducted by Casey et al. [70] echoed similar results.

4. Conclusions

A lasting and properly functioning access is crucial to provide adequate dialysis to improve the quality of life of maintenance hemodialysis patients and to reduce the huge access-related cost in this population. We are still in dilemma as to the conflicting results of observational studies and randomized control trials (RCTs) on access surveillance. It should be noted that, in all of the studies described above, the sample size used was small and much smaller than that which would have been derived using a Pearson's events-driven model which increases the sample size 4–6-fold. Sample size of around 500 is needed even for the most simplistic RCT design to see a meaningful difference with adequate power. All available RCTs have sample size less than 200 subjects, and some were as small as 30–50 allocated to one of 2-3 groups. This could be a major reason for failure to show any beneficial effect. Another major limitation could be the lack of standardized tools to assess the success of the intervention of the stenotic lesions in most of the studies. Anatomical success does not translate to improvement of the functional/physiological parameters due to elastic recoil and other factors.

The bigger question is what we are trying to achieve by performing a surveillance program? What are the hard end points? Is angioplasty the right treatment of a dysfunctional fistula? Should we consider prevention of thrombosis without improved longevity a worthy outcome? In spite of all the recent advances and increased procedures, why has the evidence for increased life of a vascular access been eluding us? All these questions lead us to the need of the hour, that is, larger multicenter scientifically sound controlled studies with adequate sample size.

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Clinical Study

The Initial Vascular Access Type Contributes to Inflammation in Incident Hemodialysis Patients

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Background. The contribution of the hemodialysis (HD) vascular access type to inflammation is unclear. *Methods*. We conducted a prospective observational study in an incident HD population. C-reactive protein (CRP), interleukin-6 (IL-6), and interferon-γ-induced protein (IP-10) were measured before and at 6-time points after access placement for 1 year. *Results*. Sixty-four incident HD patients were included (tunneled catheter (TC), $n = 40$, arteriovenous fistula (AVF), $n = 14$, and arteriovenous graft (AVG), $n = 10$). A mixed effects model was performed to adjust for age, sex, race, coronary artery disease, diabetes mellitus, infections, access thrombosis, initiation of HD, and days after access surgery. In comparison to AVFs, the presence of a TC was associated with significantly higher levels of CRP ($P = 0.03$), IL-6 ($P = 0.07$), and IP-10 ($P = 0.03$). The presence of an AVG was associated with increases in CRP ($P = 0.01$) and IP-10 ($P = 0.07$). *Conclusions*. Patients who initiate HD with a TC or an AVG have a heightened state of inflammation, which may contribute to the excess 90-day mortality after HD initiation.

1. Introduction

The most recent 2009 USRDS report observed high first- and second-month death rates after HD initiation [1]. The type of HD vascular access is significantly associated with risk of death. The CHOICE study reported 50% higher mortality rates in patients initiating HD with a TC as compared to patients with an AVF. There was a trend toward higher mortality rates (21% increased) in incident HD patients with an AVG compared to those with an AVF; however this did not achieve statistical significance [2]. A recently published Canadian study in 40,526 incident dialysis patients reported an 80% higher 1-year mortality for HD patients with a TC compared to PD patients and HD patients with an AVF or AVG [3]. Potential reasons for these findings include the higher rate of infection and sepsis associated with TCs, relative to AVFs; however the contribution of the vascular access type, independent of infection, may also be a factor.

The prevalence of chronic inflammation is high (35–65%) in the chronic kidney disease (CKD) and end-stage renal disease (ESRD) populations [4–7]. Inflammation, as assessed by using C-reactive protein (CRP) level, is a strong predictor of all-cause and cardiovascular mortality in ESRD patients [5–9]. Multiple clinical factors and intercurrent clinical events may contribute to inflammation [10–14]. Studies analyzing the relationship between TCs and CRP levels have reported contradictory findings. Although several small studies reported an association between TCs and elevated CRP levels and observed a substantial reduction in CRP after TC removal with change of access to an AVF, these findings were not reproduced in data collected for 1,826 prevalent HD patients enrolled in the Hemodialysis (HEMO) Study [15–20]. In fact, in the HEMO study, higher CRP levels were inversely associated with TC use. The HEMO study investigators did not find a significant change in CRP when access was changed from a TC to an AVF or vice versa [20]. There are limited data on the longitudinal serial CRP values and the relationship to the vascular access type in an incident HD population and on the contribution of noninfected arteriovenous grafts (AVG) to inflammation. Furthermore,

limited data exist for other inflammatory cytokines, such as interleukin-6 (IL-6) and interferon-γ-induced protein (IP-10). To investigate the role of the vascular access type on serial inflammatory cytokines we studied a longitudinal cohort of incident HD patients.

2. Subjects and Methods

This is a prospective, observational study in a cohort of pre-HD patients. This study was approved by the Committee of Clinical Investigation at Montefiore Medical Center, (Protocol number 06-07-336). Patients with Stage-4 and -5 chronic kidney diseases (CKD) receiving their initial HD vascular access insertion were invited to participate. Patients were recruited from 2 adult outpatient renal clinics, 8 private nephrology practices, and the inpatient renal patient population at Montefiore Medical Center, Bronx, NY. Exclusion criteria included the presence of an active inflammatory state: infection, malignancy, connective tissue disease, HIV infection, organ transplant recipient, and current use of immune modulating agents. The type of vascular access to be inserted was determined by the patient's physician. Patient data that were recorded included age, race, sex, etiology of CKD, body surface area, active tobacco use, diabetes mellitus (DM), and a history of atherosclerotic diseases including cardiovascular disease, myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease (PVD), and cerebral vascular accident (CVA). A subjective global assessment (SGA) was calculated for each patient at time of entry into the study [21]. The conventional SGA is a three-tiered, semi-quantitative scoring system based on the history and physical examination and is commonly used in nephrology to quantify the degree of malnutrition. All medications at time of randomization were documented and include the use of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), aspirin (ASA), nonsteroidal anti-inflammatory agents (NSAID), erythropoiesis-stimulating agents (ESA), vitamin D supplements, beta-blockers, insulin, and the cholesterol-lowering statins. The date of HD initiation, access thrombosis, interventional procedures, and access survival were noted. Clinical events were recorded, including infections, hospitalizations, and patient death.

Blood samples were drawn at baseline (within 1 month prior to access surgery), then postsurgery on days 7, 30, 90, 180, 270, 365. In patients who initiated HD, samples were drawn pre-HD. Samples were immediately centrifuged (3000 rpm for 10 minutes) and stored at -70 degrees. All cytokine assays were performed at Vanderbilt University Medical Center using cytometric bead array (Becton DickinsonTM, San Diego, Calif). The detection limits were as follows: CRP, 0.124 mg/mL; IL-6, <2 pg/mL; IP-10, 2.7 pg/mL. The intra-assay coefficient of variation (CV) for CRP was 6%, IL-6 was 7.7%, and for IP-10 was 6.2%.

3. Statistical Analysis

Baseline laboratory data are presented as mean ± S.D, and all cytokine values are presented as the median and interquartile range (25th to 75th percentile). Univariate analyses were performed using ANOVA (with Bonferroni correction) or Chi-square analyses where appropriate. All cytokine values were analyzed using nonparametric statistical testing, namely, the Kruskal-Wallis test. Patients who receive two concomitant vascular accesses initially (TC/AVF, or TC/AVG) were included in the TC group for all tables, figures, and analyses. Significance was determined at $P = 0.05$ (2-tailed).

Multivariate analyses for repeated measures were performed using mixed effects models, with CRP, IL-6, and IP-10 as the dependent variables, and all were log transformed. Covariates that were included in the model (selected a priori)

Table 1: Patient demographic data. All cytokine values (CRP, IL-6 and IP-10) are reported as the median, and all other lab data are presented as the means ± S.D. Patients who received both a TC and an AVF or AVG concomitantly were included in the TC group. SGA: subjective global assessment, BMI: body mass index; DM: diabetes mellitus; HTN: hypertension; CHF: congestive heart failure; MI: myocardial infarction; CVA: cerebral vascular accident; PVD: peripheral vascular disease; ESRD: end stage renal disease; GN: glomerulonephritis; PCKD: polycystic kidney disease.

	TC	AVF	AVG	*P* value
N	40	14	10	
Age in years	60	55	71	0.01
	(±12)	(±11)	(±12)	
Female sex	68%	14%	80%	0.005
Race/ethnicity				
Black	46%	36%	70%	ns
Hispanic	37%	57%	20%	
Caucasian	12%	0	0	
Other	5%	7%	10%	
Co-morbid Diseases				
HTN	96%	100%	100%	ns
DM	64%	50%	100%	ns
CHF	40%	29%	40%	ns
MI	12%	29%	20%	ns
CVA	20%	7%	30%	ns
PVD	16%	0	10%	ns
Hyperlipidemia	56%	64%	90%	ns
BMI	28.0	28.6	31.0	ns
	(±8.8)	(±12.1)	(±6.5)	
SGA score				ns
Low	28%	29%	0	
Medium	36%	57%	60%	
High	36%	14%	40%	
Etiology of ESRD				ns
DM	44%	36%	70%	
HTN	12%	29%	30%	
GN	0%	14%	0	
PCKD	8%	7%	0	
Other	29%	14%	0	
Past malignancy	4%	7%	20%	ns
Tobacco use				ns
Current	4%	14%	0	
Former	32%	21%	10%	

Table 2: Baseline laboratory data. All values are presented as the means ± S.D. eGFR: estimated glomerular filtration rate; PTH: parathyroid hormone; Hgb: hemoglobin, LDL: low-density lipoprotein.

	TC	AVF	AVG	*P* value
CRP (median, mg/L)	7.2	1.3	13.9	0.035
CRP >5 mg/L (%)	54%	23%	75%	0.04
IL-6 (median, pg/mL)	16.5	11.4	12.2	0.06
IP-10 (median, pg/mL)	222	148	289	ns
GFR (mL/min)	10 (±7)	14 (±6)	11 (±4)	ns
Albumin (g/dL)	3.5 (±0.5)	3.7 (±0.5)	3.3 (±0.6)	ns
Phosphorous (mg/dL)	6.1 (±1.9)	5.1 (±1.2)	5.6 (±1.4)	ns
Calcium (mg/dL)	8.0 (±1.3)	8.5 (−0.7)	8.7 (±0.7)	ns
PTH (pg/mL)	710 (±990)	358 (±283)	256 (±134)	ns
Hgb (g/dL)	9.1 (±1.5)	10.4 (±1.0)	10.1 (±2.0)	0.009
Ferritin (ng/mL)	328 (±325)	250 (±250)	255 (±225)	ns
Total cholesterol (mg/dL)	180 (±56)	161 (±67)	184 (±39)	ns
LDL cholesterol (mg/dL)	104 (±47)	85 (±51)	94 (±26)	ns
Hepatitis C Ab	13%	14%	10%	ns

Table 3: Medications upon study entry. ASA: aspirin; ACEI/ARB: angiotensin converting enzyme inhibitor or angiotensin receptor blocker; ESA: erythropoietin stimulating agent.

	TC	AVF	AVG	*P* value
Statin	55%	50%	70%	ns
ASA	28%	64%	70%	0.009
Beta-blocker	70%	79%	80%	ns
Insulin	48%	43%	80%	ns
Oral hypoglycemic	35%	0	20%	0.03
Phosphate binder	33%	21%	30%	ns
Vitamin D	43%	43%	50%	ns
ACEI/ARB	28%	50%	60%	ns
ESA	38%	29%	90%	0.004

were age, sex, race, vascular access type, HD initiation, infection, vascular access thrombosis, cardiovascular disease, DM, and time period after vascular access surgery. Patients who had a TC and a second arteriovenous access (arteriovenous fistula [AVF] or graft [AVG]) were classified as being in the TC group for the mixed effects models. A sensitivity analysis was performed to compare the effect of a TC alone versus an AVF or AVG on inflammation (CRP, IL-6, IP-10).

4. Results

The study period was from August 2006 until April 2008. Of the 79 patients who initially consented to participate in the study, 14 patients did not show up for access surgery, and 1 patient withdrew from the study 1 week after access surgery. The mean followup for the remaining 64 patients was 10 months (range 0.25–12 months).

The baseline patient demographic data are provided in Table 1. The mean patient age was 61 years, and 52% were women. The racial distribution of the study population was 48% African American, 39% Hispanic, 6% Caucasian, and 6% other race. The incidence of comorbid illnesses was: DM 69%, HTN 98%, CHF 38%, MI 17%, CVA 14%, PVD 11%, hyperlipidemia 67%. There was a history of tobacco use in 28% (active use, 5%). The mean BMI was 29.2. The etiology of ESRD was DM 48%, HTN 17%, unknown 16%, and polycystic kidney disease 6%, representative of the general ESRD population in the United States.

The number of patients in each vascular access group was as follows: AVF, $n = 14$; AVG, $n = 10$; TC, $n = 40$ (24 with a TC only, 11 with concomitant TC and AVF placement, and 5 with both TC and AVG placement). In the AVF group, there was a significantly higher representation of men, and patients were of younger age, relative to the AVG and TC groups. There were no other significant differences in baseline demographics between access groups.

Table 2 provides baseline laboratory data, and Table 3 lists the medications upon study entry. CRP, IL-6, and IP-10 levels were significantly higher at baseline in the patients with a TC or AVG compared to patients with an AVF. None of the other baseline laboratory values differed between the access

Table 4: Mixed-effects model for CRP (log transformation) including all time points throughout the study, ($n = 662$). In an adjusted analysis, CRP levels positively correlated with the presence of a TC or AVG, history of coronary artery disease (CAD), and the time period 7 days after hemodialysis access insertion. There was an inverse correlation of CRP with male sex, and absence of infection. CRP: C-reactive protein, TC: tunneled catheter, AVG: arteriovenous graft, AVF: arteriovenous fistula, DM: diabetes mellitus, CAD: coronary artery disease, HD: hemodialysis. Definitions: CRP: C-reactive protein, TC: tunneled catheter, AVG: arteriovenous graft, AVF: arteriovenous fistula, DM: diabetes mellitus, CAD: coronary artery disease, HD: hemodialysis.

Parameter	Estimate	95% confidence interval		P
		Lower	Upper	
Access type				
AVF	Ref.			
TC	0.26	0.03	0.49	0.03
AVG	0.47	0.14	0.81	0.01
CAD (no)	−0.54	−0.89	−0.19	<0.001
Sex (male)	−0.28	−0.56	−0.01	0.04
Infection (no)	−0.30	−0.55	−0.06	0.02
Age	0.00	−0.01	0.01	0.91
Race				
Hispanic	Ref.			
African American	0.16	−0.11	0.43	0.23
Caucasian	−0.11	−0.65	0.43	0.69
DM (no)	−0.08	−0.36	0.21	0.60
HD (no)	0.01	−0.13	0.15	0.89
Access thrombosis (no)	−0.08	−0.35	0.19	0.57
Number of days after access insertion				
7 days	0.32	0.05	0.60	0.02
30 days	−0.14	−0.40	0.11	0.26
90 days	−0.09	−0.35	0.17	0.50
180 days	−0.19	−0.43	0.06	0.13
270 days	−0.06	−0.27	0.15	0.58
365 days	Ref.			

groups. Patients in the AVG group had the highest use of ASA and ESAs. Seven deaths occurred during the study period. In those 7 patients the initial vascular access and cause of death were as follows: AVF group (1 cardiac), AVG (2 sepsis, 1 cardiac death, 1 pneumonia), TC (1 sepsis, 1 pneumonia).

There were 9 patients whose initial vascular access was a TC with a developing AVF, who subsequently had the TC removed once the AVF was useable for HD. Although the median CRP values declined after TC removal, this did not achieve statistical significance (TC/AVF: CRP 8.35 mg/L ± 15.0, versus AVF alone: 3.16 mg/L ± 1.8, $P = 0.53$). CRP data were available for only 2 patients whose initial vascular access was an AVF who then required a TC (AVF: 13.5 mg/L versus TC/AVF: 7.7 mg/L). (Data were insufficient for analysis.)

5. Multivariate Analyses

Mixed effects models (Tables 4, 5, and 6) were performed for CRP, IL-6, and IP-10, adjusting for the following covariates: access type, coronary artery disease, sex, age, race, HD initiation, diabetes mellitus, infection, access thrombosis, and number of days after access surgery. The adjusted models take into account every cytokine measurement and the corresponding vascular access type for each available period. The presence of a TC was a significant predictor of an elevated CRP ($P = 0.03$) and IP-10 (0.03). IL-6 levels also positively correlated with a TC, although this did not reach statistical significance, ($P = 0.07$). The presence of an AVG also significantly correlated with an elevated CRP ($P = 0.01$) and with IP-10 ($P = 0.07$), although the latter did not reach statistical significance.

Additional predictors of an elevated CRP were a history of CAD ($P < 0.001$), female sex ($P = 0.04$), and the presence of infection ($P = 0.02$). Levels of CRP decrease over time, with the highest value at 7 days after insertion compared to the CRP values at 365 days ($P = 0.02$). IL-6 levels significantly correlated with infection ($P = 0.02$), and IP-10 levels were directly associated with diabetes mellitus (0.02), male sex (0.01), and Hispanic ethnicity (0.04).

To compare the impact of TCs with other types of vascular access on inflammation, we performed a sensitivity analysis in patients with a TC exclusively ($n = 24$) and compared them to the combined group of AVF/AVG ($n = 24$). TCs remained a predictor of a higher CRP level, (estimate = 0.29, $P = 0.055$). There was no significant association with IL-6 and IP 10 levels in the sensitivity analysis.

Table 5: Mixed-effects model for IL-6 (log transformation) including all time points throughout the study ($n = 662$). In an adjusted analysis, IL-6 levels positively correlated with the presence of a TC, although this did not reach statistical significance ($P = 0.07$). There was an inverse correlation of IL-6 with absence of infection. IL-6: interleukin 6, TC: tunneled catheter, AVG: arteriovenous graft, AVF: arteriovenous fistula, DM: diabetes mellitus, CAD: coronary artery disease, HD: hemodialysis

Parameter	Estimate	95% confidence interval		P
		Lower	Upper	
Access type				
AVF	Ref.			
TC	0.15	−0.01	0.32	0.07
AVG	0.12	−0.10	0.35	0.28
CAD (no)	−0.17	−0.38	0.05	0.14
Sex (male)	0.08	−0.08	0.25	0.33
Infection (no)	−0.24	−0.44	−0.04	0.02
Age	0.00	0.00	0.01	0.67
Race				
Hispanic	Ref.			
African American	0.10	−0.06	0.27	0.21
Caucasian	0.02	−0.30	0.34	0.89
DM (no)	−0.08	−0.25	0.08	0.32
HD (no)	−0.01	−0.13	0.10	0.85
Access thrombosis (no)	0.09	−0.09	0.26	0.35
Number of days after access insertion				
7 days	0.05	−0.16	0.27	0.61
30 days	−0.12	−0.33	0.09	0.25
90 days	−0.16	−0.37	0.04	0.12
180 days	−0.24	−0.43	−0.05	0.01
270 days	−0.14	−0.31	0.02	0.09
365 days	Ref.			

6. Discussion

This study is unique in that baseline cytokine values were obtained before first access placement and prior to HD initiation, which permitted assessing the degree of preexisting inflammation for patients in each vascular access group and comparing baseline cytokine values to those obtained at multiple time periods after access insertion. The prospective study design allowed for recording all intercurrent events, which were included in the adjusted analysis. Because patients were enrolled upon initial access placement, we were able to exclude the problem of preexisting inflammation related to abandoned accesses. Finally, the association of elevated CRP levels after initial AVG insertion adds to the relative paucity of data on AVGs and inflammation in the previously existing literature.

The findings of our study may also shade light on discrepancies between the HEMO and other studies. First, the Hemodialysis study (HEMO) included only patients who were on HD therapy longer than 3 months, whereas our data and others included incident HD patients. [18, 20] We observed, in an adjusted analysis, that CRP levels are significantly elevated only in the first week following access surgery, but, similar to the HEMO study, CRP levels were not elevated at 1 month or other points throughout the following year. Secondly, in the HEMO study, AVFs and AVGs were combined into one "AV access" group for the analysis, which may have obscured differences between the AV access and TC group and differences within the AV access group (AVFs versus AVGs). We observed significantly higher CRP values associated with AVGs, not present with AVFs.

Our data are consistent with those of Goldstein et al. who measured CRP in 73 incident HD patients (50 noninfected TCs and 23 AVFs). The median CRPs at initiation of HD were significantly higher in the TC group (44 mg/L) versus the AVF group (5 mg/L) ($P < 0.001$) [18]. Unfortunately, patients with AVGs were not included in this study. Other criticisms of this study were that only 2 CRP measurements were taken over a 6-month period, other inflammatory markers were not measured, and information about comorbid illnesses was lacking [22]. Snaedal et al. recently reported a strong association of comorbidity and clinical events with inflammation in HD patients [23]. This was a 3-month observational cohort study in prevalent HD patients. Similar to the findings of the current study, these investigators reported that a comorbidity score (including ischemic heart disease) was among those factors that were significantly associated with variations in the CRP. They did not find a significant association between vascular access type and CRP in this prevalent HD population; however as was the case in the HEMO study, AVF and AVGs were combined into the same access group for the analysis.

Table 6: Mixed-effects model for IP-10 (log transformation) including all time points throughout the study ($n = 662$). In an adjusted analysis, IP-10 levels positively correlated with the presence of a TC and AVG, although the latter did reach statistical significance, ($P = 0.07$). IP-10 levels were also significantly associated with male sex. There was an inverse correlation of IP-10 with DM and African American or Caucasian race. IP-10: interferon-γ-induced protein, TC: tunneled catheter, AVG: arteriovenous graft, AVF: arteriovenous fistula, DM: diabetes mellitus, CAD: coronary artery disease, HD: hemodialysis

Parameter	Estimate	95% Confidence Interval		P
		Lower	Upper	
Access type				
AVF	Ref.			
TC	0.26	0.03	0.49	0.03
AVG	0.30	−0.03	0.63	0.07
CAD (no)	0.17	−0.24	0.58	0.41
Sex (male)	0.43	0.12	0.74	0.01
Age	0.000	−0.01	0.01	0.65
Race				
Hispanic	Ref.			
African American	−0.30	−0.60	0.01	0.01
Caucasian	−0.64	−1.25	−0.04	0.04
DM (no)	−0.38	−0.70	−0.05	0.02
Infection (no)	−0.14	−0.38	0.10	0.27
Access thrombosis (no)	0.10	−0.09	0.29	0.31
Number of days after access insertion				
7 days	0.08	−0.17	0.34	0.52
30 days	0.06	−0.19	0.32	0.64
90 days	0.02	−0.22	0.26	0.85
180 days	−0.10	−0.29	0.09	0.31
270 days	−0.05	−0.21	0.11	0.51
365 days	Ref.			

There was a significant direct association between female sex and elevated CRP values in the present study, which was observed in a multivariate model adjusting for differences in vascular access type. This is in contradistinction to the findings reported by Snaedal et al. in which female sex was associated with lower CRP values, also a multivariate model [23]. A third study by Goldstein et al. reported that CRP values did not differ between men and women [18]. The relationship between gender and CRP levels is unclear and requires further investigation.

Snaedel et al. reported widely fluctuating CRP values in 68% of patients, indicating that frequent serial CRP measurements are superior to a single measurement [23]. These authors also studied other inflammatory cytokines, including plasma tumor necrosis factor-α (TNF-α) and interleukin-10 (IL-10), which were not found to be significant predictors of outcome.

A significant association exists between elevated proinflammatory cytokines and the presence of an AVG. We found significantly higher CRP levels associated with the presence of AVGs (estimate = 0.47, $P < 0.001$) and with TCs (estimate = 0.26, $P = 0.03$) relative to AVFs, in an adjusted analysis. These results differ somewhat with those previously reported by Movilli et al. [16] in that in our cohort of incident HD patients CRP was highest in AVG patients. In Movilli's study, which included a cohort of infection-free prevalent HD patients, TCs were associated with the highest CRP values, although both TCs (estimate = 0.88, $P = 0.0001$) and AVGs (estimate = 0.26, $P = 0.043$) were associated with significantly higher CRP levels than AVFs (adjusted analysis) [16]. It is possible that "new" AVGs placed in incident HD patients are associated with a period of peak inflammation which dampens over time as the AVG endothelializes, as was observed in the prevalent HD cohort.

The three-step hierarchy of access-associated inflammation (TC > AVG > AVF) reported in the Movilli study closely mimics the relationship of mortality risk and vascular access type in the CHOICE study [2, 15]. The choices for healthy outcomes in caring for ESRD (CHOICE) study group reported an association of mortality and vascular access type in a cohort of incident HD patients. In this study, the adjusted relative hazard of death was 1.5 (95% CI, 1.0 to 2.2) in patients using a TC and 1.2 (95% CI, 0.8 to 1.8) in those with an AVG, relative to patients with an AVF [2]. A recent study by Perl et al. also reported an adjusted, time-dependent, relative hazard of death of 1.8 (95% CI, 1.6–1.9) in incident HD patients with a TC compared to PD patients or HD patients with an AVF/AVG [3]. As with the HEMO study, because AVG and AVF are combined, the exclusive effect of AVGs with 1-year mortality is obscured. Short of a randomized controlled trial, one may conclude that it is possible that vascular access-induced inflammation,

independent of comorbidities and intercurrent illnesses, may be contributing to the excess mortality reported in TC and AVG patients in the first months of HD.

We also report that CKD patients whose future initial vascular access is a TC or AVG have preexisting heightened inflammatory state characterized by higher baseline CRP levels, which is present prior to access surgery and HD initiation, relative to those receiving AVFs. This was found despite efforts to exclude patients from the study with preexisting inflammatory states. Patients in the TC and AVG groups were older and consisted of more female and diabetic patients. Furthermore, the subjective global assessment (SGA) scores were higher at baseline in the TC and AVG groups. Patients in the AVG group were also more anemic and had more ESA use before access, possible reflecting a chronic inflammatory state. Elevated baseline CRP values that are present in AVF and TC patients may have influenced the CRP levels observed in these groups during the follow-up period. Ortega et al. studied CRP values in 66 pre-HD patients who were followed up for 1 year [4]. The baseline CRP was 8.3 mg/L, and 35% of patients had an elevated CRP level (>6 mg/L). High CRP levels at baseline were predictive of a constant inflammatory state at followup.

Although an association of TC use and higher ESA requirements was reported by Goldstein et al. in a small cohort ($n = 50$), more recent data reported by the dialysis outcomes and practice patterns study (DOPPS) in November 2010 did not find a significant association between catheter use and ESA dosing in over 2,500 patients, although there was a significant association between higher CRP levels and greater ESA dosing (presented at the American Society of Nephrology Renal Week 2010). Data exploring the association between ESA and TC use is not available in the present study.

Lastly, dialysis vintage has not been shown to correlate with inflammation in two previous studies or in the present study [18, 23].

The major limitations of this study are the small size of the trial and the limited follow-up period of 1 year. The study was not powered using mortality as an outcome. Due to the relative low mortality rate in our cohort, associations between baseline cytokine values and mortality were not observed. We attribute the low mortality due to the predetermined inclusion criteria for this study. In an attempt to isolate the HD access from other potential mediators of inflammation we chose a select patient population, excluding unstable patients and those with active infection, autoimmune diseases, use of immune modulating medications, and malignancy. A large study in an incident pre-HD population, with a longer follow-up period, is needed to better elucidate relationships between the contribution of individual HD vascular access types to noninfectious inflammation and possible excess mortality.

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