Fatigue and plasma tryptophan levels in patients on chronic hemodialysis

To the Editor: Mutsaers *et al.*[1] have recently suggested that there is a direct link between tryptophan metabolism and the circadian rhythm in patients with chronic kidney disease (CKD) and that altered tryptophan metabolism as etiology for CKD-associated fatigue warrants further investigation. We have recently measured, by liquid chromatography with fluorometric detection previously described,[2] plasma free tryptophan (FTRP) levels, large neutral amino-acid (LNAA) levels, and the FTRP/LNAA ratio in 50 patients on chronic hemodialysis and correlated with fatigue assessed through the SF-36 Vitality subscale.[3] Patients were divided into two groups, fatigued (SF-36 Vitality subscale score $\leqslant 50$) and not-fatigued (SF-36 Vitality subscale score $\leqslant 50$).[4] The two groups were similar for age, sex, primary cause of end-stage renal disease, body mass index, dialytic age, serum albumin, creatinine, and urea. As shown in the Table 1, the two groups did not differ significantly for the plasma levels of FTRP, LNAA, and FTRP/LNAA ratio. In addition, the correlation between fatigue and FTRP (correlation coefficient: -0.001; $P=0.999$), LNAA (-0.072; $P=0.606$), and FTRP/LNAA ratio (0.035; $P=0804$) was not statistically significant.

Table 1 | Fatigue and plasma levels of FTRP and other LNAA in fatigue and not-fatigued patients (large neutral amino-acids)

	Fatigued ($n=25$)	Not-fatigued ($n=25$)	*P*
FTRP (nmol/ml)	15.2 ± 7.7	14.6 ± 12.6	0.839
LNAA (nmol/ml)	529 ± 163	533 ± 107	0.918
FTRP/LNAA	0.029 ± 0.014	0.026 ± 0.021	0.551

Abbreviations: FTRP, plasma free tryptophan; LNAA, large neutral amino-acids.
It seems that there is no correlation between fatigue and plasma tryptophan levels in patients on chronic hemodialysis.

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The Authors Reply: Chronic kidney disease (CKD) is characterized by a cornucopia of changes in the metabolic status of patients. Therefore, we postulated that alterations in tryptophan catabolism might be causative for CKD-associated fatigue.[1] In their letter, Bossola *et al.*,[2] provide preliminary data showing that tryptophan levels are similar between fatigued and nonfatigued dialysis patients, and they conclude that there is no correlation between fatigue and plasma tryptophan levels. We applaud these first steps aimed at unraveling the mechanism underlying CKD-associated fatigue. Yet, Bossola *et al.* do not provide enough data to irrefutably debunk the link between tryptophan metabolism and fatigue. Tryptophan is the precursor of a myriad of bioactive metabolites, and our group as well as others have previously observed changes in tryptophan metabolite levels and indoleamine 2,3-dioxygenase activity while tryptophan concentrations remained unaltered.[3,4] Therefore, determination of the levels of these compounds in the cohort studied by Bossola would undoubtedly be very interesting. Moreover, there is a high interindividual variability in the metabolome of CKD patients due to a multiplicity of factors, including diet,[5] as well as fluctuations in solute levels over time within a patient (Van den Brand *et al.*, submitted). Therefore, we propose to assess the levels of tryptophan, its metabolites and fatigue (via the SF-36 Vitality Subscale) at certain intervals during a prolonged period of time. All in all, we thank Bossola *et al.* for sharing their thought-provoking results, and we believe that the role of tryptophan metabolism in CKD remains an interesting avenue of research.

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