IMPAIRED FUNCTION OF MACROPHAGE Fc_γ RECEPTORS IN END-STAGE RENAL DISEASE

PEDRO RUIZ, M.D., FRANCISCO GOMEZ, M.D., AND ALAN D. SCHREIBER, M.D.

Abstract Infection is a frequent complication in patients undergoing hemodialysis for end-stage renal disease and is the primary cause of mortality among such patients. Macrophages are important in host defense against infection largely because their Fc_γ receptors recognize antibody-coated bacteria. We therefore studied macrophage Fc_γ-receptor function in vivo and in vitro in 56 patients with end-stage renal disease who were on hemodialysis and in 20 healthy volunteers.

The clearance of IgG-coated (sensitized) autologous red cells was decreased in 53 patients. The inhibition of clearance in the 56 patients was 52±3 percent at 1 hour, 41±5 percent at 1½ hours, and 29±5 percent at 2 hours ($P<0.001$). The clearance of unsensitized erythrocytes and heat-altered autologous erythrocytes was normal. The impairment of clearance was not correlated with age, sex, nutritional status, HLA haplotype, or the presence of circulating immune complexes. The recognition of these IgG-sensitized red cells in vitro by $Fc_\gamma RI$ (an Fc_γ-receptor protein that binds monomeric IgG) on blood monocytes from the patients was also significantly decreased ($P<0.001$) but was partially improved by hemodialysis.

Nine patients had severe infections during a two-year follow-up period. The clearance of IgG-coated cells in these patients (half-time, 12.9±1.7 hours) was significantly impaired, as compared with that in the 47 patients without severe infections (half-time, 4.4±1.8 hours; $P<0.001$).

We conclude that macrophage Fc_γ-receptor function is impaired in patients with end-stage renal disease who are undergoing hemodialysis, and that this impairment probably contributes to the observed immunodepression and high prevalence of infection among such patients. (N Engl J Med 1990; 322:717-22.)

MACROPHAGE Fc_γ receptors are important in the clearance of IgG-coated particulate antigens and immune complexes. The functional integrity of these receptors has been widely studied in patients with autoimmune disease, by measuring the clearance of radiolabeled IgG-sensitized erythrocytes by splenic macrophages.[1,2] Macrophage Fc_γ-receptor function has been observed to be decreased in patients with certain HLA haplotypes and in patients with the autoimmune disorders systemic lupus erythematosus, Sjögren's syndrome, and dermatitis herpetiformis.[1,2] This finding has been attributed to occupation of these Fc_γ receptors on the macrophages by immune complexes.

Patients with end-stage renal disease have an increased incidence of infection.[3-6] Although immunologic abnormalities have been observed in these patients, the precise mechanism responsible for the increased incidence of bacterial infection is uncertain. Macrophage Fc_γ receptors are important in host defense since they participate in the clearance of IgG-coated microorganisms. Therefore, we evaluated macrophage Fc_γ-receptor function in patients with end-stage renal disease. We studied an important macrophage Fc_γ-receptor function that represents the initial step in the recognition of IgG ligand — the binding of IgG-sensitized cells. In addition, we examined the clearance of these IgG-coated cells in vivo. The results indicate that these patients have impaired macrophage Fc_γ-receptor function that may contribute to their high incidence of infection.

METHODS

Patients

We studied 56 consecutive patients (36 women and 20 men) whose mean (±SD) age was 44±12 years and whose mean duration of hemodialysis was 45.7±23.2 months. All patients were followed up for a period of two years after study; two died within this period — one of an acute myocardial infarction in the 16th month and the other of sepsis due to *Pseudomonas aeruginosa* in the 20th month. All patients received their medical care at the hemodialysis unit of the Hospital of the University of Cadiz, Spain. Twenty healthy volunteers (14 women and 6 men; age, 42±15 years) served as concurrent controls.

The cause of end-stage renal disease was glomerulonephritis in 21 patients, chronic interstitial nephritis in 14, polycystic renal disease in 9, and miscellaneous causes in 12, including lupus nephritis in 3. Patients who had an infection or were taking immunosuppressants were excluded from study. Five of the 56 patients had received a kidney homograft that had been rejected more than five years before study.

Study Protocol

Blood was drawn at the end of a hemodialysis session for the following measurements and tests: (1) blood glucose and urea nitrogen, sodium, potassium, chloride, total calcium, phosphate, creatinine, uric acid, total lipids, triglycerides, cholesterol, serum aspartate and alanine aminotransferases, and alkaline phosphatase, serum protein electrophoresis, and a complete blood count; (2) serum IgG, IgA, and IgM, determined by radial immunodiffusion (Behring Diagnostics, Madrid); (3) serum C4, determined by hemolytic titration,[7] and serum C3 and C3a desArg, determined by radial immunodiffusion (Behring Diagnostics); (4) plasma levels of zinc, measured by absorption spectrophotometry (Pye Unicam SP 190); (5) circulating immune complexes, determined by [^{125}I]C1q binding[8]; (6) peripheral-smear examination after Wright–Giemsa staining to assess the presence of Howell–Jolly bodies as an index of splenic function[9] (negative in all patients); (7) macrophage Fc_γ-receptor–dependent clearance in vivo; and (8) Fc_γ-receptor–mediated recognition of sensitized cells by peripheral-blood monocytes in vitro.

Preparation of Human IgG Anti-Rh(D)

Human IgG anti-Rh(D) was prepared from serum from a single donor (Ortho Pharmaceutical, Madrid) by ammonium sulfate precipitation followed by Sephacryl S-300 gel filtration and QAE ion-exchange chromatography (Pharmacia, Madrid). No IgM was detected by double immunodiffusion (Ouchterlony analysis). The final IgG fraction was passed through a Millipore filter and tested for pyrogenicity and sterility.

Macrophage Fc_γ-Receptor–Mediated Clearance

Clearance studies were performed as previously described.[1,10] In brief, erythrocytes (RhD) were isolated from all subjects, washed three times in physiologic saline, spectrophotometrically standard-

From the Department of Medicine, Hospital of the University of Cadiz, Spain (P.R., F.G.), and the University of Pennsylvania Graduate Group in Immunology, Cancer Center and Hematology/Oncology Section, Philadelphia (A.D.S.). Address reprint requests to Dr. Schreiber at the Graduate Group in Immunology, University of Pennsylvania School of Medicine, 7 Silverstein Bldg., 3400 Spruce St., Philadelphia, PA 19104.

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ized to a concentration of 6.6×10^8 cells per milliliter, and radiolabeled with ^{51}Cr (potassium dichromate, Amersham, Buckinghamshire, England). An aliquot of cells was sensitized by adding to it drop by drop an appropriate dilution of the purified human IgG anti-Rh(D). The mixture was incubated at 37°C for 30 minutes, and the sensitized ^{51}Cr-labeled erythrocytes were washed four times in saline and resuspended to a concentration of 3.3×10^6 per milliliter in Hanks' balanced salt solution (M.A. Bioproducts, Madrid). An aliquot of cells (usually 10 ml, with 2.5 μCi of radioactivity) was injected through an antecubital vein, and the survival of red cells was determined in serial blood samples obtained over a period of 48 hours. Clearance curves were plotted by expressing the number of counts per minute at each time point as a percentage of the number of counts at 10 minutes, the zero point. The time required for clearance of 50 percent of the inoculated IgG-coated red cells (half-time) was calculated and then correlated with clinical and serologic data. In addition, for the clearance on each day, the percentage for the inhibition of clearance above control was calculated at 1, 1½, 2, 8, 24, and 48 hours, according to the formula

$$\%\ \text{inhibition} = 100 \times 1 - \left(\frac{\text{CPMb} - \text{CPMx}}{\text{CPMb} - \text{CPMc}}\right),$$

where CPMb denotes the number of counts per minute in a control subject who received an injection of unsensitized autologous red cells, CPMx the number of counts in a patient who received IgG-coated (sensitized) autologous red cells, and CPMc the number of counts in a control subject who received autologous IgG-sensitized red cells. By means of this formula patients could be compared with controls studied on the same day, and results could be expressed as the percentage of change in clearance, where 100 percent inhibition of clearance indicated that clearance in a patient who received IgG-coated red cells (CPMx) was identical to clearance in a control who received unsensitized red cells (CPMb).[11] In two additional control groups — five patients with end-stage renal disease and five healthy volunteers — we examined the clearance of autologous ^{51}Cr-labeled but unsensitized red cells and the clearance of ^{51}Cr-labeled heat-damaged autologous red cells.

Duplicate studies were performed in five of the patients with end-stage renal disease in whom severe infection had developed, five of the patients with end-stage renal disease without a history of complications due to infection, and five controls. The results of the repeat studies of clearance were unchanged from those of the original studies in each subject.

After hemodialysis was completed and 30 minutes after the IgG-coated autologous red cells were injected, serum C3, C3a desArg, and serum C4 were measured to assess complement activation during hemodialysis and during the clearance of the IgG-coated red cells. No significant complement activation was observed.

Number of IgG (Anti-RhD) Molecules per Red Cell

The number of IgG molecules per red cell was determined as previously described with the use of ^{125}I-labeled anti-IgG reagent.[12] Clearance studies were always performed with erythrocytes sensitized sufficiently so that approximately 600 molecules of IgG were present on each red cell. When Fc_γ-receptor–dependent recognition by blood monocytes was studied in vitro, each red cell (RhD) was coated with 400, 800, or 1600 molecules of IgG.

Binding of IgG (Anti-RhD)-Coated Red Cells

The recognition of IgG-coated red cells (RhD) by monocytes isolated before and after hemodialysis was determined as previously described.[13,14] In brief, confluent monolayers of 5.5×10^5 monocytes were obtained from defibrinated blood after density-gradient centrifugation (Ficoll–Isopaque) and plastic adherence to petri dishes (Nunc, Amsterdam). An aliquot of 2×10^7 ^{51}Cr-labeled, IgG-coated red cells (RhD) was added to each monocyte monolayer. The petri dishes were then incubated at 37°C in an atmosphere of 5 percent carbon dioxide for 45 minutes, washed to detach unbound red cells, and treated with 0.086 M EDTA solution to remove adherent monocytes and monocyte-bound IgG (anti-RhD)-sensitized red cells. The treatment with EDTA removed all adherent monocytes and all radioactivity. The percentage of ^{51}Cr-labeled and IgG-sensitized red cells (RhD) recognized by peripheral-blood monocytes was determined according to the formula

$$\%\ \text{red-cell IgG bound to monocyte monolayers} = \frac{\text{cpm for IgG (anti-RhD)-coated red cells removed with EDTA}}{\text{cpm for IgG (anti-RhD)-coated red cells added to monocyte monolayers}} \times 100.$$

No phagocytosis of anti-RhD–sensitized erythrocytes by peripheral-blood monocytes occurs under the experimental conditions.[13,14] The studies were repeated in 5 controls and 10 patients; the results of the repeat studies were unchanged from those of the original studies in each subject.

HLA Typing

HLA typing was performed by the tissue-typing laboratory of the Virgen del Rocio General Hospital, Seville, Spain.

Assessment of Nutritional Status

Nutritional status was evaluated according to anthropometric, biochemical, and immunologic measurements.[15,16] Dry body weight, relative body weight, and the percent ideal body weight were also determined. The anthropometric data were compared with standard values for the local population. Serum albumin and transferrin were measured to evaluate the serum protein level. Malnutrition was classified according to previously established criteria[15,16] as marasmus, kwashiorkor, or mixed type. All malnourished patients had malnutrition of the mixed type. We observed a high incidence of protein-calorie malnutrition of the mixed type in 24 of the 56 patients (43 percent). Total body weight did not change.

Cutaneous hypersensitivity responses to standard concentrations of four antigens — purified protein derivative, *Trichophyton rubrum*, *Candida albicans*, and streptokinase–streptodornase — were used to evaluate cell-mediated immunity as previously described.[16,17] A response was considered positive when the diameter of induration was more than 5 mm. A normal response was indicated by a positive response to either three or four antigens, an abnormally low response by a positive response to either one or two antigens, and anergy by a lack of positive response to any of the four antigens.

Statistical Analyses

The in vivo clearance curves were analyzed at the different time points to calculate a P value for the difference between the controls and patients by Student's t-test. The in vitro Fc_γ-receptor–dependent recognition of red cells by monocytes and the clearances in patients and controls were assessed with the Wilcoxon rank-sum test for unpaired data. The relation of the clearance rate (as half-time) or monocyte Fc_γ-receptor–dependent recognition of IgG-coated red cells in vitro to the serologic tests was analyzed with the Spearman rank-correlation test.

Results

Clearance studies were performed in the 56 patients with end-stage renal disease immediately after they underwent hemodialysis. The results demonstrated that the clearance of IgG-coated red cells was significantly impaired ($P<0.001$) (Fig. 1). At 1 and 1½ hours, the mean (±SEM) inhibition of macrophage Fc_γ-receptor–mediated clearance was 52±3 percent and 41±5 percent, respectively. Clearance was inhibited by more than 10 percent in 53 patients and by 5 to 10 percent in 3. In contrast, the clearance of unsensitized red cells and of heat-damaged red cells in the patients did not differ from the clearance of these cells in the healthy volunteers (Fig. 1).

The patients were followed up for at least two years after the clearance studies were performed. Two pa-

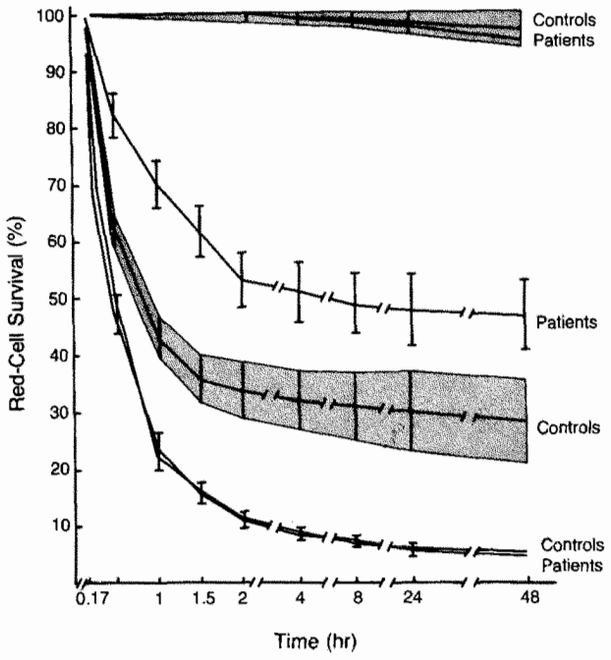

Figure 1. Macrophage Fc_γ-Receptor–Mediated Clearance of IgG-Sensitized Radiolabeled Red Cells in Patients with End-Stage Renal Disease Immediately after Hemodialysis (n = 56) and in Healthy Volunteers (n = 20).

The middle pair of curves (means ±SEM) represents values for clearance in these 76 subjects; the upper pair of curves, the clearance of unsensitized autologous red cells in five patients and five controls; and the lower pair of curves, the clearance of heat-damaged red cells (heated for 30 minutes at 56°C) in five patients and five controls.

tients died — one of an acute myocardial infarction in the 16th month of follow-up and the other of sepsis due to *Pseud. aeruginosa* in the 20th month. Nine patients had severe infection: seven had pneumonia (due to *Streptococcus pneumoniae* in four, *Staphylococcus aureus* in one, *Haemophilus influenzae* in one, and *Pseud. aeruginosa* in one), and two had sepsis (due to *Escherichia coli* in one and *Pseud. aeruginosa* in the other). One other patient had a urinary tract infection due to *E. coli*. One of the infections (*Staph. aureus*) was related to an infection of an arteriovenous fistula. When the clearance of IgG-coated red cells in the patients with severe infection was compared with the clearance in the patients without infection, those with infection were found to have a significantly longer half-time (12.9±1.7 vs. 4.4±1.8 hours; $P<0.001$) (Fig. 2).

We analyzed the clearance of IgG-coated red cells in the patients (half-time) in relation to the serum creatinine level. Hemodialysis reduced the serum creatinine level from 981±159 μmol per liter (11.1±1.8 mg per deciliter) to 575±106 μmol per liter (6.5±1.2 mg per deciliter). Neither the levels measured before hemodialysis nor those measured afterward correlated with the extent of impairment of clearance of IgG-coated red cells.

We also studied peripheral-blood monocytes isolated before and after hemodialysis (Fig. 3). Erythrocytes from a single Rh(D)-positive donor were sensitized with three different concentrations of IgG (400, 800, and 1600 IgG molecules per red cell). Monocytes isolated from the patients bound significantly fewer IgG-coated red cells than did those from the controls ($P<0.001$). This effect was diminished by hemodialysis. Monocytes isolated from patients after hemodialysis were more effective in binding red cells sensitized with 400 ($P<0.01$), 800 ($P<0.001$), or 1600 ($P<0.05$) IgG molecules per red cell than monocytes isolated before hemodialysis. There was no correlation between the extent of binding by monocytes and the degree of impairment of clearance of IgG-coated red cells. No difference was observed between this alteration in monocyte $Fc_\gamma RI$ (an Fc_γ-receptor protein that binds monomeric IgG) in patients in whom severe infection developed and those in whom it did not.

Three patients had elevated levels of circulating immune complexes. The clearance of IgG-coated red cells in these patients did not differ from that observed in the patients in general (Fig. 4). Furthermore, there was no correlation in these three patients between the level of circulating immune complexes and the extent of impairment of the recognition of IgG-coated red cells by monocytes.

Neither the clearance of IgG-sensitized erythrocytes nor the recognition in vitro of IgG-coated red cells by monocytes from the patients correlated with their sex, age, duration of hemodialysis (in months), creatinine concentration, or change in blood urea nitrogen level after hemodialysis, or with any of the se-

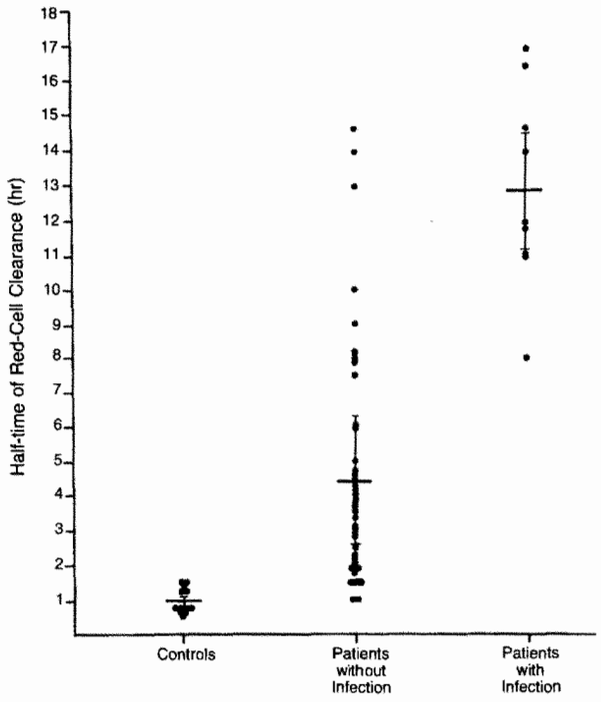

Figure 2. Macrophage Fc_γ-Receptor–Mediated Clearance of IgG-Coated Red Cells (as Half-time) in Patients after Hemodialysis (n = 56) and in Controls (n = 20).

The half-time was significantly longer in the nine patients in whom severe infection developed during follow-up.

rologic measurements, including the immunoglobulin level. Furthermore, there was no relation between either the clearance of IgG-coated red cells or their recognition in vitro by monocytes and the underlying cause of the end-stage renal disease, the HLA haplotype, or the nutritional status of the study population.

The plasma zinc level was 18.4±0.7 μmol per liter (120±4.5 μg per deciliter) in the healthy volunteers and 10.4±0.6 μmol per liter (68.2±4.0 μg per deciliter) in the patients with end-stage renal disease ($P<0.001$). However, there was no correlation between the plasma zinc level and the degree of impairment of clearance in vivo or the monocyte recognition of IgG-coated red cells in vitro. Similarly, malnutrition was not necessarily linked with greater impairment of the clearance rate or a lower value for in vitro monocyte recognition of IgG-sensitized red cells. The prevalence of malnutrition was significantly higher in the patients who had been undergoing hemodialysis for more than two years ($P<0.05$) and the patients who had more than a twofold increase in the serum levels of aminotransferases ($P<0.01$). However, neither the macrophage Fc_γ-receptor–mediated clearance nor the binding of IgG (anti-RhD)-coated red cells by monocytes correlated with the nutritional status of these patients, as indicated by anthropometric, biochemical, and immunologic values.

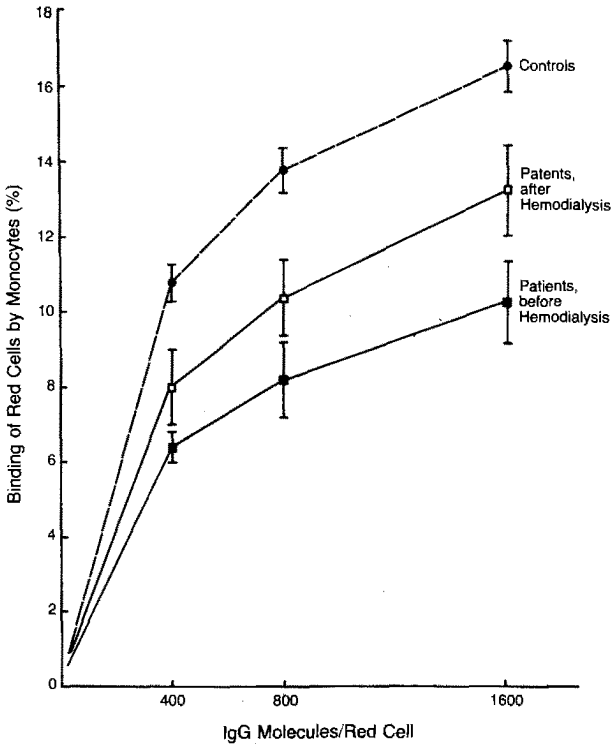

Figure 3. Recognition of Human IgG (anti-RhD)-Coated Red Cells by Monocytes from Patients (n = 56) and Controls (n = 20). IgG-sensitized, ^{51}Cr-labeled (2×10^7) erythrocytes were added to monolayers of monocytes, and the percentage of red cells bound by monocytes was determined by measuring the radioactivity. Values are means ±SEM.

Discussion

Infection is a major cause of morbidity and mortality in patients with end-stage renal disease.[3,6,18] In our study, severe infection developed in 9 of 56 patients over a two-year period and led to fatal complications in 1 of them. The predominance of infection among patients with chronic renal insufficiency has led to the supposition that such patients are immunocompromised. Investigations of immune function in patients with end-stage renal disease have revealed depression of cell-mediated immunity and lymphocyte abnormalities[3,6,18-21] and depression of phagocytosis and chemotaxis by granulocytes.[22] These patients have been observed to have an absolute lymphopenia, with a particular reduction of B lymphocytes that is partially or completely reversed by hemodialysis. B-lymphocyte function has been generally normal, and antibody production normal to slightly decreased.[23] T-lymphocyte function is commonly abnormal and can be improved by the removal of uremic plasma and on occasion by hemodialysis.

Most studies of immune function in end-stage renal disease have focused on lymphocyte function, despite the fact that infection with pyogenic organisms is common. We studied the function of Fc_γ receptors in patients with end-stage renal disease, since these receptors are likely to have a major role in defending against bacterial infection. Previous investigations of macrophage function in renal failure have primarily involved studies of the clearance rate of radiolabeled microaggregated human serum albumin.[4,5] Such studies, which demonstrated normal results in patients with end-stage renal disease, did not assess macrophage Fc_γ-receptor function.

We observed that the clearance of human IgG-coated autologous red cells was impaired in end-stage renal disease. Clearance is mediated by splenic macrophage Fc_γ receptors,[1,10,11,24] and thus impairment indicates dysfunction of splenic macrophage Fc_γ receptors in these patients. This abnormality was a universal finding in the 56 consecutive patients studied. The clearance of heat-altered red cells by splenic macrophages was not impaired, consistent with published normal values for clearance of heat-aggregated albumin in such patients. Impairment of splenic macrophage Fc_γ-receptor function predisposes these patients to bacterial infection, as demonstrated by the finding that the patients who subsequently had severe infections had had the most marked impairment of splenic macrophage Fc_γ-receptor function (Fig. 2).

Patients with systemic lupus erythematosus also have defective macrophage Fc_γ-receptor–dependent clearance, and this defect correlates with the level of circulating immune complexes.[24] Patients with both this disorder and renal disease have the most marked abnormality in macrophage Fc_γ-receptor function.[25] We observed that defective macrophage Fc_γ-receptor function occurs in end-stage renal disease in the absence of circulating immune complexes. It is known

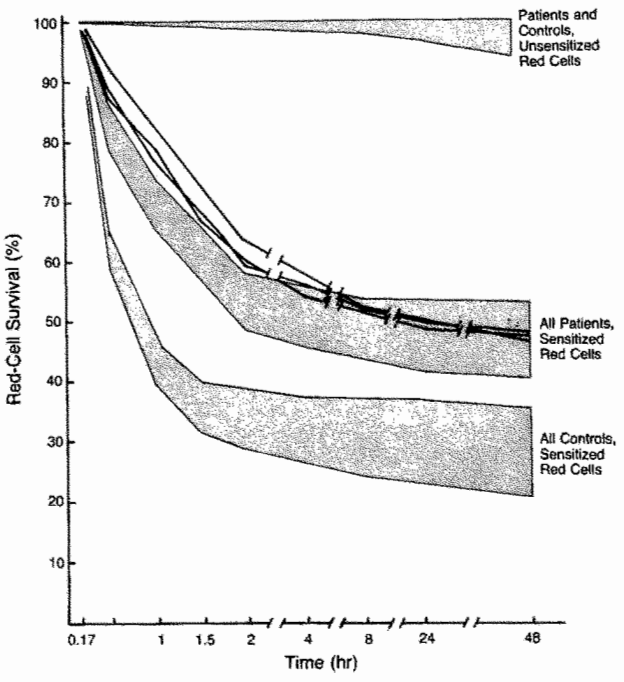

Figure 4. Macrophage Fc_γ-Receptor–Mediated Clearance in Patients with Circulating Immune Complexes (n = 3).

The curves for these three patients fell into the range for the patient group. The shaded areas contain both the values for the mean and those for the SEM in the patient and control groups (see Fig. 1).

that patients with systemic lupus also have an increased incidence of infection.[26] However, there has not been a systematic study of the incidence of infection in relation to the defect in Fc_γ-receptor–dependent clearance in systemic lupus erythematosus. Macrophage Fc_γ-receptor function is of importance in the clearance of IgG-containing immune complexes and in host defense. Our study demonstrates a correlation between dysfunction of tissue macrophage Fc_γ receptors and the incidence of infection.

We addressed the nature of the Fc_γ-receptor abnormality in our patients. Their peripheral-blood monocytes were defective in binding the same human IgG-coated red cells whose clearance was impaired in vivo. This defect persisted after hemodialysis and was present in monocytes washed free of uremic plasma. These findings suggest an intrinsic, partly reversible cellular defect. Monocytes express two Fc_γ-receptor proteins, Fc_γRI and Fc_γRII.[27] Data from our laboratory indicate that the recognition of IgG (anti-RhD)-coated erythrocytes by monocytes is mediated by Fc_γRI and not by Fc_γRII.[28,29] Thus, monocyte Fc_γRI function is defective in patients with end-stage renal disease.

It is uncertain, however, whether this abnormality in Fc_γRI function is responsible for the altered clearance of IgG-coated red cells in vivo. When patients were studied individually, there was no correlation between the extent of the monocyte Fc_γ-receptor abnormality and the extent of the impairment of macrophage clearance. In addition, the presence of a change in monocyte Fc_γRI function did not differentiate patients who later had infection from those who did not. This may indicate that Fc_γ receptors other than or in addition to Fc_γRI are responsible for the clearance of these IgG-coated cells or that macrophage Fc_γ receptors other than Fc_γRI are defective in patients with end-stage renal disease. It has previously been observed that Fc_γRI may be involved in the clearance of IgG-coated cells.[30] However, the function of a third Fc_γ receptor, splenic macrophage Fc_γRIII, appears to be important in this clearance[31] and may also be abnormal in end-stage renal disease.

Low plasma zinc levels, liver disease, and protein-calorie malnutrition have been associated with immunodepression in end-stage renal disease.[18,19,32,33] However, we found no relation between plasma zinc levels, liver dysfunction, malnutrition, and the alteration of Fc_γ receptors in our patients, either in vivo or in vitro. Abnormalities in the expression or function of Fc_γ receptors have been observed in association with certain HLA haplotypes.[34-36] However, in our study there was no correlation between HLA haplotype and either macrophage Fc_γ-receptor–dependent clearance or monocyte recognition of IgG-coated cells. Similarly, defective Fc_γ-receptor–dependent clearance has been observed in patients with the acquired immunodeficiency syndrome,[37,38] but none of our patients was positive for antibodies to human immunodeficiency virus or had any evidence of diseases related to the acquired immunodeficiency syndrome.

High plasma levels of endogenous glucocorticoids have been found in patients with end-stage renal disease.[21] We have observed that steroid hormones and their analogues regulate the expression of macrophage Fc_γ receptors,[11,39] with a substantial effect on Fc_γRI.[40] Thus, changes in the metabolism of steroid hormones may contribute to the depression of Fc_γ-receptor expression in end-stage renal disease.

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