et al. [8] reported that inflammation is associated with hypoalbuminaemia and increased mortality in HD patients.

These studies and many others suggest that inflammation plays a central role in the development of malnutrition and cardiovascular mortality in patients with chronic kidney disease. On the other hand, more recently, Pupim *et al*. [7] showed that surrogate markers of nutritional status (S-albumin, pre-albumin and serum creatinine) were, indeed, significantly related to all-cause mortality in HD patients, even after adjustment for serum CRP. Although in our study we could not confirm a negative correlation between S-albumin and CRP, taking into account only the baseline measurements, it should be noted that in patients who were persistently inflamed in our study, a negative correlation was, indeed, found between S-albumin and CRP in the four consecutive measurements preceding the study, demonstrating the influence of inflammation on S-albumin levels. We could speculate why this finding could not be verified in the patients who were not persistently inflamed. One reason could be the high prevalence of malnutrition, verified by SGA, in the Brazilian HD population, which differs from American and European HD populations where the majority of earlier studies on these relationships were done. Another reason is that we excluded patients with clinically significant inflammatory events, which in turn could be reflected by the absence of correlation in the whole studied HD population.

In summary, we agree with Tsirpanlis and colleagues that (i) clinically significant inflammatory events modify the levels of S-albumin, (ii) this effect is not immediate and (iii) these factors should be taken into account when analysing the relationship between S-albumin and short acute-phase reactants, such as CRP. We therefore advocate [9] sequential measurements of CRP, which may provide a better approach in the interpretation of decreasing S-albumin levels. On the other hand, it seems reasonable to assume that the S-albumin will remain as a valuable predictor of uraemic malnutrition, inflammation and increased risk for mortality.

Conflict of interest statement. None declared.

[1]Renal, Diabetes and Hypertension Research Center
Pró-Renal Foundation
Brazil
[2]Karolinska University Huddinge Hospital
Divisions of Renal Medicine and Baxter Novum
Karolinska Institutet
Sweden

Marcelo Mazza do Nascimento[1]
Peter Stenvinkel[2]
Miguel Riella[1]
Bengt Lindholm[2]

1. Nascimento MM, Pecoits-Filho R, Qureshi AR *et al*. The prognostic impact of fluctuating levels of C-reactive protein in Brazilian haemodialysis patients: a prospective study. *Nephrol Dial Transpl* 2004; 19: 2803–2809
2. Tsirpanlis G, Bagos P, Ioannou D *et al*. Exploring inflammation in hemodialysis patients: persistent and superimposed inflammation. *Kidney Blood Press Res* 2004; 27: 63–70
3. Kaysen GA, Dubin JA, Müller HG, Rosales L, Levin NW, Mitch WE and the HEMO Study Group. Inflammation and reduced albumin synthesis associated with stable decline in serum albumin in hemodialysis patients. *Kidney Int* 2004; 65: 1408–1415
4. Kaysen GA, Chertow GM, Adillkarla R *et al*. Inflammation and dietary protein intake exert competing effects on serum albumin and creatinine in haemodialysis patients. *Kidney Int* 2001; 60: 333–340
5. Stenvinkel P, Heimburger O, Paultre F *et al*. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int* 1999; 55: 1899–1911
6. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 1999; 55: 648–658
7. Pupim LCK, Hakim RM, Shiyr Y, Ikitzler TA. Uremic malnutrition is a predictor of death independent of inflammatory status. *Kidney Int* 2004; 66: 2054–2060
8. Stenvinkel P, Heimbürger O, Lindholm B, Kaysen GA, Bergström J. Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA-syndrome). *Nephrol Dial Transplant* 2000; 15: 953–960
9. Stenvinkel P and Lindholm B. CRP in end-stage renal disease – are there reasons to measure it? *Blood Purif* 2005; 23: 72–78

doi:10.1093/ndt/gfh663

Drug interaction between sevelamer and cyclosporin

This letter was originally published in *NDT* volume 19, issue 7, but without the Reply. The publisher would like to apologise for this error and would now like to publish the paper again to include the Reply.

Sir,

We read with interest the original report made by Miguel-Angel Guillen-Anaya and Michel Jadoul [1] of a drug interaction between sevelamer and cyclosporin (CsA) occurring in a liver transplant patient treated also by chronic haemodialysis. After sevelamer was started, the CsA trough levels reached values as low as 35 ng/ml and they dropped again after rechallenge. As potential explanation, the authors suggest that CsA absorption, which is bile-dependent [2], could be hampered by the fact that sevelamer binds bile acids in the gastrointestinal (GI) tract. Interestingly, in the clinical study performed by Jensen *et al*. [3], the bile-acid sequestrant cholestyramine, 4 g given at noon, did not interfere with CsA absorption.

We would like to mention that sevelamer is a poly(allylaminehydrochloride) polymer that may bind not only phosphate and bile acids, as the authors point out, but also cholesterol, vitamins D, E and K and folic acid [4]. A direct binding of a lipophilic substance such as CsA – and by extension also tacrolimus – appears, therefore, as an additional and more likely explanation.

This observation points to the distinction to be made between the two types of phosphate binding in the GI tract: a specific one achieved by aluminium hydroxide and calcium salts and a non-specific binding attained by polymers such as sevelamer. This absence of specificity might be of less importance for vitamins or folic acid absorption, but may put the patient at risk when lipophilic agents, such as immunosuppressive and/or other drugs (lipophilic statins?), are prescribed. Under those circumstances, it appears that sevelamer should be used with caution, i.e. at least at a time distant of potentially interfering drugs and only when specific (and less expensive) phosphate binders are contraindicated.

Conflict of interest statement. None declared.

Division of Nephrology – Hypertension
University Hospital
Bern
Switzerland
Email: jean-pierre.wauters@insel.ch

Jean-Pierre Wauters
Dominik Uehlinger
Hans-Peter Marti

1. Guillen-Anaya MA, Jadoul M. Drug interaction between sevelamer and cyclosporin. *Nephrol Dial Transplant* 2004; 19: 515
2. Trull AK, Tan KKC, Tan L *et al*. Absorption of cyclosporin from conventional and new micro-emulsion oral formulations in liver transplant recipients with external bile diversion. *Br J Clin Pharmacol* 1995; 39: 627–631
3. Jensen RA, Lal SM, Diaz-Arias A *et al*. Does cholestyramine interfere with cyclosporine absorption? Prospective study in renal transplant patients. *ASAIO J* 1995; 41: 704–706
4. Product Information Brochure USA and Summary of Product Characteristics of the EMEA.

doi:10.1093/ndt/gfh788

Reply

Sir,
We thank Jean-Pierre Wauters and colleagues for their helpful comments. The lower level of cyclosporin A (CsA) under sevelamer may indeed be due to a direct binding of CsA by sevelamer, rather than to an indirect impact of sevelamer on bile acids. Thus, the recommendation of a delay between the intake of sevelamer and that of drugs such as CsA is fully warranted. We disagree, however, on the claim that calcium-based binding is fully specific for phosphate. Indeed, the co-administration of either calcium acetate or sevelamer with ciprofloxacin recently has been shown to reduce the oral bioavailability of the latter drug by some 50% [1].

Conflict of interest statement. None declared.

Miguel-Angel Guillen-Anaya
Michel Jadoul

1. Kays MB *et al*. Effects of sevelamer hydrochloride and calcium acetate on the oral bioavailability of ciprofloxacin. *Am J Kidney Dis* 2003; 42: 1253–1259

doi:10.1093/ndt/gfh788

Sevelamer and pharmacokinetics of cyclosporin A after kidney transplantation

Sir,
In their interesting article, Pieper *et al*. analysed prospectively the effect of sevelamer on the pharmacokinetics of cyclosporin (CsA) and mycophenolate mofetil (MMF) in kidney transplanted patients [1]. They provide the reassuring message that, in contrast to MMF, CsA kinetics are not significantly modified by the intake of sevelamer. These results are in sharp contrast to the observation and potential mechanisms that we reported recently [2,3].

The short duration (4 days) and limited statistical power (10 adults and eight children) of the study of Pieper *et al*. make such a strong message rather questionable [4]. Indeed, only 4 days after starting sevelamer, none of the CsA parameters (measured by Cedia and FPIA assays) was completely stable: the area under the curve (AUC) decreased from 3547 ± 660 to 3230 ± 612 ng/h/ml, C_{max} decreased from 955 ± 193 to 855 ± 272 ng/ml and T_{max} increased from 1.3 to 1.5 h. In addition, when measured with polyclonal antibodies, the CsA levels decreased significantly and, among its primary metabolites determined by HPLC, the AUC and C_{max} of AM1—which also has an immunosuppressive action [5]—decreased significantly by 30 and 25%, respectively.

Despite these observations, the authors conclude that 'sevelamer intake for several days does not significantly influence CsA kinetics'. Based on their data, this conclusion appears at least premature, especially if the risk of transplant rejection due to insufficient immunosuppression is considered [6]. Great caution in the use of sevelamer in transplanted patients is still warranted until a careful long-term, large size study on the potential interaction of sevelamer with CsA solves the question.

Conflict of interest statement. None declared.

[1]Division of Nephrology-Hypertension
University Hospital
Bern
[2]Division of Nephrology
University Hospital
Zurich
Switzerland
[3]Division of Nephrology
Cliniques Universitaires Saint-Luc
Brussels
Belgium
Email: jean-pierre.wauters@insel.ch

Dominik Uehlinger[1]
Hans-Peter Marti[2]
Michel Jadoul[3]
Jean-Pierre Wauters[1]

1. Pieper AK, Buhle F, Bauer S *et al*. The effect of sevelamer on the pharmacokinetics of cyclosporin A and mycophenolate mofetil after renal transplantation. *Nephrol Dial Transplant* 2004; 19: 2630–2633
2. Guillen-Anaya MA, Jadoul M. Drug interaction between sevelamer and cyclosporin. *Nephrol Dial Transplant* 2004; 19: 515
3. Wauters JP, Uehlinger D, Marti HP. Drug interaction between sevelamer and cyclosporin. *Nephrol Dial Transplant* 2004; 19: 1939–1940
4. Felipe CR, Silva HT, Pinheiro Machado PG, Garcia R, da Silva Moreira SR, Medina Pestana JO. Time-dependent changes in cyclosporine exposure: implications for achieving target concentrations. *Transplant Int* 2003; 16: 494–503
5. Copeland KR, Yatscoff RW, McKenna RM. Immunosuppressive activity of cyclosporine metabolites compared and characterized by mass spectrometry and nuclear magnetic resonance. *Clin Chem* 1990; 36: 225–229
6. Waiser J, Slowinski T, Brinker-Paschke A *et al*. Impact of the variability of cyclosporin A trough levels on long-term renal allograft function. *Nephrol Dial Transplant* 2002; 17: 1310–1317

doi:10.1093/ndt/gfh700