Release of Interleukin-6 and Its Soluble Receptors by Activated Peripheral Blood Monocytes Is Elevated in Hypocholesterolemic Hemodialysis Patients

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\textbf{Key Words}  
Soluble IL-6 receptor \cdot Peripheral blood mononuclear cell \cdot Reverse epidemiology \cdot Cardiovascular disease \cdot Renal failure \cdot Triglycerides \cdot Cholesterol \cdot Inflammation \cdot Cell culture \cdot Cytokines \cdot Soluble receptors \cdot Lipids

\textbf{Abstract}

\textbf{Background:} A reverse association between cholesterol level and cardiovascular disease mortality is observed in hemodialysis (HD) patients; this paradoxical relationship may be explained by the coexistence of inflammation. Interleukin-6 (IL-6) is a central regulator of inflammation; its action is augmented by the soluble IL-6 receptor (sIL-6R) and inhibited by the soluble gp130 (sgp130). In order to investigate the potential association of inflammation with cholesterol levels in the HD population, release of soluble IL-6 components by peripheral blood mononuclear cells (PBMCs) was measured in two groups of HD patients with distinctly different lipid profile and in a control group. \textbf{Methods:} Twenty-two HD patients with low serum cholesterol (range 85–171 mg/dl), 23 HD patients with high cholesterol (189–342 mg/dl) and 21 normolipidemic non-renal failure subjects were enrolled in the study. IL-6, sIL-6R and sgp130 were measured by ELISA in the serum and in the supernatant collected from cell cultures of activated or resting PBMCs isolated from all three groups. \textbf{Results:} Serum IL-6 and sgp130 level was higher while sIL-6R was lower in both groups of HD patients compared to the control group. The ex-vivo release of the IL-6 and sgp130 by unstimulated PBMCs did not differ significantly between the three groups but that of the sIL-6R was higher in non-renal failure than in hypocholesterolemic HD subjects. Production of sIL-6R by stimulated PBMCs was higher in low-cholesterol HD patients (p < 0.001) and the same was valid for the sgp130 release (p = 0.034). Release of IL-6 by activated PBMCs was higher in the low-cholesterol compared to the high-cholesterol HD patients group (p = 0.011 for post hoc test). Major serum lipid fractions were inversely correlated to IL-6 and sIL-6R production from stimulated PBMCs in HD but not in non-renal failure subjects. Finally, release of the sgp130 by PBMCs was significantly reduced in 13 hypertriglyceridemic – and hypercholesterolemic – HD patients. \textbf{Conclusion:} Production of soluble components of a crucial pro-inflammatory and potentially atherogenic cytokine, namely the IL-6, by stimulated PBMCs appears to be inversely correlated with the serum cholesterol levels in HD patients.

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Introduction

Hypercholesterolemia is a main risk factor for atherosclerotic cardiovascular disease (CVD). Unexpectedly, in end-stage renal failure (ESRF) patients [1] a reverse association between cholesterol and CVD mortality is observed. Apparently, high serum cholesterol levels seem to be protective in these patients. A recent study showed that in hypo-cholesterolemic dialysis patients increased CVD mortality may be due to the co-existence of inflammation [2]. Moreover, inflammation is itself implicated in atherosclerosis generation and progression [3].

Interleukin-6 (IL-6) is a central regulator of the inflammatory and potentially of the atherosclerotic process [3, 4]. Its activity depends on two distinct cellular membrane-bound glycoproteins, a cognate receptor subunit (IL-6 receptor, IL-6R) and a signal-transducing element (gp130) [5]. Both of these trans-membrane proteins circulate in the serum as soluble molecules as well. The soluble IL-6 receptor is an agonist augmenting IL-6 action. Adversely, the soluble form of gp130 (soluble gp130, sgp130) is an inhibitor of IL-6 action [6].

The reverse association of cholesterol to CVD mortality in ESRF patients and specifically its correlation to the inflammation that is prominent in this atherosclerotic population lacks a biological explanation. We hypothesized that hypo- and hypercholesterolemic HD patients react in a different way to inflammatory or atherosclerotic stimuli. To explore this hypothesis, we assessed the ex-vivo release of all three active soluble components – IL-6, sIL-6R and sgp130 – of the IL-6 system by activated or not peripheral blood mononuclear cells (PBMCs) isolated from two groups of HD patients, one with low and another with high serum cholesterol level as well as from a control group.

A probably stronger inflammatory and potentially atherosclerotic response in hypocholesterolemic HD patients could provide a biological link for the paradoxical association of the low serum cholesterol level with the increased incidence of the inflammatory atherosclerotic CVD observed in this population.

Methods

Patient Selection: Characteristics

Medical records of HD patients from an outpatient renal unit (Dragini Clinic) were reviewed. Patients who had at least 2 measurements of serum cholesterol (tChol) in the last semester were initially divided into 2 groups: hypo- and hypercholesteroleemics (group 1, total serum cholesterol, tChol <200 mg/dl, group 2, tChol ≥ 200 mg/dl, in all measurements). Subsequently, patients with clinically evident infection, malignancy, collagen tissue disease, trauma or a major CVD event at the time of blood sample collection (June 2004) were excluded from the study. The remaining 45 patients, 22 in the hypo- and 23 in the hypercholesterolemic group, gave their informed and written consent and were included in the study. None of the patients was on any anti-lipidemic treatment. The lipid profile, at the time of blood collection, as well as other characteristics of these patients are shown in table 1. The cause of ESRF in the hypo- and hypercholesterolemic group was: chronic glomerulonephritis in 13 patients (6 and 7, respectively), diabetic nephropathy in 9 patients (4 and 5, respectively), hypertensive glomerulosclerosis in 11 patients (6 and 5, respectively), polycystic disease in 9 patients (5 and 4, respectively). ESRF cause was undermined in 3 patients (1 and 2, respectively). The average time on HD was 46.8 ± 56.4 (range: 5–249 months) in hypocholesterolemic and 48.7 ± 45.3 months (range: 7–164 months) in hypercholesterolemic patients (p = 0.901). All patients were on conventional HD, using bicarbonate dialysate and the same type of dialyser (EVAL; polyethylene-vinyl-alcohol membrane, Kawasaki Laboratories, Inc.). Water processing (central reverse osmosis water treatment system) and the type of concentrate were identical for all patients in the two groups. Twelve patients, 7 in the hypocholesterolemic and 5 in the hypercholesterolemic group, were being treated with sevelamer hydrochloride, 7 with angiotensin-converting enzyme inhibitors (ACEI), 4 and 3 in the two groups respectively, and 5 with acetylsalicylic acid (100 mg/day), 2 and 3 respectively.

Non-Renal Failure Subjects

Twenty-one non-renal failure volunteers (Department of Nephrology, General Hospital of Athens hospital staff) were also included in the study as a control group (estimated glomerular filtration rate with Cockroft-Gault formula ≥ 80 ml/min). The lipid profile and other characteristics of this group are shown in table 1. Two volunteers were being treated with ACEIs.

Blood Samples and Cell Cultures

In all groups a heparinized 15-ml blood sample and a non-heparinized 10-ml blood sample were drawn after an overnight fast, for obtaining serum samples and PBMCs. In HD patients, blood samples were drawn just before the onset of the midweek dialysis session.

Preparation of PBMCs and cell cultures were performed in a slightly modified way, compared to the method previously described [7]. Peripheral blood mononuclear cells were obtained by a Ficoll-Hypaque (Sigma Aldrich, St. Louis, Mo., USA) gradient density centrifugation (400 g for 30 min). The mononuclear layer was then collected, washed twice in RPMI 1640 culture medium (Sigma Aldrich) and finally resuspended in 15 ml polypropylene round-bottom tubes (Falcon, Becton Dickinson, Lincoln Park, N.J., USA) at a concentration of 2 × 10^6/ml in Iscove’s culture medium (Sigma Aldrich) and finally resuspended in 15 ml polypropylene round-bottom tubes (Falcon, Becton Dickinson, Lincoln Park, N.J., USA) at a concentration of 2 × 10^6/ml in Iscove’s culture medium (Sigma Aldrich) supplemented with 1% heat-inactivated fetal bovine serum (Sigma Aldrich), 5,000 U/ml penicillin and 3,000 µg/ml streptomycin.

Peripheral blood mononuclear cell cultures were prepared both with and without a mitogenic stimulation of 10 µg/ml bacterial lipopolysaccharide (LPS, Sigma Aldrich). After incubation for 24 h at 37°C in a humidified atmosphere containing 5% CO₂, cell-free supernatants were collected by centrifugation and were stored at −80°C.
The cell cultures contained about 90–95% PBMCs with 60–85% lymphocytes. Peripheral blood mononuclear cells were viable as determined by trypan blue dye exclusion at the beginning of the culture and more than 85% were viable before supernatants were collected.

Cytokine Assays and Analytical Determinations

Serum IL-6 and cell culture supernatant IL-6 levels were quantified with a sandwich enzyme immunoassay technique based on a monoclonal-polyclonal antibody pair (R&D Systems, Minneapolis, Minn., USA).

For the determination of sIL-6R and gp130 a sandwich enzyme immunoassay technique based on a monoclonal-biotinylated monoclonal antibody pair was used (Diaclone Research, Besançon, France). All assays were carried out in the same run and in duplicate.

Serum levels of all biochemical markers were determined utilizing Olympus AU 560 random access analyzer (Olympus Corp., Japan). Low-density lipoprotein cholesterol (LDL) was calculated using the Friedwald formula. Non-high-density lipoprotein cholesterol was calculated as tChol – high-density lipoprotein cholesterol (HDL) (non-HDL-C).

Statistical Analysis

Statistical analysis was performed using the analysis of variance (ANOVA) followed by the Bonferroni test, as post-hoc test. Due to skewed distribution, IL-6, sIL-6R and sgp130 values were transformed to their natural logarithms. All statistical analyses for the above mentioned parameters were performed using log-transformed values. Unless otherwise reported, results are expressed as mean ± SD of the natural numbers. IL-6 values >132,000 pg/ml were interpreted as 150,000 pg/ml. Correlations were performed using the Spearman Rank test. To compare values between groups one-way ANOVA and Bonferroni post-hoc test were used. Differences of distribution of groups’ 2 × 2 contingency tables were measured using the χ² test. In all cases, significant results were declared to be those with p < 0.05. Analyses were performed using the SPSS version 11.0 (SPSS Inc., Chicago, Ill., USA).

Results

Serum Levels of the IL-6 System Soluble Constituents

Serum IL-6 level was significantly higher in both groups of HD patients (46.9 ± 57.0 pg/ml in hypo- and 64.5 ± 108 pg/ml in hypercholesterolemic group) than in the non-renal failure group (1.9 ± 0.5 pg/ml) (ANOVA, p < 0.001). No difference between hypo- and hypercholesterolemic HD patients was observed.

Serum sIL-6R was higher in non-renal failure (313 ± 85.1 ng/ml) than in HD patients (186.6 ± 108 ng/ml and 215 ± 137 ng/ml, in the low- and high-cholesterol group respectively, ANOVA, p = 0.022), but the product of the two agonistic IL-6 components (sIL-6R × IL-6) was higher in HD patients (data not shown). Serum sgp130 values did not differ significantly between the 3 groups: 876 ± 1,296, 1,028 ± 1,168 and 577 ± 163 ng/ml in the low-cholesterol, the high-cholesterol and the non-renal failure group, respectively (ANOVA, p = 0.471).

Table 1. Lipid profile and characteristics of the hemodialysis and non-renal failure subjects

<table>
<thead>
<tr>
<th></th>
<th>Hemodialysis patients</th>
<th>Non-renal failure subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>low lipid profile (n = 22)</td>
<td>high lipid profile (n = 23)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>140 ± 25a (85–171)c</td>
<td>234 ± 45b (189–342)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>78.3 ± 21.9</td>
<td>149 ± 34b</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>34.5 ± 7.5d</td>
<td>43.4 ± 11.1</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>135 ± 110d</td>
<td>207 ± 112</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mg/dl</td>
<td>105 ± 23</td>
<td>191 ± 43b</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>10/12</td>
<td>12/11</td>
</tr>
<tr>
<td>Age, years</td>
<td>58.5 ± 15.9</td>
<td>66.0 ± 9.7c</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.4 ± 2.6</td>
<td>23.5 ± 2.9</td>
</tr>
<tr>
<td>Smoking</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4</td>
<td>6a</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14</td>
<td>10b</td>
</tr>
</tbody>
</table>

a Mean ± SD; b p < 0.001 vs. low lipid profile HD patients; c range; d p = 0.018 vs. high lipid profile HD patients; e p = 0.043 vs. high lipid profile HD patients; f p = 0.132 vs. low lipid profile HD patients; g χ² = 0.175; h χ² = 0.524.
Serum LDL level was positively and significantly correlated ($r = 0.444, p = 0.044$) to serum IL-6 level in non-renal failure subjects.

**Release of IL-6 System Soluble Constituents from Unstimulated PBMCs**

Release of IL-6 from unstimulated PBMCs after incubation for 24 h did not differ significantly between the three groups: $2.360 \pm 2.176$ pg/ml in the low-, $2.643 \pm 2.372$ pg/ml in the high-cholesterol HD patients and $2.525 \pm 2.469$ pg/ml in non-renal failure subjects ($p$ for ANOVA $= 0.714$). Production of sIL-6R from PBMCs was low in all three groups, $1.72 \pm 2.63$ ng/ml in the low-, $1.06 \pm 1.27$ ng/ml in the high-cholesterol HD patients and $1.91 \pm 1.17$ ng/ml in non-renal failure subjects, $p$ for ANOVA $= 0.007$) but was higher in non-renal failure than in HD subjects with high cholesterol ($p = 0.05$). Release of sgp130 from unstimulated PBMCs after incubation for 24 h did not differ significantly between the three groups: $102 \pm 189$ ng/ml in the low-, $26.9 \pm 32.6$ in the high-cholesterol HD patients and $20.8 \pm 34.3$ ng/ml in non-renal failure subjects ($p$ for ANOVA $= 0.111$).

Serum TG level was negatively correlated ($r = -0.356, p = 0.028$) to sgp130 level while all the other lipid fractions, including non-HDL-C, were also negatively but non-significantly correlated to sIL-6R and sgp130 produced from unstimulated PBMCs in HD patients (data not shown).

**Release of IL-6 System Soluble Constituents from Stimulated PBMCs**

Release of IL-6, sIL-6R and sgp130 from PBMCs stimulated with LPS after incubation for 24 h is shown in table 2. IL-6 production was higher in hypo- than in hypercholesterolemic HD patients (table 2). Compared to non-renal failure subjects, sIL-6R production was significantly higher in both HD groups. Its release was higher in the low-cholesterol than in the high-cholesterol HD group (table 2). Finally, sgp130 production was higher in HD patients with low-lipid profile than in non-renal failure subjects.

**Inverse Correlations between Serum Lipid Fractions and IL-6 System Constituents Released by Stimulated PBMCs in HD Patients**

Significant inverse correlations between the production of IL-6 system constituents from stimulated PBMCs and serum lipid fractions were observed in HD patients (table 3). The negative correlation between LDL and IL-6 produced from stimulated PBMCs was the stronger one, while the only statistically significant inverse correlation to sgp130 production was observed with serum TG (table 3). Specifically, the release of sgp130 from stimulated PBMCs in the subgroup of hypertriglyceridermic HD patients (mean serum TG for the whole HD cohort $= 172$ mg/dl, 13 patients $\geq 172$ and 32 patients $< 172$ mg/dl) was significantly lower ($26.7 \pm 39.1$ ng/ml) than in the hypotriglyceridermic ones ($310 \pm 343$ ng/ml) ($p < 0.001$). It is worth noting that the hypertriglyceridermic HD group also had higher serum cholesterol level ($243 \pm 55$ vs. $165 \pm 46$ mg/dl in the hypotriglyceridermic group).

On the contrary, no statistically significant correlations were found between lipid fractions and IL-6, sIL-6R or sgp130 production from stimulated PBMCs, except that serum TG level was positively correlated ($r = 0.461, p = 0.035$) to IL-6 production in non-renal failure subjects.

### Table 2. IL-6, sIL-6R and sgp130 release after incubation for 24 h, of stimulated – with LPS – PBMCs isolated from all the subjects included in the study

<table>
<thead>
<tr>
<th></th>
<th>Hemodialysis patients</th>
<th>Non-renal failure subjects</th>
<th>ANOVA p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>low cholesterol</td>
<td>high cholesterol</td>
<td></td>
</tr>
<tr>
<td>IL-6, pg/ml</td>
<td>$127,866 \pm 28,309^a$</td>
<td>$70,771 \pm 43,803$</td>
<td>$0.014$</td>
</tr>
<tr>
<td>sIL-6R, ng/ml</td>
<td>$59.0 \pm 34.3^{b,c}$</td>
<td>$34.9 \pm 32.9^d$</td>
<td></td>
</tr>
<tr>
<td>sgp-130, ng/ml</td>
<td>$320 \pm 368^e$</td>
<td>$141 \pm 238$</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean $\pm$ SD.

$^a$ $p = 0.011$ vs. high-cholesterol hemodialysis patients; $^b$ $p = 0.031$ vs. high-cholesterol hemodialysis patients; $^c$ $p < 0.001$ vs. non-renal failure subjects; $^d$ $p = 0.006$ vs. non-renal failure subjects; $^e$ $p = 0.039$ vs. non-renal failure subjects.
Discussion

The main finding in this study is that the PBMCs response to stimuli, regarding production and release of IL-6 soluble components, is inversely correlated to the lipid profile in HD patients. This activation is stronger in patients with low cholesterol but it seems to be balanced; the increased ex vivo release of the molecules enhancing IL-6 action (IL-6 and sIL-6R) by stimulated PBMCs coincides with an also increased production of their inhibitor (sgp130). In the same population, the release by PBMCs of this later soluble antagonist of the IL-6 system is reduced in patients with high serum TG levels. These associations are not observed in non-renal failure subjects.

Our initial hypothesis that hypocholesterolemic HD patients have a stronger inflammatory and potentially atherosclerotic response, as assessed by the release of IL-6 components by peripheral mononuclear cell, was partially confirmed. This cell type crucial for inflammation and atherosclerosis [8], isolated from hypocholesterolemic patients, reacted to LPS stimulation by releasing larger quantities of IL-6 and mainly sIL-6R. The sIL-6R, apart from prolonging the plasma half-life of IL-6, also forms a complex with the circulating cytokine (sIL-6R/IL-6) capable of activating cell types which do not inherently express IL-6 receptor, widening in this way the repertoire of IL-6 responsive cell types [5]. On the other hand, this ‘overreaction’ of PBMCs isolated from HD patients with low cholesterol is counterbalanced by the release of a large quantity of the sgp130 which is the natural inhibitor of IL-6 [6], since by binding to the sIL-6R/IL-6 complex it neutralizes its action.

A biological explanation of our findings can only be speculated. A recently published study showed that cellular cholesterol depletion triggers shedding of IL-6-R from cell surface [9]. This shedding, which is one of the two mechanisms for sIL-6R production [5], could increase the concentration of this soluble molecule. Furthermore, depletion of cellular cholesterol, a condition that may be observed in chronically hypocholesterolemic HD patients, increases shedding of other molecules involved in the immune response [10], and this depletion also involves the lipid rafts [11] which are cellular membrane structures that might also be related to IL-6 activity [12]. However, these experimental data do not explain why an inverse association between IL-6 production by activated PBMCs and lipid levels was not also observed in non-renal failure subjects. Other conditions, specific for uremic patients, might induce this phenomenon. Advanced glycation end products [13] or oxidative stress could be implicated in this process. On the other hand, increased prevalence of lipid sub-fractions (although not assessed in the present study), such as small-sized LDL or oxidized LDL, in renal-failure subjects may predispose crucial cell types towards a more intense inflammatory – and atherogenic – response [14]; this latter possibility should not be excluded, particularly since recent studies showed a strong relation between inflammation and atherogenic modification of the main lipid fractions [15]. A genetic predisposition connecting lipid metabolism, inflammation and atherosclerosis, such as apolipoprotein-E polymorphisms, might also account for the more intense inflammatory response in HD patients [16]. Finally, it is of interest that Axelson et al. [17] recently reported that IL-6 was significantly higher in malnourished ESRF patients. Although we did not examine the nutritional status of our patients, wasting and its multiple consequences may influence the inflammatory response in this population [18].

Table 3. Inverse correlations between IL-6, sIL-6R and sgp130 released by stimulated PBMCs isolated from HD patients and serum lipid fractions of the same patients

<table>
<thead>
<tr>
<th>Serum lipid fractions</th>
<th>Stimulated PBMCs production in HD patients</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>IL-6</td>
</tr>
<tr>
<td></td>
<td>r</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-0.473</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>-0.512 &lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.357</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.225</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>-0.454</td>
</tr>
</tbody>
</table>

r = Correlation coefficient (Spearman Rank test).
An interesting finding in the present study was the inverse correlation between serum TG level and sgp130. The underproduction of the natural inhibitor of the IL-6/sIL-6R complex [6] not only from activated but also from resting PBMCs isolated from hypertriglyceridemic HD patients (see ‘Results’) may potentially enhance IL-6 activity, which may potentially be correlated to the increased CVD mortality, also observed in this population; both patients with low and high cholesterol have high CVD mortality [1]. Although the study of Liu et al. [2] the increased mortality in the high-cholesterol group was observed in patients without inflammation, our data show that in patients with high triglycerides, who concomitantly have high cholesterol, production of the natural inhibitor of a main pro-inflammatory – and probably atherosclerotic – cytokine is reduced. The number of patients in this group was too small and the degree of hypertriglyceridemia was not very high for solid conclusion extraction; it seems though that, paradoxically, these patients might also have increased IL-6 activity, which may potentially be correlated to the increased CVD mortality, also observed in this population. Quaschning et al. [20] showed that hypertriglyceridemic HD patients have lower lipase activity, increased LDL oxidation and larger quantities of small-dense LDL; these characteristics may predispose this specific subgroup to a higher inflammatory and atherogenic response.

Although the two groups of HD patients in our study were homogenous in all the parameters examined (age, HD duration, diabetes mellitus and hypertension presence, medications, dialyser type, etc.), one should note that non-renal failure subjects were younger, non diabetic and only 2 of them were hypertensive. This is a limitation of the study that has to be taken into consideration. The absence of a second control group (hyper- and hypo-lipidemic) should also be noted. Moreover, the number of our patients was rather small, thus further investigation in larger series of patients is necessary to exclude statistical bias. Finally, endotoxin measurement in the dialysate was not available to us and although patients included in the study came from only one dialysis facility with a common water treatment system and a single type of dialysar, this data could be useful.

In conclusion, an inverse correlation between serum cholesterol level and production of circulating IL-6 constituents from activated PBMCs of HD patients was observed in the present study. Although the final systemic activity of this central inflammatory and potentially atherogenic cytokine seems to be self-controlled, the sensitivity of peripheral mononuclear cells to common inflammatory stimuli in hyper-lipidemic dialysis patients appears to be increased. Paradoxically, high-triglyceride, high-cholesterol ESRF patients behave in a similar way. In case these findings are confirmed in future studies, a connection between inflammation (and eventually atherosclerosis-related CVD mortality) and hypcholesterolemia as a basis for inverse epidemiology explanation in this population will be further supported.

Acknowledgments

We thank Janssen-Cilag, Pharmaceutical, S.A.C.I. and Genesis Pharma, S.A. for financial support.

We would like to thank Erasmia Psimenou, MD, for her critical reading of the manuscript.

This work was presented in abstract form in the XLII Congress of the European Renal Association – European Dialysis and Transplant Association, Istanbul, Turkey, 4–7 June 2005 and in the 8th International Conference on Geriatric Nephrology and Urology, Thessaloniki, Greece, 5–8 May 2005.

References


