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RESEARCH ARTICLE

Antibody response to pneumococcal capsular polysaccharide vaccination in patients with chronic kidney disease

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ABSTRACT. Patients with chronic kidney disease (CKD) or on dialysis are at greater risk of infection, which might be due to a defective immune function. While there are controversial reports on efficacy of vaccination in this group of patients, the aim of this study was to evaluate the antibody response to pneumococcal capsular polysaccharide vaccine (PPV23) in CKD patients. Sixty-six patients with CKD and 40 healthy individuals were vaccinated with PPV23. Blood samples were taken before and four weeks after vaccination. Specific antibodies against whole pneumococcal antigens were measured using an enzyme-linked immunosorbent assay (ELISA) technique. Among the 66 vaccinated patients, 14 (21%) were hypo-responsive to vaccine (group 1), while 52 had a normal specific-antibody response (group 2). Post-vaccination, anti-pneumococcal IgG titers in group 1 were significantly lower than those in group 2 ($p = 0.012$ for IgG post-vaccination and $p = 0.020$ for IgG2 post-vaccination). The fold increase or ratio increase of the anti-pneumococcal IgG titer in patients of group 1 was also significantly lower than that in group 2 or the healthy control group ($p = 0.001$ *versus* group 2 and $p = 0.005$ *versus* control group). During follow-up of both patient groups, group 1 patients developed more episodes of pneumococcal infections than those patients in group 2 ($p = 0.007$). In conclusion, although the majority of patients with CKD were responders to the polysaccharide vaccine, a substantial proportion of patients failed to mount an adequate antibody response to PPV23 and remained at significant risk of pneumococcal infection. Nevertheless, this vaccination policy should be administered as it could prevent infection in responder patients.

Keywords: chronic kidney disease, pneumococcal vaccination, polysaccharide vaccine, antibody response

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Chronic kidney disease (CKD) is a progressive loss of renal function. Patients with this condition have an increased risk of infections, possibly due to deficient mucocutaneous barrier, contamination of vascular access and peritoneal dialysis catheters, and a defective immune function [1, 2]. In addition, patients with CKD might have a reduced response to vaccines [2, 3].

Some studies have shown that patients with CKD are more susceptible to recurrent respiratory infection, resulting in morbidity and mortality [4-7]. The report from the US Renal Data System indicates that the prevalence of pneumonia requiring hospital admission is high in dialysis patients [8]. More than half of the reported cases of pneumonia in dialysis patients seems to be due to *Streptococcus pneumoniae* [9]. Indeed the incidence of pneumonia infection is also increased in renal transplant recipients [10].

There are controversial reports on the efficacy of vaccination in patients with renal disease [11-16]. Although a protective antibody level after immunization with the 23-pneumococcal vaccination was denied in some studies [5, 11, 12, 15, 16], there are a few reports suggesting benefit from vaccination in this group of patients [13, 14].

The aim of this prospective study was to determine the antibody response to vaccination with 23-valent pneumococcal capsular polysaccharide vaccine (PPV23) in CKD patients. The response of this group of patients to pneumococcal vaccination was compared with the response of a group of healthy individuals.

DONORS AND METHODS

Patients

A total of 66 patients with CKD, who were referred to a hospital in Tehran, were enrolled to this prospective study. Forty, healthy individuals were also selected as the control group. Diagnosis of patients with CKD was based on criteria suggested by Guidelines of National Kidney Foundation [17, 18]. Exclusion criteria for all the patients included: previous pneumococcal vaccination within the past five years, any treatments for allograft rejection or immunosuppressive therapy in the previous six months, use of pooled immunoglobulin product within the last six months, and a history of immunodeficiency. This study was carried out from March 2006 to February 2007. The study protocol was reviewed and approved by the Hospital Ethics Committee, and informed consent was obtained from each patient.

Methods

A questionnaire was designed to collect demographic information and medical histories for each patient by reviewing the patient's records. All patients and the healthy individuals in the control group received a single dose of 0.5 mL of unconjugated pneumococcus polyvalent vaccine (PPV23, PNEUMO 23® Aventis Pasteur, France) intramuscularly; blood samples were taken before and four weeks after vaccination. Serum samples were aliquoted and stored at - 20˚C until assayed for antibody measurements. Specific antibodies against pneumococcal capsular polysaccharide (PCP) were measured using the protocol of the third-generation enzyme-linked immunosorbent assay format [19].

The assay is designed for measuring the IgG antibody responses to pneumococcal vaccine incorporating 23 polysaccharides isolated from *Streptococcus pneumoniae*. These polysaccharides represent approximately 80% of the commonly encountered, virulent serotypes. The measurements of specific IgG antibodies against PCP were determined by an enzyme immunoassay kit (the "VaccZyme Anti-PCP IgG and IgG2, The Binding Site Ltd, Birmingham, U.K.). In this assay, microwells were precoated with the PCP antigen. The antigen has the same composition as that of the licensed 23-valent vaccine. Serum samples were tested in accordance with the manufacturer's instructions. Preadsorption of antibodies onto pneumococcal cell wall polysaccharide (C-PS) was performed using diluents containing highly purified C-PS. Pyrogen-free water was used to avoid nonspecific background binding, and serum samples were diluted 1:100 as recommended and were further diluted down to 1:1000 in case of higher titers. The titers for anti PCP IgG antibodies were determined with reference to the standard serum included in the kit and were expressed as microgram/mL (μg/mL). A reference plasma pool with preassigned values was used as control. The lower limit of the assay quantitation was 3 μg/mL. Serum samples were tested in duplicate. Results were reported as end-point titer, determined by the highest dilution giving an optical density of 0.2 or higher. There are no universal criteria for adequate antibody response to pneumococcal-specific antibody levels, and each laboratory has to consider the response in normal healthy controls in order to generate criteria to define hypo-responsivness to vaccine.

The control group, made up of forty healthy donors, was studied to establish a criterion for a normal response to 23-valent pneumococcal vaccine. None of them had a history of primary or secondary immunodeficiency or recurrent infections. The response to vaccination with *S. pneumoniae* in 30% of subjects is attributable to C-PS antibodies and not to specific anti-PCP IgG. These C-PS antibodies confer limited protection against pneumococcal infection; consequently C-PS absorption has been incorporated in these assays.

All subjects showing an increase in specific antibody titers equal to or greater than lower limit of the 2- tailed, 90% probability interval of post-immunization specific IgG of the healthy adults were defined as normally responsive subjects [20, 21]; the subjects with antibody titers lower than this limit were defined as hypo-responsive cases.

Statistical analysis

Data were analyzed using an SPSS 14.0 software package. Specific antibody titers were expressed as the geometric mean. Comparisons between groups were performed using the Fisher Exact Test. Wilcoxon Signed Ranks Test was performed for analyzing non-parametric data.

RESULTS

A total of 66, consecutive, adult patients with CKD (45 males and 21 females), aged 18 to 64 years (mean age, 41 ± 13 years), and 40 control subjects were evaluated for antibody response to PPV23. Antibodies against PCP antigens were measured before and 28 days after vaccination. The geometric means for the anti-pneumococcal IgG titer before and after vaccination in the control group were 71 and 395 μg/mL respectively *(table 2)*. The lower limit of the two-tailed, 90% probability interval of post-immunization specific IgG was 129 μg/mL, which is used as the minimum, significant increase for adequate response in the patient group. Of 66 vaccinated patients with CKD, 14 (21%) were found to be hypo-responsive to vaccine (group 1). Patients who had a normal specific antibody response were regarded as responding patients or group 2 (n = 52). Pre- and post-immunization (four weeks) antibody titers (IgG and IgG2) for patients in group 1, group 2 and the controls (n = 52) are presented in the *tables 1* and *2* as well as in *figures 1-3*.

The pre-immunization, post-immunization and absolute increase of anti-pneumococcal IgG levels in group 1 patients were much lower than those in group 2 patients *(table 2)*. Post-vaccination titers in group 1 were significantly lower than those in group 2 ($p = 0.012$ for IgG post-vaccination and $p = 0.020$ for IgG2 post-vaccination). The lower anti-pneumococcal response in patients of group 1 is also reflected in the fold increase (the ratio of post- to pre-immunization IgG titers), which is significantly lower in this group *(figure 4)* compared to

Table 1
Characteristics of patients with chronic kidney disease who were deficient in specific antibody production (n = 14)

No.	Age	Sex	Total IgG level (µg/mL) to PPV 23 Before and four weeks after vaccination		Increase (µg/mL)	IgG2 level (µg/mL) to PPV 23 Before and four weeks after vaccination		Response to PPV23
1	39	F	18	32	14	12	14	Hypo
2	46	F	50	170	120	22	72	Hypo
3	49	M	20	116	96	9	52	Hypo
4	44	M	17	82	65	10	34	Hypo
5	39	F	23	80	57	8	12	Hypo
6	44	M	56	130	74	24	60	Hypo
7	49	M	14	32	18	6	15	Hypo
8	56	M	32	142	110	14	70	Hypo
9	39	F	5	18	13	3	6	Hypo
10	28	F	18	72	54	8	34	Hypo
11	23	M	20	84	64	11	40	Hypo
12	48	F	50	170	120	22	80	Hypo
13	19	M	27	30	3	12	12	Hypo
14	27	M	50	62	12	20	30	Hypo

Hypo: indicates hypo-responsive.

Table 2
The titers for antibody response to immunization with pneumococcal polysaccharide vaccine in responding patients, hypo-responsive patients with chronic kidney disease and the control group. Data are presented as geometric means. Values in parenthesis represent the range of corresponding variables

Groups	Total IgG (µg/mL) Pre-immunization	Total IgG (µg/mL) Post-immunization	Fold increase mean ratio of post- to pre-immunization)
Hypo-responsive patients (n = 14)	24 (5-56)	71 (18-170)[a]	3.2 ± 1.3[b, c]
Responder patients (n = 52)	96 (12-390)	376 (190-450)	5.6 ± 4.4
Control group (n = 40)	70 (4-450)	395 (200-450)	6.6 ± 6.8

[a] p = 0.012 *versus* responder patients.
[b] p = 0.001 *versus* responder patients.
[c] p = 0.005 *versus* control group.

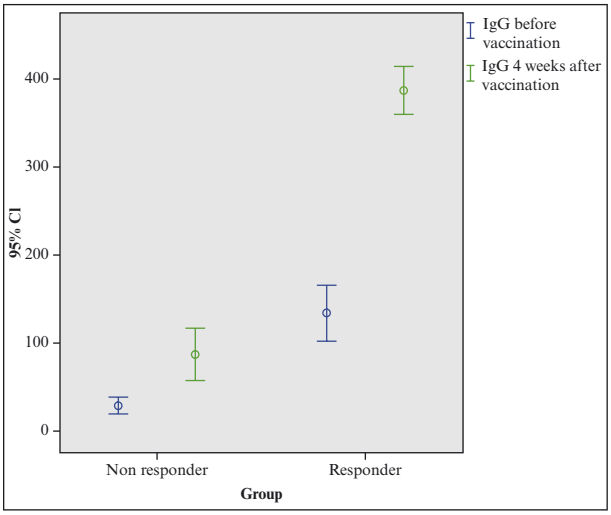

Figure 1
Pre- and post-immunization IgG antibody titers for pneumococcal polysaccharide vaccine in two groups of patients with chronic kidney disease who were either responders or hypo-responsive to the pneumococcal antigens.

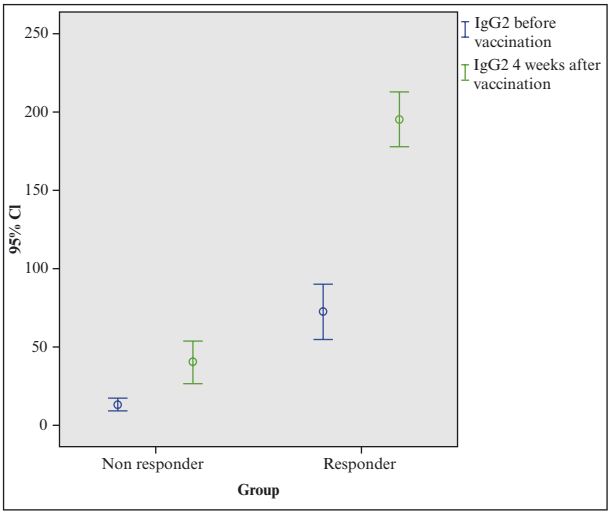

Figure 2
Pre- and post-immunization IgG2 antibody titers for pneumococcal polysaccharide vaccine in two groups of patients with chronic kidney disease, who were either responders or hypo-responsive to the pneumococcal antigens.

that in either group 2 or the control group (p = 0.001 *versus* responder patients and p = 0.005 *versus* control group) *(table 2)*. No significant difference was detected in anti-pneumococcal IgG between healthy control subjects and CKD patients with normal antibody production.

Although there was no significant difference in pre-vaccination titer between two groups, there was a direct association between IgG and IgG2 after vaccination in the studied groups (p < 0.001, R = 0.984, F = 1951.79, *figure 5*).

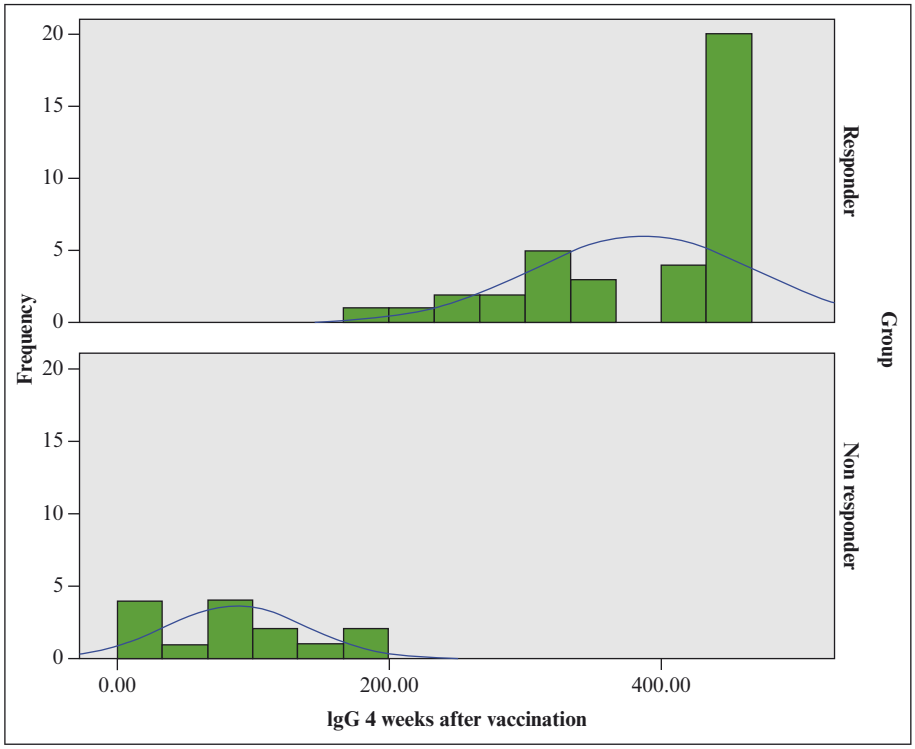

Figure 3
Post-immunization IgG antibody titers for pneumococcal polysaccharide vaccine in two groups of patients with chronic kidney disease.

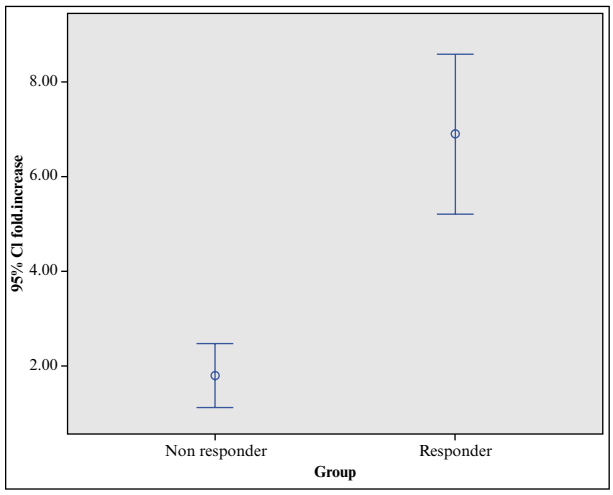

Figure 4
Fold-rise (the ratio of post- to pre-immunization IgG titer) in two groups of patients with chronic kidney disease.

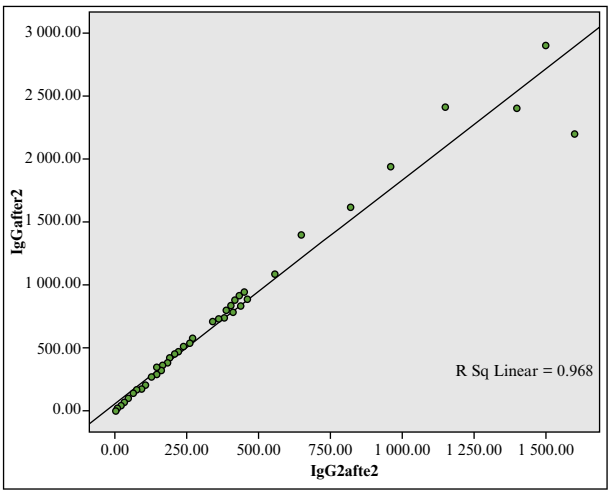

Figure 5
Direct association between IgG and IgG2 post-vaccination.

Demographic and clinical data of patients in groups 1 and 2 are shown in the *tables 1* and *3*. During follow-up of both groups of patients (median two years), patients in Group 1 developed more episodes of pneumococcal infections than those in group 2. Seven episodes of otitis media, three bacterial pneumonia, four sinusitis, two bronchitis, and two chronic diarrhea were documented in group 1 *(table 3)*.

DISCUSSION

Patients with CKD have a high risk of *Streptococcus pneumoniae* infections, which could be due to the reduced antibody response to bacterial polysaccharide antigens in these patients [8-10, 22]. Although pneumococcal immunization in patients with CKD is recommended [23], there are few reported studies involving evaluation of the antibody response to polysaccharide antigens in patients with CKD or the efficacy of pneumococcal vaccination in these patients [12, 24]. Adequate antibody response to pneumococcal antigens in CKD patients can indicate the importance of vaccination in order to protect them against pneumococcal infections.
The current study showed that 21% of patients with CKD were hypo-responsive to pneumococcal antigens, which is in agreement with the study performed by Fuchshuber *et al.* [12] showing that 83% of the patients with chronic

Table 3
Comparison of patients' characteristics and spectrum of infections in two groups of patients with chronic kidney disease

Parameters	Group 1	Group 2	P-value
Number	14	52	-
Sex (male/female)	6/8	15/37	-
Age median at the time of study (range)	41.5 (19-56)	43 (18-64)	0.46
Follow-up (months); median (range)	24 (18-30)	24 (18-30)	-
Episode of pneumonia after admission	3	0	0.007
Episode of sinusitis after admission	4	0	0.001
Episode of otitis media after admission	7	1	< 0.001
Episode of bronchitis after admission	2	0	0.042
Episode of chronic diarrhea after admission	2	0	0.042

renal disease had protective levels of antibody four weeks after immunization. This indicates that measurement of post-vaccination antibody levels can be used to identify the poor responders who most likely are at increased risk of pneumococcal infection.

In the present study, total pre- and post-geometric mean, anti-pneumococcal IgG titers in patients who had a normal specific antibody response did not differ from those of age-matched control subjects. These data are in agreement with previous immunization data from Ambrosino *et al.* [25] involving children with recurrent infections and normal serum IgG subclass levels who had been immunized with 14-valent PPV, which confirms the immungenecity of the 23-valent PPV in our population patients with CKD. Our data for post-immunization titers of anti-pneumococcal IgG in patients, who had a normal specific antibody response, are also consistent with the data of Dengler *et al.* [26], who investigated the immunogenicity of 23-valent PPV in transplanted patients.

Patients in group 1, who were hypo-responsive to polysaccharide vaccine, experienced more episodes of respiratory pneumococcal infections during the follow-up period than group 2 patients. These findings support previous studies that showed that patients with CKD are more susceptible to recurrent respiratory infection [4-7]. Infections in dialysis patients, caused by *Streptococcus pneumoniae*, occurring mainly in the lower respiratory tract, require hospital admission [8, 9].

There are limited data suggesting benefit from pneumococcal vaccination in patients with renal disease [13, 14]. In a study by Simberkoff *et al.* [27], evaluating the efficacy of the 14-valent PPV in high-risk patients, including patients with kidney disease, did not show any efficacy of the vaccine in the prevention of pneumonia or bronchitis. Later reports of case-control studies in patients who had chronic illness and an indication for PPV immunization showed significant protective efficacy of the pneumococcal vaccine in the prevention of pneumococcal bacteremia [28]. Published data indicate that those groups, including hemodialysis and renal transplant recipients, who had a nearly normal antibody response to pneumococcal vaccine will require revaccination to maintain immunity [13]. However, poor responders proved to be unresponsive to booster doses of polysaccharide antigens [29, 30]. Purified polysaccharide antigens result in T cell-independent, type-2 antibody formation and do not elicit memory B cells. T cell-independent antibody responses cannot be boosted to produce secondary responses. It is possible that conjugate vaccines (capsular polysaccharides conjugated with carrier proteins) might improve the immune response in non-responders to PPV: the 7-valent pneumococcal conjugate vaccine has improved the response rate to PPV23 in patients with selective antibody deficiency [31].

The results obtained here suggest that an immunization policy with pneumococcal polysaccharides might help to protect the majority of patients with CKD against invasive pneumococcal diseases; therefore, we suggest that the vaccine be administered. Nevertheless, some subjects who cannot mount an adequate antibody response to polysasaccharide antigens will remain at significant risk for such infections, and should be offered other, prophylactic methods such as immunization with pneumococcal conjugate vaccines.

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