



The authors' reply

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We thank Dr. Park for her interest in our published paper [1] in the last issue of this *Journal* and appreciate her valuable comments. In principle, we agree with her opinion that “a link between anemia or erythropoiesis stimulating agent (ESA) responsiveness and ‘obesity paradox’ is still open to question.” As mentioned in the discussion section of the current publication, our study was an observational one that identified a possible association between ESA dose and body mass index (BMI) in hemodialysis (HD) patients. In addition, we suggested that prospective studies are needed to provide evidence in this context and to investigate the mechanisms linking BMI values and different measures of body composition (especially fat mass) with ESA requirements in HD patients.

Dr. Park's comments included that there are many confounding factors influencing ESA dose or erythropoietin resistance index (ERI) in HD patients in addition to BMI. Of note, malnutrition and inflammation complex syndrome might influence the association of BMI and ESA responsiveness. However, even after multiple linear regression analysis in this study, the real association of obesity and ESA dose might be confused by other unadjusted confounding factors including comorbidities, residual renal function, and inflammation or nutritional status. We clearly stated in the discussion that hyporesponsive-

ness to ESAs in non-obese HD patients may simply be a marker of poor underlying overall health. Malnutrition-inflammation complex syndrome is more relevant in non-obese patients and can reduce ESA responsiveness. The authors support Dr. Park's conclusion that we still need answers to the questions whether inflammation or nutritional status could be a contributing factor to ESA dose-saving in HD patients with higher BMI and whether body composition, such as fat mass or muscle mass rather than BMI, is more important in this relationship. The effect of adipokines on anemia parameters or ESA dose need to be determined in future studies.

Dr. Park had identified important areas in the results that require enrichment. According to our results, median hemoglobin level did not differ significantly between obese and non-obese patients, whereas average dose of ESA (expressed in unit/week) was significantly lower in obese compared to non-obese HD patients. An association between higher ESA dose and mortality has been observed in many studies [2–5]. This could be the link between obesity and better anemia control in HD patients on one side and survival in this group of patients on the other side.

We compared ESA dose across BMI categories from underweight (< 18.5 kg/m²) to third-degree obesity (> 40 kg/m²). A significant difference of ESA dose in different BMI subgroups was only seen among underweight, normal weight, and overweight groups. Obesity, defined by a BMI cutoff over 30 kg/m², did not further decrease with ESA dose. This may indicate that underweight status may have a deleterious and hazardous effect on ESA responsiveness compared to an increase in BMI > 30 kg/m².

A remarkable observation by Dr. Park is that ESA dose expressed in units per kg of body weight per week was mathematically associated with body weight or BMI and has an impact on the negative correlation of ESA dose

Received July 30, 2018; Accepted July 30, 2018

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and BMI as well as other results. Obviously, body weight and composition can affect the bioavailability and volume of distribution of drugs but expressing the dose of the drug per unit BMI or body volume might alleviate this problem at least partially. However, in addition to the negative correlation between BMI and ESA doses, expressed as units/kg body weight/week, there was also a significant negative correlation between BMI and absolute ESA dose, expressed as units/week, as well as with ERI (Table 3 in the article). Had the mathematical association between ESA dose, expressed as units/kg, and BMI been the main effector in the relation between ESA dose or ERI and BMI, one would expect that this relation would be nearly linear across the dose-response curve. However, this was not the case, as the ESA dose and ERI plateaued with BMI 30 kg/m². This clearly argues against the above-mentioned point.

In addition, in multiple linear regression analysis, we evaluated predictors of the dose–response effect of ESAs; accordingly, we used the ERI as the dependent factor (and not ESA dose in units per kg of body weight per week). Multiple linear regression analysis also revealed that BMI and urea reduction ratio were the strongest predictors of ERI.

Finally, we admit that our research had the limitation of not studying the correlation between ESA responsive-

ness, BMI with many known comorbidities, and markers of inflammation. Thus, we strongly agree with Dr. Park that this area still needs further studies.

Conflicts of interest

The author has no conflicts of interest to declare.

References

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