It is well known that most obese individuals have elevated circulating levels of leptin but they do not respond to these increased leptin levels with reduced food intake [4]. Numerous authors have supposed that in obese patients a state of relative leptin resistance may occur [5,6]. This issue has been recently reviewed by Munzberg and Myers [7]. Leptin stimulates the production of anorectic neuropeptides and inhibits the action of orexigenic peptides in the arcuate nucleus through complex mechanisms [7]. When leptin binds to its receptor (LRb) it activates the LRb-associated Jak2 tyrosine kinase, leading to the autophosphorylation of tyrosine residues on Jak2 and the phosphorylation of Tyr985 and Tyr1138 on the intracellular tail of LRb. Phosphorylation of Tyr1138 mediates the activation of the transcription factor STAT3. STAT3 also induces the transcription of SOCS3. SOCS3 binding to the LRb-Jak2 complex attenuates LRb-mediated signalling [7–10].

Munzberg and Myers postulate that when leptin levels are low and thus baseline STAT3 activation is modest, SOCS3 expression is low, and incremental changes in leptin would be almost fully translated into increased LRb signalling. When circulating leptin levels are high (as in obesity), the increased baseline STAT3 activation would lead to an increased expression of SOCS3, mitigating much of the effect of increased leptin binding to LRb.

Taking into account these considerations and the results of our clinical study, it could be suggested that a state of relative leptin resistance may occur also in patients with end-stage renal disease receiving haemodialysis in which circulating leptin levels are significantly higher than in healthy subjects. If further studies in the next future will confirm these hypotheses, the title of the article by Wiecek could be changed in ‘Does leptin really contribute to uraemic cachexia?’.

Conflict of interest statement. None declared.

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Reply

Sir,

I would like to thank Bossola et al. for their interesting Letter and commentary on my article, which entirely confirmed my statement concerning the role of leptin in uraemic cachexia. I would like to express my gratitude for providing additional evidence which clearly explains the possible mechanism(s) of leptin resistance in these patients. The comparison of the results obtained by Cheung et al. [1] with the current clinical data once again confirmed that the simple and mechanical transmission of results obtained in experimental studies can not be applied directly in humans and in clinical practice. It seems that we are very close to the point when the proposed title of a new article concerning leptin in uraemic patients will be more adequate.

Conflict of interest statement. None declared.

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Association between BP and mortality in patients on chronic peritoneal dialysis

Sir,

We read with interest the article by Goldfarb-Rumyantzev et al. [1] on the association between blood pressure (BP) and mortality in patients on chronic peritoneal dialysis. It brought out certain surprising observations, such as the protective effect of high BP on hospitalization as well as higher mortality with higher creatinine clearance. Because adverse effects of high BP take a long time to manifest, the authors may not have been able to demonstrate adverse effects. Foley et al. also showed that each increment of 10 mmHg mean BP was associated with a higher risk (44%) of developing heart failure [2]. The higher mortality with higher peritoneal creatinine clearance could reflect the confounding effect of the high transport status. Rapid transporters face higher mortality on continuous ambulatory peritoneal dialysis
et al. Sir, 

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Conflict of interest statement. None declared.

Report

Sir,

We read with interest the letter by Alok Kumar et al. regarding our paper 'The association between blood pressure and mortality in patients on chronic peritoneal dialysis' published in NDT this year. We are glad that the authors are bringing up the epidemiological issues of interpreting the results of the analysis. We tried to be very careful in our publication not to 'overinterpret' the data, in that we always try to emphasize the difference between the statistical association and causation. The presence of an association between lower blood pressure (BP) categories and higher mortality (that was indeed demonstrated by our analysis) should not be extended to conclude that lower BP actually causes the patient's death. While the latter might in fact be true, one cannot conclude this from the results of the retrospective analysis. We tried to address end-of-life bias, reverse causation and potential confounding in the Discussion section of the manuscript. We feel that after carefully reading the manuscript, including the above-mentioned points in the Discussion section, the reader should be aware of potential misinterpretation of the data. As for a protective effect of higher BP on hospitalization, with all the potential flaws of the retrospective study, it is conceivable that patients with lower BP (i.e. intradialytic hypotension or symptomatic hypotension) might be admitted more often than those with hypertension. This particular analysis has the rate of hospitalization as an outcome, which might or might not translate into long-term outcome of the patients, and therefore does not necessarily contradict Foley's paper. In other words, patients who are hospitalized less might still theoretically have a higher degree of mortality and chronic heart failure than those who are hospitalized more.

Furthermore, we do not think that a demonstration of the association between lower BP and risk of death in the subgroup of patients with 'poor cardiac status' means that poor heart status is confounding the results as Kumar et al. imply. The stratification of the analysis and examining the group of patients with 'poor cardiac status' is actually performed to reduce this potential confounder, so that the potential confounding factors (i.e. poor cardiac status) are homogenous in the particular subgroup. We would interpret the results to mean that in patients with poor cardiac status, lower BP is associated with a higher risk of death. Again, as indicated above, the mechanism of this association cannot be established in this retrospective study.

Finally, in the last paragraph of their letter, the authors say 'it is difficult to conclude that SBP <111 mmHg is associated with higher mortality in patients on PD'. We want to emphasize again that association (as opposed to causality) has to do with the statistically significance relationship of the factors studied to the outcome. That relationship was clearly demonstrated in our analysis. As for causative relationships between the lower BP and mortality, we could not and did not address this question in our project, and we tried to make this very clear to the reader of the paper.

Again we very much appreciate the interest in and analysis of our paper by Kumar et al., which does contribute to the discussion of the important topic of improving the survival of patients with end-stage renal disease.

Conflict of interest statement. None declared.

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Reply

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