Naïve and central memory T-cell lymphopenia in end-stage renal disease

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End-stage renal disease (ESRD) is associated with increased propensity to infections, diminished response to vaccination, impaired cell-mediated immunity, and reduced CD4 + / CD8 + T-lymphocyte ratio. Four subsets of CD4 + and CD8 + T cells have been recently identified: naïve cells (as yet uncommitted), central memory (CM) cells (previously programmed), and CD45RA-positive and CD45RA-negative effector memory (EM) cells (programmed to perform specific effector functions). The effect of ESRD on subpopulations of T lymphocytes is unclear and was studied here. Twenty-one hemodialysis patients and 21 age-matched controls were studied. Pre- and post-dialysis blood samples were obtained and analyzed by three-color flow cytometry. CD4 + /CD8 + ratio and the numbers of the naïve and CM CD4 + and CD8 + T cells were significantly reduced, whereas the numbers of EM CD4 + and CD8 + T cells were unchanged in the ESRD group. The reduction of the naïve and CM T-cell counts in the ESRD group was associated with increased apoptosis of these cells. Negative correlations were found between severity of azotemia, oxidative stress, and hyperphosphatemia with the number of naïve T cells. Comparison of diabetic with non-diabetic ESRD patients revealed higher numbers of total CD8 + cells and EM CD8 + T cells in the diabetic group. Dialysis did not significantly change the naïve and CM CD4 + or CD8 + cell counts, but significantly lowered CD8 + EM cell count. Thus, ESRD results in increased apoptosis and diminished populations of naïve and CM T lymphocytes. This phenomenon may, in part, contribute to the impaired immune response in this population.

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Although bacterial infections have diminished as a cause of death in the general population, they constitute the second most common cause of death in the end-stage renal disease (ESRD) population.[1–3] This is thought to be largely owing to the impaired host immune response in uremia.[1,4,5] The reported immunological abnormalities in ESRD patients include decreased granulocyte and monocyte/macrophage phagocytic function,[4,6,7] defective antigen presentation by monocyte/macrophages,[4,8,9] reduced antibody production by B lymphocytes,[4,10,11] and impaired T-cell-mediated immunity.[4,12,13] The exact mechanisms responsible for these derangements are not fully understood.

T lymphocytes play a central role in generation of the adaptive immune response. In the presence of infection, naïve (pre-immune) T cells recognize epitopes of the structural molecules expressed by the invading microbe. This leads to activation, massive expansion, and differentiation of these cells into two types of antigen-experienced lymphocyte subsets, short-lived effector T cells and long-lived memory T cells.[14] Once, re-challenged with the same antigen, the long-lived memory T cells can elicit the full immunologic response rapidly.[14,15] Recently, several studies have identified two major subsets within the memory cell population, namely central memory (CM) and effector memory (EM) T lymphocytes.[14,15] The EM T cells have been further divided into two subpopulations, the CD45RA-negative effector memory (TEM) and CD45RA-positive effector memory (TEMRA) T cells[14,15] (Figure 1). The EM cells exert effector functions at the sites of inflammation, whereas the naïve and CM cells express homing receptors that allow them to lodge in the secondary lymphoid organs.[14–16] A limited number of studies have examined the distribution and function of T lymphocytes in the ESRD patients.[17–19] However, little information is available on the effect of ESRD on the naïve and memory T-lymphocyte subsets. Therefore, we evaluated T-lymphocyte subsets pre- and post-hemodialysis in a group of ESRD patients and compared the results with those obtained in a group of age-matched control individuals.

RESULTS

General data

Data are summarized in Tables 1 and 2. The underlying causes of ESRD were diabetic nephropathy in 12, hypertension

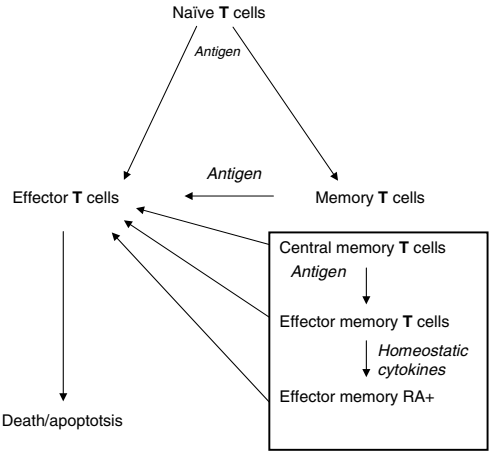

Figure 1 | A linear model of central and effector T-cell memory generation in primary response to infection.

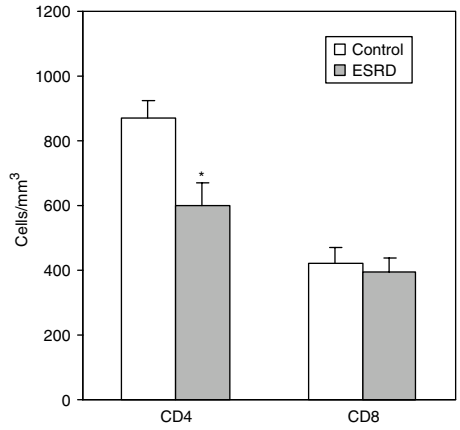

Figure 2 | Distribution of CD4+ and CD8+ T cells in control and ESRD groups. *$P<0.05$.

Table 1 | Clinical and biochemical parameters in normal control and ESRD groups

	Control (n=21)	ESRD (n=21)	P-value
Age (years)	46±1.8	49±3.4	NS
BUN (mg/dl)	13.33±1.02	69.28±4.66	<0.001
Creatinine (mg/dl)	0.85±0.18	10.45±0.63	<0.001
Calcium (mg/dl)	9.14±0.24	9.10±0.20	NS
Phosphorus (mg/dl)	3.20±0.16	5.43±0.30	<0.001
iPTH (pg/ml)	40.00±3.84	293.95±57.45	<0.001
Hemoglobin (g/dl)	14.03±0.38	11.72±0.23	<0.001
Ferritin (ng/ml)	32.63±6.26	209.90±23.79	<0.001
Transferin saturation (%)	18.66±2.12	26.80±2.15	0.012
Albumin (g/dl)	3.8±0.14	3.97±0.43	NS
Cholesterol (mg/dl)	159.50±5.47	139.09±7.09	0.031
Triglyceride (mg/dl)	100.16±15.51	146.71±16.80	0.052
MDA (μmol/l)	1.72±0.08	2.01±0.06	<0.001
K_t/V	—	1.53±0.16	—

BUN, blood urea nitrogen; ESRD, end-stage renal disease; iPTH, immunoreactive parathyroid hormone; MDA, malondialdehyde; NS, nonsignificant.

Table 2 | Leukocyte and differential counts in normal control and ESRD groups

Test	Controls	Pre-dialysis	Post-dialysis
Leukocytes (cells/mm^3)	5852±187	6803±499[a]	6014±454[b]
Neutrophils (cells/mm^3)	3433±169	4490±435[a]	4052±389[b]
Monocyte (cells/mm^3)	415±122	523±192[a]	347±147[b]
Lymphocyte (cells/mm^3)	1795±108	1557±118	1367±118[a,b]
CD4+/CD8+ (ratio)	2.63±0.34	1.81±0.21[a]	2.42±0.27[b]

ESRD, end-stage renal disease.
[a]$P<0.05$ compared to controls.
[b]$P<0.05$ compared to pre-dialysis.

in three, chronic glomerulonephritis in five patients, and polycystic kidney disease in one. The types of vascular access included A-V fistulas in 14 and A-V grafts in seven patients. As expected, serum creatinine and blood urea nitrogen concentrations were significantly higher in the ESRD patients compared to the control group. Likewise, serum concentrations of phosphorus, triglylcerides, and lipid peroxidation product, malondialdehyde (MDA), were significantly elevated in the ESRD group. Blood hemoglobin concentration was significantly lower, whereas serum ferritin level and transferin saturation were higher in ESRD patients than the corresponding values found in the control group. However, serum cholesterol, albumin, and calcium concentrations in the ESRD patients were not significantly different from those observed in the control group. The mean K_t/V value in the ESRD patients was greater than 1.5, reflecting adequacy of dialysis regimen in the study participants. In the pre-dialysis samples, total white blood cell counts and the number of granulocytes and monocytes were significantly higher in the ESRD patients as compared to the corresponding values found in the control group. However, the total lymphocyte count and CD8+ T-cell count in the pre-dialysis blood samples were not significantly different from the corresponding values in the control group. As expected, the number of CD4+ cells and the ratio of CD4+ to CD8+ cells were significantly reduced in the ESRD group.

T-lymphocyte subset data

Data are shown in Figures 2–8. The ESRD patients exhibited a marked reduction of the naïve subsets of CD4+ and CD8+ T cells as compared to the corresponding values in the normal control group (Figure 2). Likewise, the CM subsets of both CD4+ and CD8+ T cells were reduced in the ESRD group (Figures 3 and 4). However, EM subsets (TEM and TEMRA) of the CD4+ and CD8+ T cells in the ESRD group were not significantly different from those observed in the control group (Figures 3 and 4).

Comparison of data obtained in the diabetic ($n=12$) and non-diabetic ($n=9$) ESRD patients revealed higher numbers of CD8+ T cells and EM T-cell subsets (TEM and TEMRA) in the diabetic ESRD patients (Figures 5 and 6). However, the number of naïve and CM cells did not significantly differ among the diabetic and non-diabetic subgroups. Comparison of data obtained before and after a 3-h hemodialysis treatment revealed significant reductions in total white blood cell count, monocytes, lymphocyte, and CD8+ T cells after