Mortality among hemodialysis patients remains unacceptably high in the USA, especially among newly diagnosed end-stage renal disease patients. Chronic inflammation is a risk factor for cardiovascular disease among HD patients. It has been shown that complications of the arteriovenous (AV) access are not just limited to overt infectious complications but they may also pose a threat as a haven for occult infection and can aggravate the chronic inflammatory state. This inflammatory state is characterized by failure to thrive, erythropoietin-resistant anemia, hypoalbuminemia, elevated plasma C-reactive protein levels, which are well-known risk factors for increased morbidity and mortality on dialysis. In this issue, Wasse et al. presents a paper that demonstrates in a large cohort that failed AV grafts are associated with increased chronic inflammatory markers. They have provided a

Correspondence and offprint requests to: Juan Carlos Ayus; E-mail: carlosayus@yahoo.com

ABSTRACT

Mortality among hemodialysis patients remains unacceptably high in the USA, especially among newly diagnosed end-stage renal disease patients. Chronic inflammation is a risk factor for cardiovascular disease among HD patients. It has been shown that complications of the arteriovenous (AV) access are not just limited to overt infectious complications but they may also pose a threat as a haven for occult infection and can aggravate the chronic inflammatory state. This inflammatory state is characterized by failure to thrive, erythropoietin-resistant anemia, hypoalbuminemia, elevated plasma C-reactive protein levels, which are well-known risk factors for increased morbidity and mortality on dialysis. In this issue, Wasse et al. presents a paper that demonstrates in a large cohort that failed AV grafts are associated with increased chronic inflammatory markers. They have provided a

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Steven G. Achinger¹
and Juan Carlos Ayus²,³

Correspondence and offprint requests to: Juan Carlos Ayus; E-mail: carlosayus@yahoo.com

¹Department of Nephrology, Watson Clinic, LLP – Lakeland, FL, USA,
²Renal Consultants of Houston, Houston, TX, USA and
³Nephrology and Medicine, Hospital Italiano, Buenos Aires, Argentina
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mechanistic insight into the causes of the chronic inflammatory state among dialysis patients. Along this line, it has also been demonstrated that failed renal allografts are also harbors of a chronic inflammatory state and that the removal of a failed renal allograft will lead to resolution of both overt inflammation and subclinical inflammatory states. This suggests that in select dialysis patients the surgical removal of foci of chronic inflammation can have an impact on the overall inflammatory state and perhaps survival.

Chronic inflammation is a risk factor for cardiovascular disease in both the general population and in the dialysis population; however, there are key differences between these groups and a specific approach for inflammation in the dialysis population is warranted. Chronic inflammation among dialysis patients is a complex syndrome, the pathogenetic mechanisms of which are closely intertwined with the protein energy malnutrition leading to the recognition of the so-called malnutrition–inflammation complex syndrome [1]. Protein malnutrition begins early in chronic renal failure [2, 3] and has many causes that are beyond the scope of this review. Relevant to our topic is the acute phase reaction, which has some biochemical similarities (e.g. hypoalbuminemia) to protein malnutrition but is a physiologic response to acute infections, trauma or toxic injuries. Acute phase reactions are characterized by elevated pro-inflammatory cytokines and markers such as C-reactive protein, ferritin and interleukin-6 [4]. When there is a persistent inflammatory state, a pathophysiologic condition develops that can lead to anorexia, muscle protein depletion, fat depletion and possibly atherosclerosis [5]. Chronic inflammation is very common among dialysis patients and contributes to the excess cardiovascular morbidity and mortality among hemodialysis (HD) patients. Causes of chronic inflammation in HD patients have been traditionally listed as many, including oxidative stress, carbonyl stress, depleted anti-oxidants, foreign body exposure (dialysis grafts and catheters) and comorbid diseases (e.g. human immunodeficiency virus infection, systemic lupus erythematosus, diabetes mellitus, advanced age) [1, 6, 7]. There are many factors associated with chronic inflammation among dialysis patients, including cardiovascular disease and protein energy malnutrition. The paper by Wasse et al. focuses on the association of vascular access type and chronic inflammation. The vascular access type is well known to have a significant impact on the dialysis survival among HD patients [8–10] and may even explain some observed differences in the mortality risk between dialysis modalities [11]. Our group has focused on reversible causes of chronic inflammation, including the presence of occult infection of arteriovenous (AV) grafts and failed renal transplants [12–15].

The HD access is a common source of complications for HD patients, as infectious complications of the dialysis access cause a staggering disease burden in this population. The risk of death from sepsis has been reported to be 100- to 300-fold above that of the general population. Central venous catheters and AV grafts are frequent sources of bacteremia and local infection [16]. The HD access is frequently implicated as the source of sepsis in the HD population and is often associated with devastating metastatic complications such as endocarditis, epidural abscesses, septic emboli and osteomyelitis. While these serious infectious complications of the dialysis access contribute to the excess mortality of dialysis patients in an unambiguous manner, our group has shown that the complications of the AV access are not just limited to overt infectious complications but that the AV access may pose an equally ominous threat as a safe haven for occult infection and can aggravate the chronic inflammatory state which is a risk factor for cardiovascular death among dialysis patients [12].

HD catheters are an obvious source of overt infection, although, even without known infection, it has recently been shown that HD catheters contribute to chronic inflammation. The removal of a non-infected, tunneled dialysis catheter and the use of an AV fistula as the permanent dialysis access is associated with a reduction in inflammatory markers [7]. This association with inflammation undoubtedly plays a role in the increased risk of death associated with the use of a dialysis catheter.

AV grafts have been over-utilized in the USA for two decades following their introduction. Initially proposed as an alternative when an AV fistula was not technically feasible, AV graft utilization increased steadily in the USA for a multitude of factors, at times eclipsing AV fistulae as the predominant permanent dialysis access. Unfortunately, the AV graft is fraught with infectious complications almost at the outset, although the introduction of perioperative antibiotics can reduce this risk [12]. Repeated cannulation, difficult cannulation and peri-graft hematoma can contribute to subsequent infections as the graft ages. The infectious complications do not seem to abate after the graft has been abandoned as the thrombosed lumen of the graft seems to serve as a safe haven for bacterial infection. More ominous, these AV graft infections may be subclinical and typically escape detection and often present with bacteremia or a metastatic infectious complication [12, 17].

Furthermore, we realized that occult infection of the AV graft, beyond being a risk factor for bacteremia, incited a chronic inflammatory state [18]. This inflammatory state is characterized by a constellation of clinical signs and laboratory features, including failure to thrive, erythropoietin-resistant anemia hypoalbuminemia, elevated plasma C-reactive protein levels, which are well-known risk factors for increased morbidity and mortality on dialysis [18–20]. In patients with a chronic inflammatory state, a significant percentage was positive for occult infection and resection of AV grafts with occult infection brought about resolution of the chronic inflammatory state. It was urged that clinicians should have a high index of suspicion of occult infection of AV graft in HD patients exhibiting the clinical syndrome of a chronic inflammatory state. Our group has advised surgical resection of old clotted AV grafts as the treatment of choice for both the occult infection as well as the chronic inflammatory state [12, 16]. It is important to note that failed
AV grafts without any clinical signs of local reaction can be a harbor of bacterial infections and that the diagnosis of an occult infection in the failed AV graft usually requires nuclear medicine abscess localization scanning to identify small areas of abscess formation in the graft.

Subsequently, it was also noted that consequences of occult infection of AV grafts were not limited to patients on HD, but could also be found among patients with kidney transplants [21]. We presented various untoward complications due to occult infection of old clotted AV graft in kidney transplant recipients, ranging from local infection around the AV graft to recurrent bacterial endocarditis and subsequent death. One of the patients exhibited anemia and hypoalbuminemia, and resection of the AV graft led to improvement in the hemoglobin level, rise in serum albumin and resolution of the a chronic inflammatory state. We then extended our advice to clinicians urging a high index of suspicion for AV graft infection in kidney transplant patients presenting with bacteremia, fever of unknown origin or evidence of a chronic inflammatory state [21]. Additionally, we advised careful screening of prospective renal transplant recipients for occult infection in old clotted AV grafts prior to transplantation.

In light of the excess mortality seen among HD patients returning to dialysis with failed renal allografts, we proposed that the same could be true of the failed renal allograft: that a failed renal allograft, like a failed AV graft, could lead to chronic inflammation and contribute to the chronic inflammation among dialysis patients. Along this line, it was demonstrated that failed renal allografts are also harbors of a chronic inflammatory state and that the removal of a failed renal allograft will lead to resolution of both overt inflammation and subclinical inflammatory states [13]. We subsequently showed that the removal of a failed renal allograft is associated with a lower risk of all-cause mortality among a large cohort of HD patients [15].

Traditionally, renal allografts are retained following chronic allograft failure, and low-dose immunosuppression is continued and typically weaned off over time. Pathologic examination of a removed renal allograft often shows chronic inflammatory infiltrate in the kidneys even when they have been removed from patients who do not have clinical signs such as fever and graft tenderness [13]. An open question has been how to most effectively manage this type of patients. It has long been noted that mortality is unacceptably high among patients who lose renal allografts and return to dialysis following allograft failure [22]. Furthermore, it is clear that immunosuppressive therapy is an inadequate treatment for the graft intolerance syndrome since transplant nephrectomy is ultimately necessary in a majority of cases of failed transplants [13]. In this context, we have challenged the common practice of leaving failed allografts in situ.

Unlike the heterogeneity of practice patterns among transplant centers, there is very little enthusiasm for the removal of failed, clotted AV grafts. In contrast to failed renal transplant, very little literature is available on the issue of the safety of the retained AV graft. It has generally been accepted that the failed AV graft is a benign pathology and retention of it has little or no long-term consequence and this practice has been essentially unchallenged since the introduction of the AV grafting procedure. In patients with overt infections, most would argue that surgical excision is mandatory and such a move would not be controversial. We have identified subclinical infection in failed AV grafts as a source of recurrent bacteremia and the current paper by Wasse et al. shows in a large cohort that failed AV grafts are a source of chronic inflammation in addition to being a harbor of subclinical inflammatory infections. The potential exists that the presence of the failed AV graft is a risk factor for both infectious and cardiovascular death. In this setting, it is tempting to postulate that the removal of a failed, clotted AV graft reduces mortality due to cardiovascular risk. This would require a prospective study although it is an enticing hypothesis. Wasse et al. have led us one step closer toward re-examining the issue of the failed AV graft, although much work in this area needs to be done before the prophylactic removal is recommended.

As far as amelioration of the chronic inflammatory state is concerned, there are several steps that can be taken in order to reduce chronic inflammation. It has been shown that the removal of HD catheters and beginning the use of an AV fistula will lead to a reduction in chronic inflammatory markers. The removal of the failed renal allograft, as noted previously, reduces chronic inflammatory markers and is associated with reduced mortality rates [14, 15]. We have subsequently shown that increasing dialysis intensity through 3-h daily HD is a maneuver that can significantly reduce chronic inflammation [23]. For the patients with a chronic inflammatory state with an emphasis on reversible sites of chronic inflammation, we propose the following approach: silent infection of old, failed AV grafts should be screened for; consider the use of nuclear medicine abscess localization scanning (or other appropriate nuclear medicine study) when the infection is not obvious. Failed renal transplants need also to be considered as a source of chronic inflammation and graft removal should be considered. Finally, the use of 3-h daily dialysis is an option for reducing inflammation when the above considerations are not applicable or not feasible.

This paper demonstrates in a large cohort that failed AV grafts are associated with increased chronic inflammatory markers. Wasse et al. have provided an important mechanistic insight into the causes of the chronic inflammatory state among dialysis patients. Therefore, despite the complexity of the malnutrition/chronic inflammatory state that we see in dialysis, clinicians should pay particular attention to areas where we can make an impact. Previous complacency toward failed renal allografts, old clotted AV grafts and central venous catheters should be replaced with a proactive/preventative approach that involves increased AV fistulae use, avoidance of central venous catheters and active surveillance for old clotted AV grafts and failed renal allografts that are causing inflammatory states.
CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Wasse et al. Accumulation of retained nonfunctional arteriovenous grafts correlates with severity of inflammation in asymptomatic ESRD patients. Nephrol Dial Transplant 2013; 28: 991–997.)

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