

*Original Article*

## **IGG and complement receptor expression on peripheral white blood cells in uraemic children**

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### **Abstract**

**Background.** Phagocytosis of IgG- or complement-opsonized bacteria and antibody production by lymphocytes are regulated by cell surface receptors for IgG (FcγRI, FcγRII and FcγRIII) and complement (CR1 and CR3). We measured the effect of uraemia and dialysis treatment on FcγR and CR expression on leukocytes in blood.

**Methods.** Blood samples were obtained from children: 40 treated with peritoneal dialysis (PD), 23 with haemodialysis (HD), 46 not yet dialysed (CRF) and 33 healthy (HC). White blood cells, isolated from EDTA-blood by centrifugation after cell fixation with paraformaldehyde, were labelled with FITC-conjugated CD16 (FcγRIII), CD32 (FcγRII), CD64 (FcγRI), CD11b (CR3) and CD35 (CR1) monoclonal antibodies and analysed by flow cytometry.

**Results.** In PD, HD, CRF and HC, monocytes and neutrophils were all positive for FcγR and CR, except for CD16 on monocytes (20% positive). Lymphocytes expressed CD16 and CD32 but not CD64. PD, HD and CRF children had lower percentages of CD16<sup>+</sup> and CD32<sup>+</sup> lymphocytes compared with HC. The percentage of CD11b<sup>+</sup> lymphocytes was lower only in PD and the percentage of CD35<sup>+</sup> lymphocytes was lower in HD and CRF compared with HC. The median CD32 mean fluorescence intensity (MFI) on lymphocytes, monocytes and neutrophils was lower in PD, HD and CRF compared with HC. On the other hand, CD11b MFI on lymphocytes, monocytes and neutrophils was higher in PD, HD and CRF children compared with HC. CD16 and CD64 MFI

were not different among the groups and CD35 MFI was only lower on lymphocytes from PD, HD and CRF compared with HC.

**Conclusions.** In children with chronic renal failure, whether dialysed or not, FcγRII expression on lymphocytes, monocytes and neutrophils was reduced and CR3 expression was increased. Furthermore, CR1 expression on lymphocytes, important for the humoral response, was lower in children with renal failure. Age and uraemia are associated with these abnormalities and might contribute to impaired immune function in children with chronic renal failure.

**Keywords:** chronic renal failure; complement receptors; FcγR; haemodialysis; immunoglobulin G receptors; peritoneal dialysis

### **Introduction**

Immunoglobulin (Ig) and complement receptors are important for the interaction between humoral and cellular immunities. These receptors bind to IgG- and complement-opsonized micro-organisms and facilitate phagocytosis. Immunoglobulin receptors for IgG, also called FcγR, can be divided into three different types, designated FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16), each with unique binding characteristics for IgG and its subclasses [1]. FcγR are present on monocytes, neutrophils, natural killer cells and lymphocytes.

Four different complement receptors (CR) are known: CR1, CR2, CR3 and CR4. CR1 (CD35), an opsonin receptor for C3b, is present on neutrophils and monocytes that mediate phagocytosis. CR1 on B lymphocytes, together with CR2, mediate lymphocyte

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activation. The cleavage of C3b by factors H and I results in an inactive complement protein, iC3b, which has a low affinity for CR1. However, iC3b still has an important opsonic activity, binding also to CR3 (CD11b) and CR4. CR3 and CR4 augment the activities of Fc receptors and CR1 in activating phagocytosis [2,3]. CR1 and CR3 are especially important for inducing the phagocytosis of complement-coated bacteria.

Little information is available on the expression of Fc $\gamma$ R and CR in the blood of patients with chronic renal failure, whether treated with dialysis or not. Some studies have investigated their expression on peritoneal macrophages [4,5]; others have measured their expression during a haemodialysis session in order to explore the effects of the dialyser membrane and the dialysis treatment itself on receptor expression. Some authors have described an increased CD16 (Fc $\gamma$ RIII)-positive monocyte population in peritoneal dialysis and haemodialysis patients compared with healthy controls, a phenotype that has been linked to tissue macrophages in the context of the stage of maturation [6–9]. During haemodialysis, this CD16<sup>+</sup> monocyte population decreased [8,9]. No difference was found between adult peritoneal dialysis patients and healthy controls by Brauner *et al.* [7] in the expression of CD11b (CR3) on monocytes. No information is available on the expression of Fc $\gamma$ RII (CD32) and Fc $\gamma$ RI (CD64) on leukocytes in the blood of stable peritoneal dialysis and haemodialysis patients. In children on peritoneal dialysis, a longitudinal study (3 years) has been performed by Wasik *et al.* [10] on CD16 (Fc $\gamma$ RIII) and CD35 (CR1) expression on phagocytic cells. They found a temporary increase of the percentages of CD16<sup>+</sup> and CD35<sup>+</sup> neutrophils in blood, during the first 3 months of peritoneal dialysis. Studies on the effect of age on receptor expression in children are not available.

In order to further explore the mechanisms responsible for immune system abnormalities during chronic renal failure in childhood and the influence of dialysis on them, the Fc $\gamma$ R and CR expression of white blood cells (WBC) were analysed in children with chronic renal failure not yet dialysed and in children treated with haemodialysis or peritoneal dialysis.

**Table 1.** Patients' characteristics

	HC	PD	HD	CRF
Number	33	40	23	46
Age (years)	6.0 <sup>a</sup> (0.8–17.5)	10.1 (1.7–18.3)	12.7 (1.7–19.2)	10.3 (0.5–19.9)
Duration of dialysis (years)		1.4 (0.2–8.9)	2.2 (0.4–7.2)	
GFR (ml/min/1.73 m <sup>2</sup> )				15 (4–50)

Results are presented as median (range).

<sup>a</sup>The median age of HC is lower than that of PD, HD and CRF children ( $P < 0.05$ ).

## Subjects and methods

Blood samples were obtained for Fc $\gamma$ R and CR expression analysis from children: 40 treated with peritoneal dialysis (PD), 23 on haemodialysis (HD), 46 with chronic renal failure not yet dialysed (CRF) and 33 healthy controls (HC). Blood samples were drawn just before starting the haemodialysis session in the HD children. The medians (ranges) of age, glomerular filtration rate (GFR) and duration of dialysis treatment are summarized in Table 1. In CRF patients, the GFR was estimated by the Schwartz formula [11]. Of those, 30% (14/46) had moderate renal insufficiency (30–60 ml/min/1.73 m<sup>2</sup>), 20% (9/46) a severe renal insufficiency (15–30 ml/min/1.73 m<sup>2</sup>) and 50% (23/46) pre-terminal renal failure ( $\leq 15$  ml/min/1.73 m<sup>2</sup>). The primary renal diseases of the patients are listed in Table 2. Blood samples were collected in EDTA tubes by venipuncture. WBC were isolated by centrifugation (500 g, 10 min, 4°C) after cell fixation with paraformaldehyde 1% (PFA). Erythrocytes were lysed with ammonium chloride (0.155 mol/l) and potassium-EDTA (0.5 mmol/l) and WBC were subsequently washed with PBAP [phosphate-buffered saline solution supplemented with 0.5% (wt/vol) bovine serum albumin, 0.01% (wt/vol) sodium azide and 0.5 mmol/l potassium-EDTA]. WBC were again fixed with 4% PFA for 10 min followed by centrifugation (500 g, 10 min, 4°C). The Fc receptor of WBC was blocked with 10% normal human pool serum. WBC were incubated for 30 min on ice in the dark with saturating amounts of FITC-labelled CD16 (Fc $\gamma$ RIII) obtained from the CLB Sanquin Blood Supply Foundation, Amsterdam, the Netherlands (clone CLB-Fc-gran/1, 5D2), CD32 (Fc $\gamma$ RII) (clone AT10; Instruchemie Hilversum B.V., The Netherlands), CD64 (Fc $\gamma$ RI) (clone P3/NS1/1-Ag4-1; Medarex, Annandale, USA), CD11b (CR3) (clone CLB-mon-gran/1, B2; CLB) and CD35 (CR1) (clone E11; Instruchemie) monoclonal antibodies (mAb). After incubation, the cells were washed with PBAP and again fixed with PFA 1%. Flow cytometry was performed within the following 12 h with the FACScan (Beckton Dickinson Immunocytometry Systems, San Jose, CA, USA). Lymphocytes, monocytes and neutrophils were distinguished on the basis of their size and granularity by

**Table 2.** Primary renal diseases of the patients

	PD	HD	CRF
Urological malformation	13	7	17
Glomerulopathy	10	3	10
Haemolytic uraemic syndrome	4	3	4
Metabolic disease	1	2	1
Congenital disease	7	4	12
Other diseases	3	1	2
Unknown	2	3	0
Total	40	23	46

Urological malformation: 22 children with urethral values, 12 reflux nephropathy, one bilateral duplicated kidney, one neurogenic bladder, one bladder exstrophy. Glomerulopathy: 12 children with focal segmental glomerulosclerosis, five congenital nephrotic syndrome, two rapidly progressive glomerulonephritis, one Alport's syndrome, two Henoch-Schönlein purpura nephritis, one lupus nephritis. Congenital disease: nine children with renal dysplasia, six polycystic kidney disease, seven nephronophtisis, one tuberous sclerosis. Other diseases: five children with acute tubular necrosis, one bilateral Wilms' tumour.

using a dot plot of forward scatter (FSC) vs side scatter. To adjust the monocyte population, PE-conjugated anti-CD14 mAb was used; for the neutrophils anti-CD16 was used. Peripheral blood mononuclear cells from a buffy coat of a healthy person were included in every FACS analysis to control for interassay variations. A total of 20 000 counts was taken for each leukocyte sample. The positively labelled fraction was determined by comparing with an isotype-matched control antibody. The percentages of Fc $\gamma$ R- and CR-positive cells were calculated. Fluorescence-labelled mAb are used to detect certain cell receptors. The number of receptors per cell is directly related to the intensity of the fluorescence, measured by the FACS after incubation of the cells with these antibodies. The mean fluorescence intensity (MFI) is the average fluorescence intensity of all analysed cells. Data are given as percentages of receptor-positive cells and MFI.

The study was approved by the Medical Ethical Review Committee of the hospital and written informed consent was obtained from children or their parents or both.

### Statistical analysis

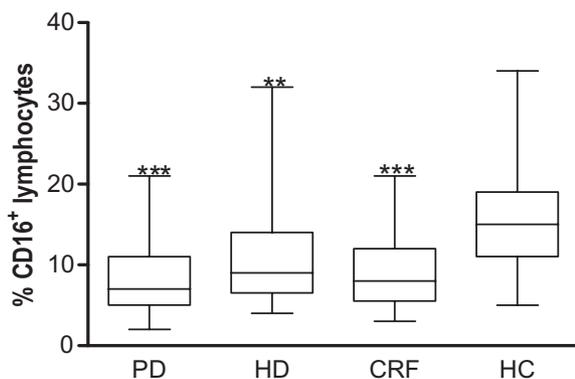
The results are expressed as medians and ranges. Differences between all groups were tested with the Kruskal–Wallis one-way analysis of variance (non-parametric ANOVA). Differences between two groups were tested with the non-parametric unpaired Mann–Whitney test.

## Results

### CD16 (Fc $\gamma$ RIII)

**Percentage of receptor-positive cells.** The percentages of CD16<sup>+</sup> lymphocytes, which represent the natural killer cell population, were lower in PD, HD and CRF compared with HC children (Figure 1). All neutrophils were positive for CD16, whereas only 20% of the monocytes were positive for CD16. The percentages of CD16<sup>+</sup> monocytes were slightly lower in CRF (18%) compared with HC (22%;  $P < 0.01$ ). No differences were found between PD, HD and CRF children.

**MFI.** The CD16 MFI was not different among the groups (Table 3).



**Fig. 1.** Proportions of Fc $\gamma$ RIII (CD16)-positive lymphocytes (natural killer cells). Box-and-whisker plot; minimum, maximum, 25% and 75% percentiles and median. \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

### CD32 (Fc $\gamma$ RII)

**Percentage of receptor-positive cells.** The percentages of CD32<sup>+</sup> lymphocytes were lower in PD, HD and CRF children compared with HC ( $P < 0.01$ ; Figure 2). Monocytes and neutrophils were all positive for CD32.

**MFI.** The CD32 MFI of lymphocytes, monocytes and neutrophils was lower in PD, HD and CRF children compared with HC (Table 3).

### CD64 (Fc $\gamma$ RI)

**Percentage of receptor-positive cells.** Lymphocytes were not positive for CD64 whereas both monocytes and neutrophils were positive for CD64.

**Table 3.** The median (range) of Fc $\gamma$ R and CR expressions (MFI) on WBC

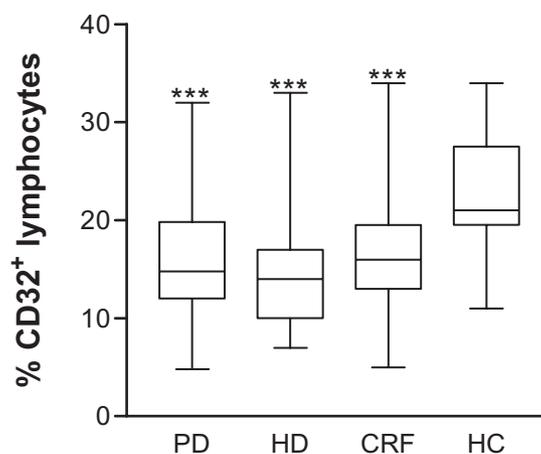
	HC	PD	HD	CRF	
CD16	Ly	41 (17–106)	36 (14–72)	37 (13–56)	35 (13–130)
	Mo	53 (21–109)	45 (19–93) <sup>a</sup>	58 (8–88)	48 (13–151)
	Neu	167 (57–282)	138 (46–345)	145 (59–268)	151 (43–418)
CD32	Ly	156 (21–905)	33 (11–245) <sup>b</sup>	33 (15–280) <sup>c</sup>	35 (17–356) <sup>b</sup>
	Mo	77 (37–308)	54 (36–141) <sup>b</sup>	55 (37–160) <sup>b</sup>	52 (16–251) <sup>b</sup>
	Neu	69 (39–162)	47 (30–112) <sup>b</sup>	51 (40–83) <sup>c</sup>	50 (29–108) <sup>b</sup>
CD64	Mo	50 (14–92)	51 (27–105)	45 (23–72)	43 (18–91)
	Neu	13 (6–66)	14 (9–58)	13 (5–27)	13 (7–66)
CD11b	Ly	15 (11–38)	19 (11–42) <sup>c</sup>	26 (11–82) <sup>d</sup>	27 (11–57) <sup>b</sup>
	Mo	28 (17–61)	36 (16–79) <sup>c</sup>	39 (16–76) <sup>d</sup>	39 (15–100) <sup>b</sup>
	Neu	25 (15–62)	43 (12–217) <sup>b</sup>	42 (18–129) <sup>d</sup>	44 (15–411) <sup>b</sup>
CD35	Ly	47 (18–137)	30 (6–62) <sup>b</sup>	30 (19–131) <sup>d</sup>	31 (14–82) <sup>b</sup>
	Mo	17 (9–180)	14 (9–113)	19 (9–74)	12 (8–105)
	Neu	22 (11–73)	17 (8–56)	32 (9–67) <sup>f</sup>	15 (8–64) <sup>c</sup>

Ly, lymphocytes; Mo, monocytes; Neu, neutrophils. The CD16<sup>+</sup> lymphocyte population represents the natural killer cells.

<sup>a</sup>PD vs HD:  $P = 0.03$ .

<sup>b</sup> $P < 0.001$ ; <sup>c</sup> $P < 0.01$ ; <sup>d</sup> $P < 0.05$ ; <sup>e</sup> $P = 0.057$  when compared with HC.

<sup>f</sup>HD vs CRF:  $P = 0.04$ .



**Fig. 2.** Proportions of Fc $\gamma$ RII (CD32)-positive lymphocytes. Box-and-whisker plot; minimum, maximum, 25% and 75% percentiles and median. \*\*\* $P < 0.001$ .

**MFI.** The expression of CD64 on neutrophils and monocytes was low and not different between the groups (Table 3).

### CD11b (CR3)

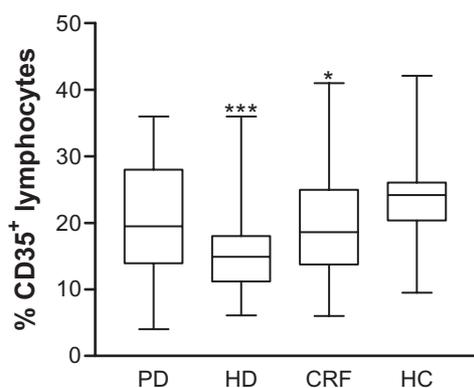
**Percentage of receptor-positive cells.** The fraction of CD11b<sup>+</sup> lymphocytes was 20% in PD children ( $P < 0.01$ ), 28% in HD [not significant (NS)] and 24% in CRF patients (NS) compared with 27% in HC. PD children had a lower percentage of CD11b<sup>+</sup> lymphocytes than HD and CRF children ( $P < 0.01$ ). Both monocytes and neutrophils were positive for CD11b.

**MFI.** The MFI of CD11b on lymphocytes were higher in PD, HD and CRF compared with HC (Table 3). The CD11b expression on monocytes was higher in HD and CRF than in HC (Table 3). For the PD group, this was just below significance ( $P = 0.057$ ). The MFI of CD11b on neutrophils was also higher in PD, HD and CRF children compared with HC (Table 3).

### CD35 (CR1)

**Percentage of receptor-positive cells.** The percentages of CD35<sup>+</sup> lymphocytes were lower in HD and CRF compared with HC children. In PD children, the difference was not significant (Figure 3). Both monocytes and neutrophils were positive for CD35.

**MFI.** The MFI of CD35 on lymphocytes were lower in PD, HD and CRF children compared with HC (Table 3). No differences were found in the MFI of CD35 on monocytes between the groups. The MFI of CD35 on neutrophils was lower only in CRF children compared with HC (Table 3). Furthermore, CRF children had a slightly lower CD35 expression on neutrophils compared with HD (Table 3).



**Fig. 3.** Proportions of CR1 (CD35)-positive lymphocytes. Box-and-whisker plot; minimum, maximum, 25% and 75% percentiles and median.  $P < 0.05$ , \*\*\* $P < 0.001$ .

## Discussion

The possible differences of FcγR and CR expression on WBC between children with chronic renal failure, whether dialysed or not, and their healthy controls were investigated in this study. Differences were found especially for FcγRII (CD32) and CR3 (CD11b) on all cell populations and for CR1 (CD35) only on lymphocytes. The percentages of CD32<sup>+</sup> lymphocytes, monocytes and neutrophils and CD32 MFI were lower in PD, HD and CRF children in comparison with HC. On the other hand, CD11b MFI, but not the percentage of positive cells, was higher on lymphocytes, monocytes and neutrophils in all patient groups compared with HC. Compared with HC, CD35 expression on lymphocytes was reduced in children with chronic renal failure. Differences between the FcγRs or CRs were not studied by age group; therefore, we cannot exclude completely that the differences we found are related to age, since the groups were not equally matched for age. However, this possibility is doubtful, since there was no direct correlation between receptor expression and age, except for the percentage of CD32<sup>+</sup> cells (data not shown;  $r = -0.4$ ,  $P < 0.001$ ). Moreover, statistically significant differences were found in all patient groups in comparison with controls. Therefore, we think that the most probable explanation for the differences that we found is the uraemic state of the patients.

It is difficult to compare our results with other studies performed in dialysis patients, because many studies observed the effect of the dialysis procedure itself on membrane expression and, therefore, did not include normal controls. Furthermore, the methods and the expressions of results are often different, which makes comparison impossible.

It is well established that the binding of opsonized particles to FcγR and CR enhances the efficiency of phagocytosis [12]. The exact mechanism behind the increased susceptibility to infections in dialysis patients has still not been elucidated. The lower FcγRII expression on monocytes and neutrophils might result in a reduced phagocytic capacity and, thus, increased susceptibility to infections. This assumption is strengthened by a study by Rossmann *et al.* [13] who found a positive correlation between macrophage FcγRII expression and FcγR function.

CR3 is not competent to mediate phagocytosis in resting unactivated phagocytes, but this receptor is activated after the phagocyte is exposed to cytokines and chemoattractants [14]. The increased CR3 expression in our patients might be a reflection of a state of chronic inflammation caused by chronic renal failure. The consequence of the combination of a lower FcγRII and a higher CR3 expression in children with renal failure remains unclear.

The influence of lymphocyte FcγR and CR expression on the regulation of antibody production in humans is not understood completely. In one study performed on mice, Takai *et al.* [15] found a negative feedback mechanism between FcγRII expression and antibody production. If this was the case in the

population of our present study, high IgG levels would have been expected. However, we previously reported the presence of low Ig levels in the same population of children with chronic renal failure [16]. Reduced Fc $\gamma$ RII expression and low Ig serum levels together might, therefore, result in a reduced capacity to kill micro-organisms. The exact role of CD35 (CR1) on B lymphocytes in the humoral immune response remains unclear. Both activating and inhibiting effects have been observed [17].

It has been demonstrated that, in children with solid tumours, treatment with granulocyte/macrophage colony-stimulating factor (GM-CSF) results in a decline of Fc $\gamma$ RII and Fc $\gamma$ RIII expression on neutrophils combined with an increase of CR3 [18]. However, an increase of the expression of Fc $\gamma$ RII was found on monocytes. Only one study in adult peritoneal dialysis patients reported increased plasma GM-CSF levels [19]. Thus, it might be that the reduced Fc $\gamma$ RII expression combined with the increased CR3 expression found in our study could be caused by increased GM-CSF plasma levels. This hypothesis should be investigated further, because no information is actually available on plasma GM-CSF levels in children with chronic renal failure.

The expression of Fc $\gamma$ R and CR on WBC is regulated by cytokines [1,11,20]. Interferon- $\gamma$  (IFN- $\gamma$ ) is an important cytokine for the killing of bacteria by macrophages. After IFN- $\gamma$  treatment, an increase of Fc $\gamma$ RI expression is observed on monocytes from newborns and adults. However, Fc $\gamma$ RII expression on monocytes increased only in newborns, but not in adults [21]. Erbe *et al.* [20] demonstrated an upregulation only of Fc $\gamma$ RI on monocytes and neutrophils *in vitro* after IFN- $\gamma$  treatment [20]. Pan *et al.* [22] found an increased expression of Fc $\gamma$ RII and Fc $\gamma$ RIII on human endothelial cells after stimulation with IFN- $\gamma$ . Gasparoni *et al.* [23] showed that in infants the synthesis of IFN- $\gamma$  by CD4<sup>+</sup> and CD8<sup>+</sup> cells is impaired when compared with older children and adults. Thus, the differences in cytokine production by lymphocytes and monocytes, which is related to age and state of uraemia, might theoretically play a role in the alterations of Fc $\gamma$ R and CR expression on WBC. However, this was not investigated in our study.

The expressions of the other Fc $\gamma$  receptors were not different among the groups, except for a slightly lower Fc $\gamma$ RIII (CD16)-positive monocyte population in CRF children when compared with HC. This is in contrast to other studies, performed in adult peritoneal dialysis and haemodialysis patients, which described a higher CD16<sup>+</sup> monocyte population [7–9]. CD16 appears on the cell surface of monocytes during their maturational process. This might imply that monocytes from children with chronic renal failure are less mature compared with their healthy age-matched controls and, possibly, also when compared with adult patients with chronic renal failure. For CR1 (CD35) only, the lymphocytes of the patient groups showed lower percentages of CD35<sup>+</sup> cells combined with lower

MFI than HC – something that might also influence antibody production by B cells.

In summary, children with chronic renal failure, whether dialysed or not, showed a down-regulation of Fc $\gamma$ RII (CD32) on lymphocytes, monocytes and neutrophils, combined with an upregulation of CR3 (CD11b) expression levels. Furthermore, CR1 (CD35) expression is reduced on lymphocytes in children with chronic renal failure. Whether or not these alterations might result in the diminished effectiveness of the immune system is speculative.

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*Conflict of interest statement.* None declared.

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