Homocysteine, age, gender and vascular access thrombosis in end-stage renal disease patients: retrospective analysis.


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ABSTRACT
Introduction: Within the last decade vascular access for hemodialysis has received considerable attention due to high costs associated with access complication and failure rates [1]. More than 17%-25% of hemodialysis patient hospitalizations in the United State are access related [1-6]. Initial prospective evidence supports an independent association between tHcy levels and access thrombosis [3].

Objectives: The purpose of this study was to determine if significant associations exist between tHcy, age, gender, and vascular access thrombosis in patients with ESRD.

Material and Methods: One hundred and eighty-five (N=185) patients undergoing dialysis were selected as subjects. The experimental group participants were identified as those having one or more vascular access thromboses (VAT) during the previous 16-month period (January 2000 to April 2002) and the control group participants were those with no VAT during the same period. Additional sub-group analyses included gender and age.

Results: The Mann-Whitney U non-parametric t-Test for variance between groups revealed no significant difference in tHcy values between VAT groups (U = 3654.0, p= 0.993). A two-sample t-Test for variance between tHcy and age revealed no significant differences (F-ratio=0.601, p=0.55). A chi-square analysis revealed no significant differences in gender and VAT groups (X2 = 1.59, p = 0.21). A Kolmogorov Smirnov test for normality was calculated for tHcy with a p-value of 0.9118 revealing insufficient evidence that the distribution is not normal. Spearman Rank Correlations were calculated revealing low to moderate associations among variables.

An extremely low effect size (0.04) revealed extremely low effect size differences between the VAT and control group's tHcy level.

Discussion: Study of ESRD patients revealed evidence of recurring VAT as well moderate to high levels of tHcy levels. Due to these recurring VAT's and elevated tHcy levels, a natural area of inquiry is the relationship of VAT and tHcy.

Conclusions: While some studies have demonstrated a relationship between tHcy and VAT, this study found chronically high homocysteine levels in patients with ESRD were not associated with incidence of VAT. There were no significant differences in the number of VAT's across additional variables of age and gender.

INTRODUCTION
Within the last decade vascular access for hemodialysis has received considerable attention primarily due to high costs associated with access complication and failure rates [1]. Maintaining successful hemodialysis services is dependent upon an access to circulation that is reliable and stable [2]. Complications of vascular access such as dysfunction, thrombosis, or infection are major causes of hospitalization [3] with thrombosis being the most common reoccurring problem [2]. More than 17%-25% of hemodialysis patient hospitalizations in the United State are access related [1,2,4-7]. Roy-Chaudhury et al. (2002) suggest hemodialysis vascular access dysfunction is the single most important cause of morbidity in the hemodialysis population and has been identified as a risk factor for mortality [8]. Due to increasing trends toward the use of polytetrafluoroethylene (PTFE) grafts the cost of access morbidity appears to be accelerating [2,4] with $1.3 billion spent each year in the United States to maintain a viable vascular access and control serious morbidity [1,3,6,8-11]. Though pathology in ESRD patients with high tHcy can be established [9], the research findings with vascular access thrombosis (VAT) and homocysteine are equivocal. Moderate and high concentrations of homocysteine in the blood are common in patients with ESRD [11] and have been associated with early-onset VAT in ESRD and other chronic conditions [12-14]. Boushey, Beresford, Omenn, and Motulsky (1995)
identified hyperhomocysteinemia as an independent risk factor for VAT. Investigators have found significantly higher homocysteine levels in patients with recurrent VAT compared with one or more episodes of thrombosis [14]. Total homocysteine levels were higher among those with a history of previous VAT when compared to those who did not have a history of such events. Initial prospective evidence supports an independent association between tHcy levels and the development of hemodialysis access thrombosis [4]. In one study it was demonstrated that a 1 uM/L increase in plasma tHcy was associated with a 4% increase in the risk for access thrombosis [4]. Mallamaci et al. (2002) also reported a strong association between hyperhomocysteinemia and ESRD. Recently, Hojs et al (2002) found no significant differences in tHcy concentrations in patients with recurrent access thrombosis compared with those with one or less episodes of thrombosis. Hojs et al. (2002) also found a higher average tHcy levels in patients with one or less episodes of VAT, but was small and not statistically significant. Shemin et al. (1999) have been unable to replicate retrospective findings stating, "recently there has been conflicting retrospective analyses reported regarding the potential association between total homocysteine levels and hemodialysis VAT" (p. 1095). Manns et al. (1999) found no difference in homocysteine levels between patients that had at least one documented episode, multiple episodes or no episodes of VAT [4]. No significant differences in plasma homocysteine concentrations were found between thrombosis-prone and no thrombosis groups in another recent study [12].

OBJECTIVES
The purpose of this study was to determine if significant associations exist between tHcy, age, gender, previous morbidity and vascular access thrombosis in patients with ESRD.

MATERIAL AND METHODS
One hundred and eighty-five (N=185) patients undergoing dialysis were selected as subjects from four different dialysis clinics to obtain information archived from their respective medical files. All subject identification parameters were removed and each subject was coded to maintain confidentiality. The sample was divided into a thrombosis prone (n=109) and no thrombosis (n=74) group. The thrombosis prone group participants were identified as those having one or more vascular access thromboses (VAT) during the previous 16-month period (January 2000 to April 2002) and the no thrombosis group participants were those with no VAT during the same period. Additional sub-group analyses included gender and age. Homocysteine (mcmol/L) was drawn each quarter (every 12 weeks) in all patients with ESRD during the 16 month period. Medical files revealed VAT with listed dates. Homocysteine and VAT were recorded and matched specifically recurring VAT's. Many patients in this study had one or more VAT's (n=109, 58.9%), which to these recurring VAT's and elevated tHcy levels, a natural area of inquiry is the relationship of VAT and tHcy. The authors hypothesized that high tHcy or hyperhomocysteinemia is associated with VAT and

DISCUSSION
Study of ESRD patients reveal evidence of recurring VAT as well moderate to high levels of tHcy levels. Due to these recurring VAT's and elevated tHcy levels, a natural area of inquiry is the relationship of VAT and tHcy. The authors hypothesized that high tHcy or hyperhomocysteinemia is associated with VAT and specifically recurring VAT's. Many patients in this study had one or more VAT's (n=109, 58.9%), which significantly influenced their ability to undergo dialysis.

Initial prospective evidence has suggested that tHcy is an independent risk factor for VAT [2]. Additional findings in the literature indicate the hyperhomocysteinemia has a strong association with arterial and venous thrombosis [12]. However, the results of the current study indicate that plasma tHcy concentration was not a
valid marker, nor strongly associated with VAT despite literature suggesting that tHcy is atherogenic and thrombogenic [16]. The current findings agree with previous tHcy and VAT literature that found no significant differences in patients' tHcy and VAT [2,6,17].

Vascular access thrombosis may primarily be due to smooth muscle cell hyperplasia [1]. Indications are that tHcy affects mainly the arterial vasculature by damaging the endothelium [29]. Prolonged exposure of endothelial cells to homocysteine impairs production of nitric oxide and endothelium-dependent vasodilation combining with low-density lipoprotein cholesterol to produce arterial intima damage [26]. In this regard, vascular access would not be affected as it is applied to the venous anastomosis as opposed to arterial anastomasis. An early study into homocysteine and cardiovascular disease found arterial pathology with an absence of venous involvement [30]. A recent study suggests that hyperhomocysteinemia is not an independent risk factor for venous thromboembolism [31]. It was speculated that endothelial wall damage through high tHcy levels might result in endothelial-platelet interactions and possible association to VAT. In this case lowering tHcy levels could decrease the incidence of VAT. However, the results of this study do not support these conclusions.

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Previous studies have reported increased number of VAT’s in patients aged 65 and older [4,9] with decreasing rates of VAT for younger patients. Despite previous research, the current study found an extremely low association with age and VAT (0.24) and no significant differences between tHcy and age (F-ratio = 0.601, p = 0.55). The age of the study participants may provide insight into the non-significant results. The average age (SD) of participants was 60.64 (14.64) with average ages (SD) of the thrombosis prone group and no thrombosis group being 61.22 (14.05) and 59.54 (14.5) respectively. The skewed age of the participants in the thrombosis prone and no thrombosis groups makes it difficult to discover any differences.

Gender has been demonstrated to be a risk factor for VAT in at least one study [21] indicating an unexplained VAT probability that is higher in women than men. The current study found no significant differences in the number of VAT’s across gender (X2 = 1.59, p = .207). Additionally, a Spearman Rank Correlation Coefficient revealed a very low association (0.06). Ifudu (1997) found that women were more likely to have a PTFE graft, which has been demonstrated to be a risk factor for VAT.

CONCLUSIONS
While some studies have demonstrated a relationship between tHcy and VAT, this study found chronically high homocysteine levels in patients with ESRD was not associated with an increased incidence of VAT. Additionally, no significant differences in the number of VAT’s across the variables of age, gender, and previous morbidity at time of thrombosis were discovered. The probable arterial endothelial wall damage resulting in part by high tHcy levels does not show an affect on access clotting.

REFERENCES
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