

Original Article

The prevalence and meaning of eosinophilia in renal diseases on a nephrology consultation service

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Abstract

Background. In recent years, we have come to understand that the eosinophil is more than the end point in clearance of parasitic infection or a maladaptive response to asthma and allergic reactions. Since eosinophilia has been reported to be common in renal diseases, we thought that an evaluation of the associations of eosinophilia on a renal consultation service would add some value to the understanding of their role in renal disease.

Methods. This was a prospective cross-sectional study of 1339 consecutive patients referred to the nephrology service after hospitalization who were evaluated for the relationship of the amount of serum eosinophils to their diagnosis, gender, age and the presence of autoimmune disease, cancer, infection, liver disease, pleural effusions, allergies and use of prednisone, beta-blockers or beta agonists, in addition to the total white blood count, urine protein, serum concentration creatinine and phosphorus levels and estimated glomerular filtration rate.

Results. The presence of vascular disease correlated the most strongly with increased eosinophil count (partial correlation coefficient, $r = 0.18$, $P = 0.006$), followed by pleural effusions ($r = 0.17$, $P = 0.001$), while total white cell count ($r = -0.18$, $P = 0.008$) and administration of beta-blockers ($r = -0.13$, $P = 0.047$) demonstrated significant inverse correlations and the presence of autoimmune disease, cancer, allergies, proteinuria and serum phosphorus concentration demonstrated no significant correlation.

Conclusion. There are multiple associations with increased eosinophil counts in patients seen on a nephrology consultant service; however, their presence appears less often in association with allergies or uremia and more often with vascular disease.

Keywords: diagnosis; eosinophil; renal failure; vascular disease; vascular physiology

Introduction

Almost from the time of its first identification [1], the eosinophil has been considered strange and its function de-

bated [2]. In contrast to macrophages and neutrophils, eosinophils are only weakly phagocytic and therefore have been traditionally regarded as terminally differentiated non-replicating effector cells whose main beneficial role is in clearance of parasitic infection through exocytic release of eosinophil granule-derived cytotoxic protein, while also exhibiting a maladaptive role in asthma and allergic reactions. In recent years, however, we have now come to understand that the eosinophil is more than the end point of inflammatory pathways [3], and their complex array of cytokines and chemokines overlap with mediators that govern the immune system such as T cells [4]. As a result, eosinophils are now considered true immunoregulatory cells with roles in antigen presentation, T-cell regulation and polarization, B-cell priming, as well as regulation of dendritic cells, mast cells, basophils and neutrophils [3]. Although renal involvement is rare in hypereosinophilic syndromes [5, 6], eosinophilia, conversely, has been reported to be common in many renal diseases [7–38] (Table 1) and often attributed to uremia or an allergic reaction to dialysis equipment; however, many other causes unrelated to renal disease (Table 1) could be present that might have an effect upon the eosinophilia that is seen in the renal community. We therefore thought that an evaluation of the prevalence and associations of eosinophilia in various diseases on a renal consultation service would have some value in understanding the role of the eosinophil in renal diseases and chose to conduct the following prospective study.

Methods

This was a prospective cross-sectional study, where consecutive patients referred to the nephrology service for consultation from 1 January 2009 through 31 December 2009 who had a differential quantitation of the various cells seen in the total white blood count upon consultation were evaluated. The variables studied for their association with the eosinophil included renal diagnosis, gender, age and the presence of allergies, corticosteroids, myelosuppressive drugs, beta-blockers, interferon, presence of parasites, vascular disease, vasculitis, malignancy, nonsepsis infection, sepsis, cirrhosis, pleural effusions, in addition to serum creatinine, serum phosphorus, estimated glomerular filtration rate (eGFR) (calculated using the original Modification of Diet in Renal Disease study equation where:

Table 1. Known causes for eosinophilia

Etiology	Examples in nonrenal disease	Specific renal causes
Allergies	Asthma, drug reactions, allergic rhinitis, urticaria, atopic dermatitis, eczema	Allergic interstitial nephritis [23]
Parasites	Trichinosis, ascariasis, hookworm, visceral larva migrans, schistosomiasis, filariasis, cysticercosis, pneumocystis	
Nonparasitic infections	Cat scratch fever, brucellosis, tuberculosis, mononucleosis, chlamydial infections, aspergillosis, coccidiomycosis	
Malignancies	Carcinomas, sarcomas, lymphomas, chronic lymphocytic leukemia	Renal carcinoma [32–36]
Vasculitis	Churg–Strauss, systemic lupus erythematosus, polyarteritis nodosa, rheumatoid arthritis, sarcoid, scleroderma, inflammatory bowel disease, eosinophilic fasciitis	Thrombotic thrombocytopenic purpura [37, 38], diffuse proliferative glomerulonephritis [22], vasculitis [24–31]
Adrenal insufficiency		
Pulmonary	Löffler's syndrome, pleural effusions, bronchopulmonary aspergillosis	
Gastrointestinal	Cirrhosis, eosinophilic gastritis	
Dermatologic	Well's, Shulman's syndrome	
Specific to renal disease		13–52% of hemodialysis patients [7–11], 13–75% of peritoneal dialysis patients [12–14], transplant rejection [15–17], 16% CRF not on renal replacement therapy [18, 19], 70% cholesterol embolic disease [20], renovascular disease [21]

$$\text{eGFR} [\text{ml}/\text{min}/1.73\text{m}^2] = 186 \times [\text{Scr}] - 1.154 \times [\text{Age}] - 0.203 \times [0.742 \text{ if female}] \times [1.212 \text{ if African - American}], [39]$$

and eosinophil counts [total and % of white cells count (WBC)] and the cause for admission. Vascular disease was defined by any known history of peripheral, coronary or cerebrovascular disease that had been diagnosed by X-ray, contrast angiography, Doppler flow studies or at surgery. Since there is controversy concerning whether the dialysis procedure itself can affect the eosinophilia, all laboratory work was collected before any hemodialysis procedure was performed that day. Patients on peritoneal dialysis were also analyzed as a separate group since the eosinophilia seen in those patients may be from a different mechanism [40]. Also, since eosinophilia can be defined as >6% of the total WBC or > 450/μl of blood, we therefore recorded both the percentage of eosinophils/total WBC and the total eosinophil count. Often there was more than one differential white blood count that had been done on the patient during the hospitalization; however, only the current eosinophil count at the time of the initial consult was included.

While any drug allergy can produce eosinophilia, β-adrenergic drugs [41], interferon-α and corticosteroids are known to directly affect eosinophil counts without allergic reactions and were therefore included as study variables. Similarly, although some nonparasitic infections have been associated with eosinophilia, eosinopenia has been considered a marker of sepsis [42, 43], which is a major cause of hospitalization in patients with renal disease [44–48]. Therefore, infection needs to be considered as a potential cause for masking eosinophilia along with corticosteroids and beta-blockers. In addition, all other common causes of known eosinophilia (Table 1) were recorded.

Since systemic lupus erythematosus is known to commonly become quiescent in end-stage renal disease (ESRD) [49–51], the diagnosis of

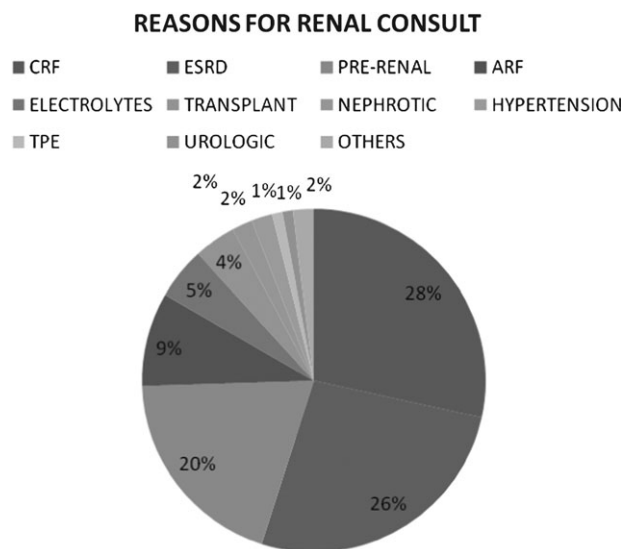


Fig. 1. The most common reasons for consultation in descending order were 1. CRF, 2. ESRD, 3. prerenal azotemia, 4. ARF, 5. electrolyte imbalances, 6. transplantation patients, 7. nephrotic syndrome, 8. hypertension, 9. plasmapheresis procedure, 10. urologic problems and 11. all others.

vasculitis was included only if it had demonstrated activity within the previous 3 months. Since phosphorus ingestion has been associated with hyperphosphatemia in some older literature [52], we also included serum

phosphorus as a risk factor. Similarly, since eosinophils are known to adhere to intercellular adhesion molecules [53] that regulate vascular integrity [54], thrombosis [55] and proteinuria [56], we also chose to include proteinuria measured in either a urinalysis or a 24-hour quantity, when possible, as a potential variable in addition to vascular disease.

Statistical analysis of chi-square was initially performed and the data were found to be not normally distributed. Mann–Whitney *U*-test, Z-test for percentages, Kruskal–Wallis analysis of variance, two-step cluster

analysis and Spearman rho correlations were subsequently performed. Afterward, because of the high correlation among several variables, partial correlation coefficients were also examined between each pair of variables, while all the other variables were held constant using the statistical package SPSS 12.0 (Chicago, IL).

Results

One thousand three hundred and sixty-two patients were seen in consultation between 1 January 2009 and 31 December 2009. Of those patients, only 1359 patients had a total WBC and only 1339 had an assessment of the eosinophil count. Those 1339 patients were considered the study group. The most common reasons for consultation were chronic renal failure (CRF), ESRD, prerenal azotemia and acute renal failure (ARF) (Figure 1). Gastrointestinal and cardiac infectious and vascular problems were the most common reasons for admission (Figure 2). Descriptive statistics of the population are listed in Table 2. There were no diagnosed cases of parasitic infections or adrenal insufficiency. No patients had been treated with interferon. When cholesterol embolic disease, drug allergy or vasculitis were considered likely diagnoses, urine eosinophils were also measured in 31 patients. That number was felt to be insufficient for statistical analysis and because the study was only designed to evaluate blood eosinophils, no analysis was performed on eosinophiluria.

Since the total eosinophilic count demonstrated no significant differences from the relative eosinophil count, all eosinophilic counts are therefore reported as a percentage of the total WBC. The presence of vascular disease correlated the most strongly with increased eosinophil counts ($P < 0.0001$) followed by pleural effusions, both of which demonstrated significant positive correlations. While total white cell count demonstrated the most significant negative correlation, this was followed by nonsepsis infection,

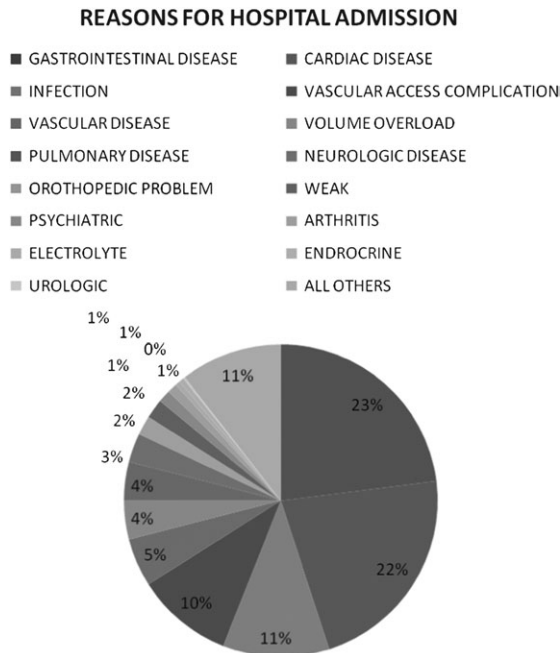


Fig. 2. The most common reasons for hospital admission in descending order were 1. gastrointestinal disease, 2. cardiac disease, 3. infectious disease, 4. vascular access complication, 5. vascular disease, 6. volume overload, 7. pulmonary disease, 8. neurologic disease, 9. orthopedic problems, 10. weak, 11. psychiatric problems, 12. arthritis, 13. electrolyte disorders, 14. endocrine problems, 15. urologic problems and 16. all others.

Table 2. Characteristics of the variables in study population

	<i>n</i>	Mean or % of population	SD
Age	1362	64.1	14.7
Gender	1362	47 Females	
Vascular disease	899	66	
Autoimmune disease	9	6.6	
Cancer	172	12.6	
Nonsepsis infection	281	20.6	
Sepsis	87	6.4	
Cirrhosis	124	9.1	
Pleural effusion	198	14.5	
Allergies	187	13.7	
Eosinophil %	1339	2.1	2.4
Total WBC ($10^3/\text{mcl}$)	1359	9.3	5.3
Serum creatinine (mg/dL)	1360	5.2	3.7
Serum phosphorus (mg/dL)	790	4.77	1.7
Spot proteinuria (1 to 5+)	739	2.5	1.9
24 Hour proteinuria (G/24 HRS)	424	1.8	2.8
eGFR (ml/min)	1360	24.5	24.1
Patients on corticosteroid	102	7.5	
Amount of steroid for those taking (mg/day)	102	10.0	146.5
Patients on beta-blocker	693	50.9	
Amount of beta-blocker for those taking (mg/day)	693	47.1	143.9
Percent of patients on beta-agonist	150	11.5	

sepsis, administration of corticosteroids, myelosuppressive drugs, age, administration of beta-blockers and eGFR. The presence of autoimmune disease, cancer, allergies, cirrhosis, proteinuria and serum phosphorus and creatinine concentrations demonstrated no correlation with eosinophil count. A high degree of correlation

between variables led to a reanalysis and partial correlation coefficients were subsequently calculated for each variable in relation to the number of eosinophils with all other variables held constant in an effort to examine for independent correlations. While vascular disease remained the most significant correlation, the presence of

Table 3. Variables that correlated with eosinophilia with Spearman and partial correlation coefficients^a

	Partial, <i>r</i>	P-value
Vascular disease	0.18	0.006
Pleural effusions	0.17	0.01
Cirrhosis	0.18	0.008
Serum creatinine	0.062	0.358
Total WBC	−0.18	0.009
Nonsepsis infection	−0.03	0.965
Sepsis	−0.04	0.529
Corticosteroid use	−0.125	0.06
Myelosuppressive drugs	−0.03	0.72
Beta-blocker use	−0.13	0.047

^aThe partial correlation coefficient listed is between the given variable and the number of eosinophils with all other variables held constant.

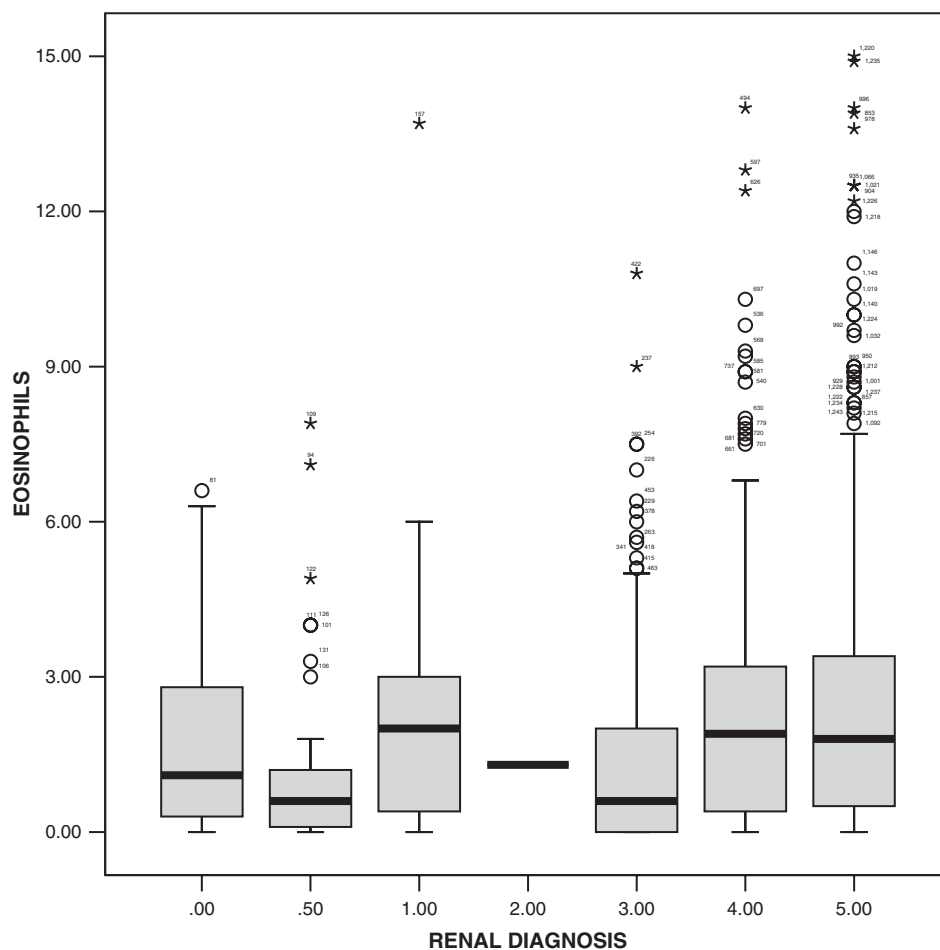


Fig. 3. Box and whisker plots of the percentage of eosinophils of total WBC for various groups of renal diagnoses: 0. Electrolyte disorders, 0.5. transplants, 1. proteinuria or hematuria, 2. prerenal azotemia, 3. ARF, 4. CRF, 5. end-stage renal disease. No group was normally distributed and all were skewed toward higher levels, particularly end-stage renal disease. Whiskers extend one standard deviation with outliers, listed above the whiskers. As noted, all had data skewed to the higher levels. **P* = 0.01.

steroids and myelosuppressive drugs, sepsis and nonsepsis infections all lost significance (Table 3).

While box and whisker plots revealed the data to be skewed toward higher values, the percentage of eosinophils of the total WBC were significantly higher in patients with proteinuria and hematuria and lowest in patients with transplants ($P = 0.0001$). There was also a trend toward higher levels in ESRD than CRF and ARF (Figure 3), with the majority of that effect being in hemodialysis rather than in peritoneal dialysis ($P = 0.01$) (Figure 4). ESRD from crack cocaine and diabetes were the most common renal diagnoses associated with clinical eosinophilia. Similarly, the reason for admission also appeared to affect the percentage of eosinophils, with infectious diagnoses being associated with lower values, while vascular diagnoses were associated with higher percentages of eosinophils. Cardiac or peripheral vascular disease and vascular access thrombosis were associated with significantly higher ($P = 0.01$) percentages, while vascular aneurysms displayed a non-significant trend toward higher levels (Figure 5).

While clinical eosinophilia (defined as $>6\%$ of total WBC) was uncommon (103/1364 patients or 7.55% of

all patients seen), it was still much more common than the general population which is often well under 1% of measured populations [56, 57] but about the same as patients with autoimmune disease [58, 59]. There was a clustering effect in patients with the renal diagnosis of the following: ESRD from crack cocaine, renovascular disease, diabetes or hypertension and CRF from cholesterol embolic disease or renovascular disease (Table 4). It was uncommon in all other diagnoses of ESRD, CRF, ARF and pre-renal azotemia. Clinical eosinophilia was nonexistent in patients with electrolyte disorders, transplants, undergoing plasmapheresis or in patients with hypertension without renal disease.

Discussion

Most physicians would associate the presence of eosinophils with allergies or infection with parasites or fungal organisms. Surprisingly, we found no association with a history of allergies, and although we had no diagnosed cases of parasitic or fungal infections, other types of infections were associated with a decrease in the eosinophil

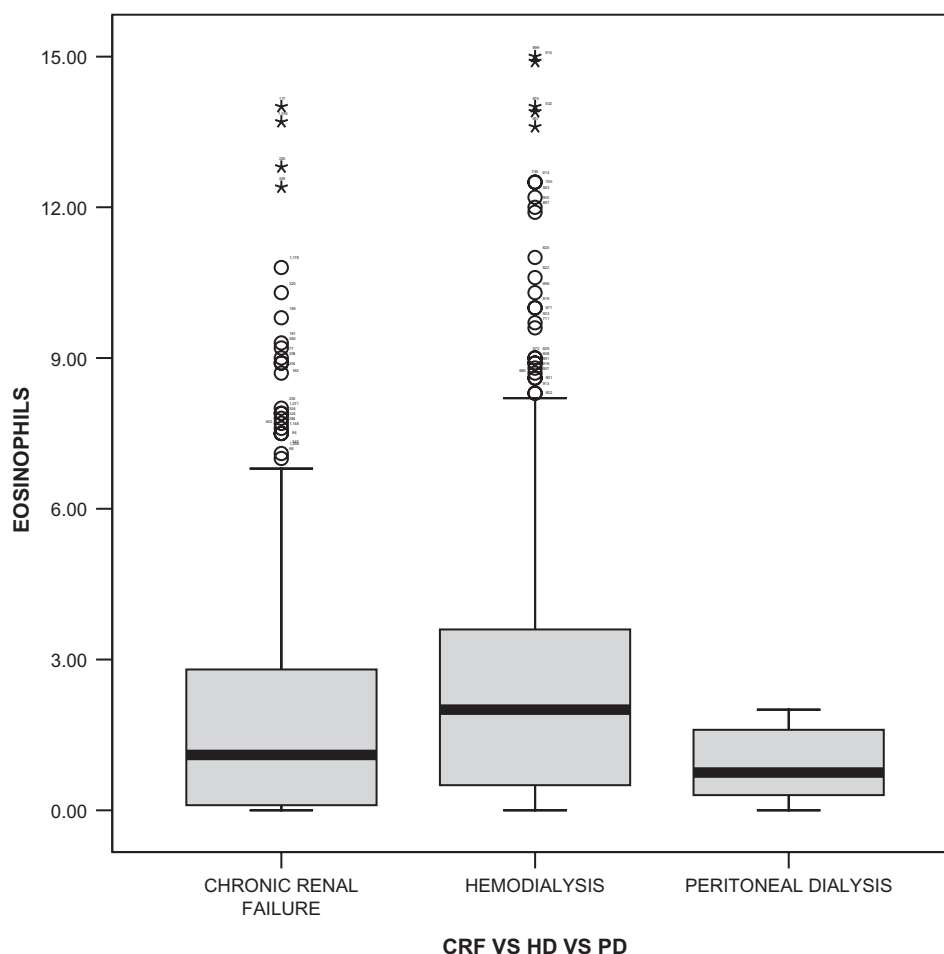


Fig. 4. Box and whisker plots of the percentage of eosinophils of total WBC for renal failure: (i) CRF and (ii) hemodialysis, peritoneal dialysis. Whiskers extend one standard deviation with outliers, listed above the whiskers. Only peritoneal dialysis was normally distributed. CRF and hemodialysis were skewed toward higher levels. * $P = 0.01$.

count. Similarly, an increase in the total WBC count for any cause generally resulted in fewer total and percentage of eosinophils. Eosinopenia has been also been previously reported as a marker of sepsis [41–43]. In contrast, while eosinophilia has been associated with transplant rejection [17], it should not be surprising that our transplant population had the fewest eosinophils and there were no episodes of rejection and they were all taking corticosteroids and myelosuppressive drugs that are well known to decrease eosinophilia. A possible limitation to this study might have been that urine eosinophil counts were not examined on every patient; however, this study was designed to evaluate the disease associations with blood eosinophils and makes no assessment of any such associations with urine eosinophils.

Although some have conjectured that eosinophilia occurs in dialysis patients due to a release of eosinophilotactic substances induced by the dialysis procedure itself [60], others have argued that it is more than an allergic reaction to extracorporeal therapy [11], while other investigators have found no relationship to medications, types of dialyzers, types of access or transfusion frequency that could account for the eosinophilia [14–20]. Finally, others have suggested that either the induction of a toxic nephropathy

alone is enough to generate eosinophilia [61] or the high prevalence of hepatitis C transmission in dialysis patients may result in a higher prevalence of eosinophilia due to cirrhosis; however, investigators have found no such activation of eosinophils in patients with hepatitis C on hemodialysis [62].

In contrast, we found that vascular disease, pleural effusions and cirrhosis exhibited the strongest association with eosinophils rather than uremia itself. Furthermore, we found that within the range of renal failure diagnoses, there was a clustering of cases of eosinophilia in patients with those renal failure diagnoses known to be associated with vascular disease, namely, diabetes, hypertension, cholesterol emboli, renovascular disease and crack cocaine. Even the high prevalence in patients with proteinuria and hematuria can be viewed as an insult to the vascular integrity of the glomerular capillary bed so severe that large molecules are then able to exit the bloodstream and can be, nevertheless, in small vessel vasculitides, only those which are drug-induced and in Churg-Strauss syndrome are known to be associated with eosinophilia. Furthermore, since not all atherosclerosis is associated with eosinophilia, more needs to be understood about the interaction of the eosinophil and vascular injury.

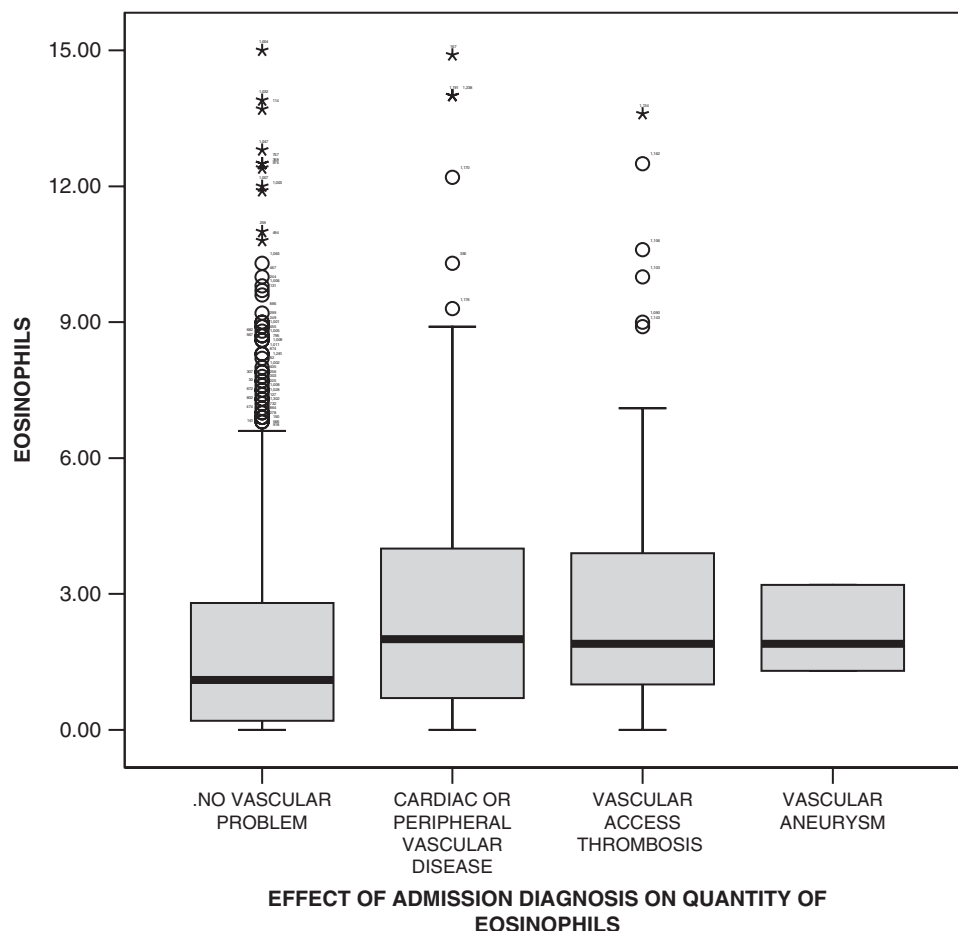


Fig. 5. Box and whisker plots of the percentage of eosinophils of total WBC for various groups of admission diagnoses: (i) no vascular problem, (ii) cardiac or peripheral vascular disease*, (iii) vascular access thrombosis* and (iv) vascular aneurysm. Whiskers extend one standard deviation with outliers, listed above the whiskers. As noted, all except vascular aneurysms had data skewed to the higher levels. * $P = 0.01$.

Like monocytes, which have recently been identified as endothelial progenitor cells [63], eosinophils appear to have an important relationship with vascular injury; however, the mechanism of the interaction of the eosinophil and the vessel wall appears more complex. One possibility is that eotaxin, an eosinophil-specific chemoattractant, has been found to be highly expressed at sites of vascular pathology and that circulating levels may reflect the extent of coronary atherosclerosis [64]. Indeed, although eosinophils are rare in atherosclerotic plaque, eotaxin secreted by vascular smooth muscle cells in the plaque is found in high concentrations in unstable lesions [65] perhaps suggesting that eotaxin has another plaque function with the occasional eosinophilia produced as a by-product. Alternatively, vascular adhesion molecules (VCAM) [66] and endothelial receptors for leukotriene B(4) [67] might induce eosinophilia through chemotaxis. The chemotaxis of eosinophils by VCAM's is similar to that of smooth muscle cells [68] and appears to be mediated by a counter receptor, very late antigen-4 that is expressed by eosinophils but not neutrophils [69]. In addition, eosinophilia is also aided by prolonging eosinophil survival by integrins [70] and adhesion molecules [71]. Furthermore, vascular inflammation through the proinflammatory p65/p50 nuclear factor- κ B pathway where increased expression of VCAMs [72] again promote eosinophil recruitment. Fibroblast and endothelial growth factor coating of decellularized vascular grafts also stimulate eosinophilic infiltration and intimal hyperplasia [73]. Once recruited, the risk of thrombosis is increased as endothelial cells modulate specific eosinophil cell surface marker and cytokine expression [74]. Hypereosinophilic

syndrome has been long known for systemic thrombosis [75], yet only recently was the mechanism revealed to be the transcriptional upregulation of tissue factor (TF) gene in endothelial cells mediated through eosinophil peroxidase. Eosinophils appear to harbor the highest concentration of preformed TF among all blood components under resting conditions [76], and while TF appears to have multiple functions for the eosinophil that include aiding in the transmigration of the endothelium, its best known function remains the initiation of the clotting cascade. Alternatively, the eosinophils may serve a protective function in otherwise previously damaged vessels since they are positively associated with endothelial nitric oxide production [77, 78] which is well known to inhibit intimal hyperplasia, platelet aggregation and thrombosis while promoting vasodilatation and maintenance of blood flow [79–81]. Unfortunately, eosinophils appear more likely to be a culprit since endothelial dysfunction is directly related to eosinophils count [82].

Therefore, eosinophils appear to be a better marker of vascular disease in nephrology patients on a consultant service rather than uremia. Unfortunately, that may also be indicative of a poor prognosis. Eosinophilia is already known to be a marker for vascular disease with increased all-cause [83] and cardiovascular mortality [84] in the general nonrenal population. In a population of 2163 middle aged men in the UK, there was a 17% increase of vascular disease for every standard deviation increase of eosinophils over the mean [85] and eosinophilia appears to be an excellent marker for progression of stenosis after coronary stenting [86, 87] and renal revascularization [88, 89].

Table 4. There was clustering of eosinophilia within just a few renal diagnoses

Renal diagnosis	n/total	%	P value
ESRD			
Crack	14/35	40.0	0.0001
Diabetes	40/147	27.2	0.0001
Hypertension	13/102	13	0.0004
PCKD	0/14	0	NS
Obstruction	0/9	0	NS
Lupus	0/9	0	NS
Chronic GN	0/8	0	NS
Sickle cell	0/4	0	NS
Drug induced	0/4	0	NS
Interstitial	0/4	0	NS
AIDS	0/3	0	NS
CRF			
Cholesterol emboli	2/2	100	NS
Renovascular	2/3	66.7	NS
Diabetes	16/159	10.6	0.0026
Hypertension	8/171	4.6	NS
Obstruction	0/14	4.1	NS
PCKD	0/10	0	NS
Chronic GN	0/9	0	NS
Lupus	0/5	0	NS
Vasculitis	0/5	0	NS
Interstitial	0/2	0	NS
Myeloma	0/1	0	NS
ARF	4/123	3.2	NS
Prerenal	6/272	2.2	NS
Electrolyte	0/73	0	NS
Transplant	0/54	0	NS
Plasmapheresis	0/26	0	NS

Although it may be merely a marker of clinically apparent vascular disease, the presence of eosinophilia on a nephrology consultation service might be able to alert the clinician to the possibility of vascular disease; however, future studies will be needed to examine that hypothesis.

Conflict of interest statement. None declared.

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