UREMIC PRURITUS IN THE MAINTENANCE OF HEMODIALYSIS PATIENTS

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Pruritus is a common symptom among patients on hemodialysis (HD). We studied 68 HD patients to assess the role of iron status, anemia, inflammation, serum beta2-microglobulin ($ß_2M$) levels and other common serum and dialysis parameters particularly in uremic pruritis. The intensity of pruritus was quantified into three groups: mild, moderate, and severe. Fifty-six percent of the patients had pruritus, with mild pruritus in 17% (n=12), moderate pruritus in 20% (n=14) and severe pruritus in 17% (n=12). The patients with pruritus had higher serum C-reactive protein (CRP) levels than patients without pruritus (1.34±2.10 vs 0.17±0.34, p=0.002). In addition, the serum CRP levels demonstrated an upward trend in patients with more severe intensity of pruritus (p<0.05). The parameters related to anemia, platelet count , serum iPTH levels, EPO dosage and iron status did not differ between patients with or without pruritus, and neither did age, sex, presence or absence of diabetes mellitus (DM), HD duration, time on HD treatment, serum $ß_2M$ levels, KT/V or nPCR. The serum calcium levels were higher in patients with pruritus than in those without pruritus (9.73±0.68 vs 9.42±0.55, p=0.046). Although the serum calcium levels also showed an upward trend in patients with more severe pruritus, it was not statistically significant (p=0.143). In summary, our findings suggest inflammation and serum calcium may play a role in the pathogenesis of uremic pruritus. (Acta Nephrologica 2003; ***17:*** *63-68)*

Key words: ***uremic pruritus, hemodialysis, C-reactive protein, calcium.***

INTRODUCTION

Pruritus is an unpleasant sensation which elicits the desire to scratch. Prutitus is a dominant symptom of skin disease and a frequent manifestation of systemic disease. Of all the systemic disorders, uremia is certainly the most important cause of pruritus. Uremic pruritus (UP) is often intractable and can lead to tremendous distress among hemodialysis (HD) patients. The incidence of pruritus in HD patients ranges from 30% to 90%.[1] The pathogenesis of UP is poorly understood. Parathyroid hormone was initially implicated as the cause of pruritus,[2] but subsequent studies have failed to confirm this.[3] The theory that altered bivalent ion metabolism, hypercalcemia and hyperphosphatemia[4] lead to HD likewise has not been confirmed.[5] Other metabolic agents such as histamine,[6] bile acids,[7] and opioids[8] have also been suggested to play a major role in UP, but the results have been inconclusive. A relationship between dialysis adequacy and pruritus has been claimed in some studies[9] but rejected in others.[7] Pruritus appears to involve multifactorial, rather than single molecular, causation. The focus of the study was the subjective sensation of pruritus among dialysis patients. We assessed the possibly interactive roles of iron storage status, anemia, inflammation status, serum beta2-microglobulin ($ß_2M$) level and other parameters as well as dialysis adequacy in the UP among HD patients.

PATIENTS AND METHODS

All of the HD patients (n=73) at a hospital in central Taiwan (Bodhi hospital) were included in this study. The patients who had acute infection (n=1), recent surgery (n=1), liver cirrhosis (n=1) or multiple blood transfusions (n=2) were excluded. The other 68 patients all consented to participate in the study. The characteristics of the study's subjects are summarized in Table 1.

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Table 1. The demographics of the included HD patients

Patients (n)	68	
M/F	18/50	
Age (years)	59.7	(25-83)
Duration of HD session (hours)	3.99	(3.5-4.5)
Time on HD therapy (months)	43.3	(3-210)
KT/V	1.37	(0.91-1.75)
Underlying disease		
Diabetic nephropathy (n)	19	
Chronic glomerulonephritis (n)	47	
Polycystic kidney (n)	1	
Obstructive nephropathy (n)	1	

All treatments were kept constant during the period of the study. The participants underwent HD three times a week. The mean duration of the HD sessions was 3.99 h (3.5-4.5 h). Eighty-five percent (58/68) of our HD patients were put on conventional HD, and only 15% (10/68) received high-flux HD. The conventional HD membranes were cellulose, from various manufacturers; all high-flux HD membranes were PMMA. We deliberately disregarded the impact of different dialyzers and techniques in this study, as only a small proportion of the patients were on high-flux HD. None of the patients presented with defined skin lesions. The patients were all questioned by the same nephrologist at a ward round two weeks before blood samplings. Symptoms of pruritus were quantified according to frequency (rare, frequently, every day) and intensity (mild, moderate, severe) based on each patient's subjective awareness (mild, moderate, severe) and response to medical treatments. The most common medical regimens we used in our patients included antihistamine, nicergoline with or without skin lotion. Patients who reported rarely having pruritus were classified in a "no pruritus group." Patients who subjectively reported "mild" symptoms of pruritus and felt free of pruritus after medication were classified in a "mild group." Patients who subjectively reported "moderate" symptoms of pruritus that were partially improved by medication were classified in a "moderate group." Patients who subjectively reported "severe" pruritus and felt no improvement after medication were classified in a "severe group." No visual analog scale (VAS) or pain scale was used to evaluate the intensity of pruritus because only the subjective sensation of pruritus among the dialysis patients was considered in this study. Blood samples were taken before dialysis at a mid-week dialysis session. The following parameters related to anemia and iron status were measured: hemoglobulin (Hb) (g/dl), hematocrit (Hct) (%), mean corpuscular volume (MCV) (μm^3), mean corpuscular hemoglobin concentration (MCHC) (g/dl), platelet ($\times 10^3$), serum iron (µg/dl), total iron binding capacity (TIBC) (µg/dl) and ferritin (ng/ml). The Transferrin saturation index (TSAT) (%) was calculated by the equation: Transferrin saturation index = serum iron/TIBC x100%. Other serum parameters related to dialysis were: urea (mg/dl), creatinine (mg/dl), albumin (g/dl), calcium (mg/dl), phosphate (mg/dl) and blood sugar (mg/dl). Serum C-reactive protein (CRP) (mg/dl) was determined by immunoassay (COBAS INTEGRA C-reactive protein). Serum $ß_2M$ (ug/L) was determined by microparticle enzyme immunoassay (AxSYM $ß_2$-microglobulin). KT/V and nPCR were calculated using Gotch's equation. All values were expressed as mean ± SD. The Student's t test was employed to compare the differences between the patients with and without pruritus. The patients were divided into three groups according to the severity of pruritus. The One-way ANOVA test was used to compare the three groups of patients according to the severity of pruritus. P values <0.05 were considered statistically significant.

RESULTS

Fifty-six percent of the HD patients (38/68) had pruritus. Pruritus was mild in 17% (n=12), moderate in 20% (n=14) and severe in 17% (n=12) as reported by the patients themselves. Parameters related to anemia, platelet count, serum iPTH levels, EPO dosage, and iron status did not differ in the patients with and without pruritus (Table 2). However, the serum CRP levels in the patients with pruritus were higher than those in the patients without pruritus (1.34±2.10 vs 0.17±0.34, p=0.002) (Table 3). The serum CRP levels showed an upward trend in the patients with more severe intensity of pruritus ($p<0.05$) (Table 4, Fig. 1). The serum calcium levels were higher in the patients with pruritus than in those without pruritus (9.73±0.68 vs 9.42±0.55, p=0.046) (Table 3), showing a weak statistical

Table 2. Comparative anemic and iron status in patients with and without pruritus.

Pruritus	No	Yes	*p*
Hb (g/dl)	9.4±1.14	9.5±1.74	NS
Hct (%)	27.7±3.22	28.1±4.92	NS
MCV (μm^3)	88.6±9.76	92.7±8.72	NS
MCHC (g/dl)	33.7±0.96	33.8±1.05	NS
Platelet ($\times 10^3$)	188.8±42.08	189.0±65.03	NS
Iron (µg/dl)	69.0±35.6	71.9±43.17	NS
TIBC (µg/dl)	273.5±65.71	259.9±55.48	NS
TSAT (%)	26.2±14.10	29.2±20.37	NS
Ferritin (ng/ml)	577.4±380.79	785.3±685.10	NS
EPO dose (u/kg)	26.0±10.97	23.2±8.18	NS

Hb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; TSAT: transferrin saturation index; NS: not statistically significant.

Table 3. Comparison of parameters other than anemia and iron status in patients with and without pruritus.

Pruritus	No (n=30)	Yes (n=28)	*p*
Age	56.23±13.81	62.531±3.34	NS
Sex (M/F)	7/23	11/27	NS
DM	8/22	11/27	NS
Td (hours)	3.97±0.29	4.0±0.26	NS
HD duration (months)	37.8±43.34	47.6±33.97	NS
BUN (mg/dl)	64.2±15.83	61.0±13.83	NS
Creatinine (mg/dl)	9.6±2.21	9.1±2.02	NS
Albumin (g/dl)	4.4±0.40	4.3±0.56	NS
Blood sugar (mg/dl)	103.6±49.58	133.3±91.29	NS
Calcium (mg/dl)	9.42±0.55	9.73±0.68	0.046
Phosphate (mg/dl)	5.0±1.58	5.0±1.11	NS
KT/V	1.37±0.17	1.36±0.22	NS
n-PCR(g/kg)	1.16±0.24	1.10±0.20	NS
CRP (mg/dl)	0.17±0.34	1.34±2.10	0.002
IPTH (pg/ml)	246.8±293.36	258.6±348.24	NS
$ß_2M$ (µg/L)	29074.56±7733.71	32701.49±8392.86	NS
EPO dose (u/kg)	26.0±10.97	23.2±8.18	NS

DM: diabetes mellitus; Td: duration of HD session; HD duration: time on HD therapy; n-PCR: normalized protein catabolic rate; CRP: C- reactive protein; IPTH: intact parathyroid hormone; $ß_2M$: Beta2-microglobulin EPO: erythropoietin.

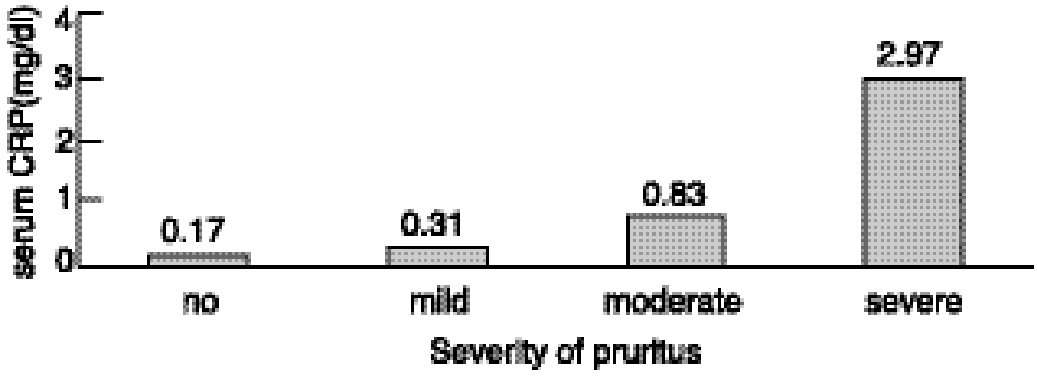

Fig. 1. The correlation of skin pruritus and serum CRP level in mild, moderate and severe patients

Table 4. Comparison of HD patients' parameters other than anemia and iron status among three severity groups

Pruritus	No (n=30)	Mild (n=12)	Moderate (n=14)	Severe (n=12)	*p*
Td (hours)	3.97±0.29	3.92±0.19	3.96±0.24	4.13±0.31	NS
HD duration (months)	37.8±43.3	56.8±39.6	41.9±32.6	45.0±30.2	NS
BUN (mg/dl)	64.2±15.8	67.4±16.2	61.4±12.4	54.1±10.7	NS
Creatinine (mg/dl)	9.64±2.21	9.44±2.20	9.14±2.32	8.78±1.51	NS
Albumin (g/dl)	4.41±0.40	4.30±0.42	4.31±0.71	4.18±0.53	NS
Blood sugar (mg/dl)	103.6±49.6	125.2±101.0	127.2±67.2	148.6±110.1	NS
Calcium (mg/dl)	9.42±0.55	9.62±0.50	9.66±0.90	9.91±0.53	NS
Phosphate (mg/dl)	5.00±1.58	5.07±0.86	4.61±1.22	5.43±1.11	NS
KT/V	1.37±0.17	1.333±0.24	1.39±0.23	1.37±0.19	NS
nPCR (g/kg)	1.16±0.24	1.16±0.21	1.14±0.17	1.00±0.20	NS
EPO dose (U/kg)	26.03±10.97	26.45±10.60	21.51±5.89	21.38±6.64	NS
CRP (mg/dl)	0.17±0.34	0.31±0.10	0.83±0.29	2.97±3.21*	p<0.05
ß$_2$M (µg/L)	29074.56±733.71	30780.7±7718.41	33633.41±9026.29	33535.03±8760.95	NS

Td: duration of HD session; HD duration: time on HD therapy; nPCR: normalized protein catabolic rate; EPO: erythropoietin; CRP: C-reactive protein; ß$_2$M: beta2-microglobulin.

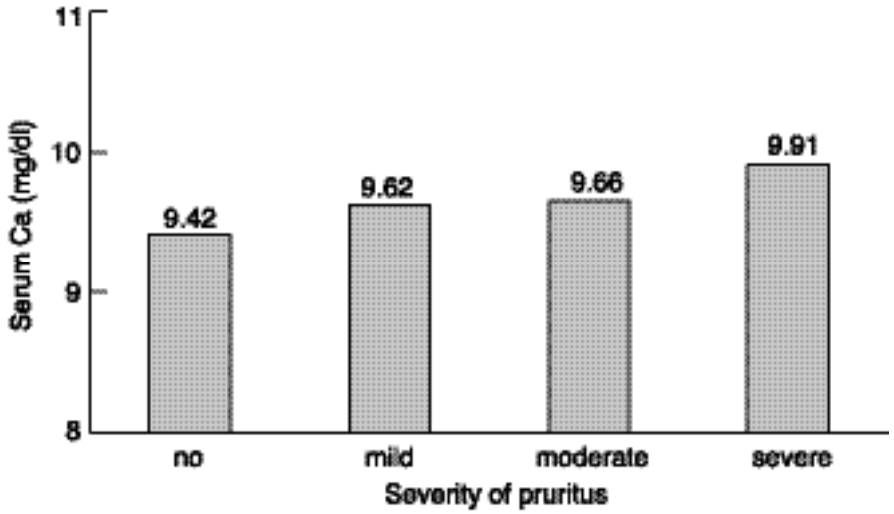

Fig. 2. The correlation between pruritus and serum Ca level

significance. Although the serum calcium levels also showed an upward trend in patients with more severe pruritus, this was not statistically significant (p=0.143) (Table 4, Fig. 2). The age, sex, DM, duration of the HD session, time on HD treatment, and KT/V and nPCR levels were comparable between patients with and without pruritus (Table 3). The blood sugar, serum urea, creatinine, albumin, phosphate, parathyroid hormone, and ß$_2$M levels were not significantly different between the groups (Table 3).

DISCUSSION

UP causes an unpleasant sensation and is often intractable; it can lead to tremendous distress. The association between uremia and pruritus was first reported more than a century ago. The percentage of HD patients suffering from UP ranges from 30% to 90%.[1] The wide variation in these figures may reflect the fact that pruritus is a subjective sensation and can be influenced by psychological factors. The proportion of the HD patients in the current study with pruritus (58%) was similar to that reported in previous studies. The frequency of pruritus has increased dramatically with the advent of HD.[10] The increase in the incidence of pruritus could be due to the prolonged survival of patients with end-stage renal failure.

Iron deficiency was a well-known cause of pruritus and skin inflammation in uremic patients[10] in the pre-erythropoietin (EPO) era. In the EPO era, however,

Table 5. Comparison of HD patients' anemia and iron status in three groups of pruritus severity.

Pruritus	Mild (n=12)	Moderate (n=14)	Severe (n=12)	*p*
Hb (g/dl)	9.1±0.6	9.3±2.0	10.1±2.1	NS
Hct (%)	27.0±1.5	27.8±6.0	29.5±5.7	NS
MCV (μm^3)	94.8±6.2	91.0±11.4	92.6±7.3	NS
MCHC (g/dl)	33.8±0.9	33.6±0.9	34.1±1.3	NS
Iron (µg/dl)	62.8±39.8	72.5±35.6	80.6±54.9	NS
TIBC (µg/dl)	252.3±53.8	250.7±43.1	278.3±68.8	NS
TSAT (%)	26.4±21.7	30.2±15.7	30.8±24.9	NS
Ferritin (ng/ml)	821.1±515.0	815.8±833.7	714.1±695.7	NS

Hb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; TIBC: total iron binding capacity; TSAT: transferrin saturation index.

iron supplementation either by intravenous or oral route is now a common, effective practice in the management of uremic anemia. Over 90% of our patients received EPO administration along with iron supplement to correct their anemia. Most of our HD patients were not iron depleted or with higher serum ferritin levels than the DOQI guideline recommendation (ferritin 300-800 ng/ml). Our study did not find an association between iron status and pruritus.

EPO was once used to treat pruritus in uremic patients in the early EPO era.[6] Its administration is very common in the treatment of uremic anemia nowadays. Over 90% of our HD patients received EPO administration. The EPO dosage was very similar among the three severity groups in our HD patients. Surprisingly, the EPO dosage in the patients with pruritus was lower than in those without pruritus, even in patients with a similar level of Hb. We also did not find any influence of EPO therapy on the intensity of UP.

Diabetes mellitus and anemia status were not associated with pruritus in the HD patients. The absence of relationships between pruritus and many common biochemical results as well as patients' sex, age, HD duration and time on HD treatment is not surprising, as several studies have reported similar findings.[6,7,9]

$ß_2M$ was once considered to be involved in the pathogenesis of UP.[11] Ordinarily, continuous ambulatory peritoneal dialysis (CAPD) and high-flux dialyzers are thought to have a higher clearance of $ß_2M$ than HD and conventional dialyzers provide. Surprisingly, the incidence of UP has been shown to be higher in CAPD than in HD patients;[11] HD patients dialyzed on high-flux dialyzers have had higher rates of skin itching than those on hemophane.[12] Our results did not indicate any association between serum $ß_2M$ levels and pruritus.

This study's finding of an inverse relationship between serum calcium levels and pruritus has not been reported before. The use of high calcium dialysate and calcium supplementation to prevent negative calcium balance and to suppress excessive parathyroid hormone has become a common practice. In our study, the serum calcium levels were higher in the patients with pruritus than in the patients without pruritus. Although the serum calcium levels showed an upward trend in patients with more severe intensity of pruritus, this was not statistically significant (Table 4, Fig. 2). One study has reported promising results using low calcium concentration dialysate in the treatment of UP.[13] However, no further studies have confirmed this finding. It has been postulated that calcium concentration contributes to itching by influencing the degranulation of cutaneous mast cells, thus appearing to be a modifier rather than an initiator.[14] Since most of the serum calcium levels of our HD patients measured within normal range (8.5-10.5 mg/dl), the qualitative and quantitative aspects of the prurigogenic properties of HD-induced high serum calcium levels warrant further study.

Uremia itself is a chronic inflammatory process. Inflammation in HD patients can be induced by pathological conditions, such as infections and tumors. Biochemically, it can be generated by complement activation and cytokine release, effects also associated with the blood-membrane contact that occurs between the blood cells and the artificial dialysis membrane.[15] We did not examine the effects of different dialysis membrane on our HD patients since patients dialyzed on high-flux dialyzers comprised only a small proportion of our dialysis patients overall (10/68). Therefore, it was not possible to make any conclusions about the effects of different dialysis membrane on pruritus in HD patients. Intradermal injection of complement activating products or cytokines can induce local itching.[16] Among these factors, the most likely culprit is interleukin-2 (IL-2).[17] Ultraviolet phototherapy, which attenuates Th1 expression[18], is accompanied by relief of UP.[19] Drugs such as thalidomide, which suppresses IL-2 production,[20] have also been quite effective in the treatment of pruritus.[21] Viral hepatitis infection was once

postulated to be involved in the pathogenesis of UP.[22] In respect to all of these, inflammation might play a role in the pathogenesis of uremic pruritus.

CRP is an acute phase response protein active in most tissue damaging processes and inflammation. Serum CRP levels in the patients with pruritus were higher than in those without pruritus, with a strong statistical significance. CRP values were positively correlated with the severity of pruritis in the study's subjects. (Table 4, Fig. 1). Our study suggests that anti-inflammatory regimens such as steroids or NSAIDs can be tried in the treatment of uremic pruritus in future studies.

In summary, the pathogenesis of pruritis in HD patients appears to be multifactorial. Although individual parameters have been associated with the disorder, the precise underlying mechanism remains elusive. Our results suggest that inflammation and serum calcium levels play important roles in the pathogenesis of UP. Further investigation is required to elucidate the intrinsic pathogenesis of UP in HD patients.

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REFERENCES

1. Schwartz IF, Iaina A: Uraemic pruritus. Nephrol Dial Transplant 1999; **14:** 834-9.
2. Massry SG, Popovtzer MM, Coburn JW, Makoff DL, Maxwell MH, Kleeman CR: Intractable pruritus as a manifestation of secondary hyperparathyroidism in uremia. Disappearance of itching after subtotal parathyroidectomy. N Engl J Med 1968; **279:** 697-700.
3. Stahle-Backdahl M, Hagermark O, Lins LE, Torring O, Hilliges M, Johansson O: Experimental and immunohistochemical studies on the possible role of parathyroid hormone in uraemic pruritus. J Intern Med 1989; **225:** 411-5.
4. Blanchley JD, Blankenship DM, Menter A, Parker TF III, Knochel JPI: Uremic pruritus and skin ion content. Am J Kidney Dis 1985; **5:** 236-141.
5. Bencini PL, Montagnino G, Citterio A, Graziani G, Crosti C, Pontecelli C: Cutaneous abnormalities in uremic patients. Nephron 1985; **40:** 316-21.
6. De Marchi S, Cecchin E, Villalta D, Sepiacci G, Santini G, Bartoli E: Relief of pruritus and decreases in plasma histamine concentrations during erythropoietin therapy in patients with uremia. N Engl J Med 1992; **326:** 969-74.
7. Mamianetti A, Tripodi V, Vescina C, et al: Serum bile acids and pruritus in hemodialysis patients. Clin Nephrol 2000; **53:** 194-8.
8. Odou P, Azar R, Luyckx M, Brunet C, Dine T: A hypothesis for endogenous opioid peptides in ureamic pruritus: role of enkephalin. Nephrol Dial Transplant 2001; **16:** 1953-4.
9. Hiroshige K, Kabashima N, Takasugi M, Kuroiwa A. Optimal dialysis improves uremic pruritus. Am J Kidney Dis 1995; **25:** 413-9.
10. Sato S: Iron deficiencies: structural and microchemical changes in hair, nails, and skin. Semin Dermatol 1991; **10:** 313-9.
11. Balaskas EV, Chu M, Uldall RP, Gupta A, Oreopoulos DG: Pruritus in continuous ambulatory peritoneal dialysis and hemodialysis patients. 1993; **13 Suppl 2:** S527-32.
12. Szepietowski JC, Sikora M, Kusztal M, Salomon J, Magott M, Szepietowski T: Uremic pruritus: a clincal study of maintenance hemodialysis patients. J Dermatol 2002; **29:** 621-7.
13. Kyriazis J, Glotsos J: Dialysate calcium concentration of < 1.25 mmol/L: is it effective in suppressing uremic pruritus? Nephron 2000; **84:** 85-6.
14. Ahmand S: Uremic pruritus. Semin Dial 1993; **6:** 348-50.
15. Schouten WE, Grooteman MP, van Houte AJ, Schoorl M, van Limbeek J, Nube MJ: Effects of dialyser and dialysate on the acute phase reaction in clinical bicarbonate dialysis. Nephrol Dial Transplant 2000; **15:** 379-84.
16. Wahlgren CF, Tengvall Linder M, Hagermark O, Scheynius A: Itch and inflammation induced by intradermally injected interleukin-2 in atopic dermatitis patients and healthy subjects. Arch Hermatol Res 1995; **287:** 572-80.
17. Mettang T, Pauli-Magnus C: The pathophysiological puzzle of uremic pruritus - insight and speculations from therapeutical and epidermiological studies. Perit Dial Int 2000; **20:** 493-4.
18. Garssen J, Vandebriel RJ, de Gruijl FR, et al: UVB exposure-induced systemic modulation of TH1- and Th2-mediated immune responses. Immunology 1999; **97:** 506-14.
19. Gilchrest BA, Rowe JW, Brown RS, steinman TI, Arndt KA: Ultraviolet phototherapy of uremic pruritus. Long-term results and possible mechanism of action. Ann Intern Med 1979; **91:** 17-21.
20. McHugh SM, Rifkin IR, Deighton J, et al: The immunosuppressive drug thalidomide induces T helper cell type 2 (Th2) and concomitantly inhibits Th1 cytokine production in mitogen- and antigen-stimulated human peripheral blood mononuclear cell cultures. Clin Exp Immunol 1995;99;160-7.
21. Silva SR, Viana PC, Lugon NV, Hoette M, Ruzany F, Lugon JR: Thalidomide for the treatment of uremic pruritus: a crossover randomized double-blind trial. Nephron 1994; **67:**270-3.
22. Hung KY, Shyu RS, Tsai TJ, Chen WY: Viral hepatitis infection should be considered for evaluating uremic pruritus in continuous ambulatory peritoneal dialysis patients. Blood Purif 1998; **16:** 147-53.