Re. "Effectiveness of protein-caloric supplementation in hemodialysis patients to improve the amino acid balance and avoid protein energy wasting: Author's response"

To the Editor:

I read with interest this valuable opinion contributing to the discussion about oral nutritional supplementation (ONS) in patients on hemodialysis (HD) as a potential measure to avoid and treat malnutrition. The authors kindly referenced our recent article [1], which aimed to evaluate ONS in a group of patients on HD. In a broad and detailed review, the authors raised doubts as to the conclusion of our research, pointing out that the "chosen kind of nutritional integration could constitute an insufficient stimulus for the protein anabolism." I beg to differ with this opinion, especially because the aim of our study was in fact to evaluate the applicability of the preformed formula of the commercially available supplement in the clinical setting.

It is difficult to disagree with the provided point-by-point considerations regarding the need to create an amino acid mixture tailored to specific needs of patients with stage 5 dialysis chronic kidney disease. However, it also is difficult to find a common denominator between this elegant, albeit purely academic, dissertation and our clinical approach focused on finding a measure to alleviate the day-to-day problems found in thousands of patients in HD units all over the world.

Two specific issues need further clarification. First, as an author, I would rather reserve myself the right to chose and define the inclusion criteria in the study protocol, especially as they are clearly stated in our work and based on established criteria according to the International Society of Renal Nutrition and Metabolism, traditionally accepted in clinical practice [2]. I must sincerely congratulate the impressive consensus statements of the Italian Society of Nephrology [3] and promise to consider them in the future. Second, we were not able to discuss the negative influence of the supplement on the uremic microbiota dysbiosis because it was not possible for us to provide data in this respect. I agree that this is an issue of great importance and I can only be thankful to the authors for addressing it.

I must admit that I highly appreciate the concerns that our results are equivocal and our study has limitations. In our experience, clinical studies are plagued with such issues. Patients fail to gain calculated weight, cease to adhere to dietary counseling, and have laboratory findings far from those hypothetically expected. We all should be aware that even widely accepted measures of nutritional status, such as bioimpedance specifically recommended by the authors, may have many limitations when applied to patients on HD [4]. This population is among the most challenging to study, and the fact that we managed to enroll a homogenous and meticulously phenotyped group of patients on HD is an essential strength of our study.

Although our previous clinical experience and recent literature lead me to conclude that the rationally administered ONS is the most prudent and practical choice in everyday practice [5,6], I fully respect the different opinion presented by authors. I want to express my gratitude for their taking this opportunity to share their expert advice and for making an effort to provide an invaluable review of our publication. The respectful, factual discussion always contributes to the development of knowledge, broadens perspectives, and is conducive to progress.

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Sylwia Małgorzewicz M.D., Ph.D.
Department of Clinical Nutrition and Dietetics, Medical University of Gdańsk, Poland

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Re. "Amino acid profile after oral nutritional supplementation in hemodialysis patients with protein-energy wasting"

In the original work by Malgorzewicz et al. [1], the authors chose to use a protein-caloric supplementation composed by 18.75 g of protein/d plus 500 Kcal/d for 3 m, but this intervention did not seem to support the hypothesis of possible future nutritional improvement or stabilization of metabolism in patients on hemodialysis (CKD5D patient). Moreover, it is not feasible to evaluate the metabolic outcome considering CKD5D patients affected by protein energy wasting (PEW) by the current criteria, because in this paper, all defined statements were not in accordance with the most recent classifications. Besides the hemodialysis methodologies used are not known [2]. In fact, despite a limited quantitative increase in total amino acids (TAA), the expected increase in plasma levels of some essential amino acids (EAA) and branched chain amino acids (BCAA), such as isoleucine, leucine, lysine, phenylalanine, and valine, did not happen.

Moreover, the authors declared only "to maintain dietary intake within the recommended range" [1]; therefore, we assume that the protein-caloric prescription would have been 1.2 g protein/kg/d plus 30 to 35 Kcal/kg/d. Thus, a constant protein supplementation of approximately +23% added to 500 Kcal /d (+24%) should have resulted in an increase in body weight of >10% and a protein catabolic rate (PCR) much higher than 12% at the end of the study.

Unfortunately, the authors did not consider the negative influences in the release and use of amino acids due to microbiota uremic dysbiosis [3]. The authors also did not consider previous work [4] that compares CKD5D patients whose diet was supplemented with 8 g/d of a mixture of EAA versus a homogeneous CKD5D patients control group without any supplement; in fact, this study showed an increase of patient body weight, equilibrated PCR, fat-free mass, albumin, hemoglobin, and a decrease of C-reactive protein compared with the control group over the course of 3 mo.

On the other hand, another determining factor is to establish the true AA dialytic mass transfer and how many and which AAs are lost using the current dialysis methodologies with high diffusion or convective efficiency. The methodology to establish this aim has to be particularly rigorous; it has to determine in triple the plasmatic concentration of all 20 major AAs, but especially in dialytic fluid coming from the dialysis filter using the *spilling* method by high-precision volumetric pumps during the entire hemodialysis session. The method has also to employ the same ultra-pure dialysis fluids, and dialysis are enable to determine the extreme volume of the dialytic output fluids, composed by the dialysate at the output of the filter (Qdout) + plasmatic water ultrafiltrate resulting from patients' interdialytic weight gain plus fluid intravenous infusion amount, especially in online haemodiafiltration methods [5].

In addition to these points, the paper by Malgorzewick et al. [1] did not consider the very strict and crucial point regarding the protein-caloric nutrition criteria for CKD5D patients. We would emphasize this gap by recalling the consensus statements of the Italian Society of Nephrology [6] that consider protein 1.2 g/kg/d (50% animal), 30 to 35 Kcal/kg/d (carbohydrates + lipids), and sodium 5 to 6 g/d. Then, when assessing fat and lean mass, the right time of detection should be considered because at least 3% to 5% of the body weight of CKD5D patients consists of body water excess. These data could be determined by use and monitoring performed by Bioimpedance [6].

The message, with the sincere aim of integrating this interesting mentioned work [1], consists of the following points: 1) the modern hemodialysis methodologies, such as online hemodiafiltration produces a dramatic annual loss of AA of approximately 900 g/y/patient, especially when it chooses high-convective methods, such as online pre-hemodiafiltration; the hemodialytic strategy must be always considered [5]; 2) these AA losses have to be compensated with the administration of mixtures of the main 20 AA in the amount of at least 4 to 8 g/d whitout urea nitrogen and phosphates contents; 3) these serious losses of AA result in an inevitable and progressive reduction of muscle mass from which all classes of AA are pulled; and 4) in CKD5D patients, whose life expectancy is only long vintage survival by dialysis, we believe that there is no other way to avoid progression toward a very relentless PEW, bypassing the enteric barrier of uremic dysbiosis through the direct nutritional administration value of AA and giving back much of the sensitivity to insulin action [3].

The future intent is to create a tailored AA mixture on the uremic status of CKD5D patients in hemodialysis. Whether or not Malgorzewick et al. [1] gave a stable diet of at least 30 to 35 Kcal/d to avoid the breakdown of proteins to develop energy and slow down or avoid PEW is unclear, considering the persistence of microinflammation markers in their work. Finally, the study shows an unconvincing total AA quantitative increase in which some EAA and BCAA do not positively influence the protein metabolism of CKD5D patients. This suggests that this chosen kind of nutritional integration could constitute an insufficient stimulus for the protein anabolism.

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Piergiorgio Bolasco M.D.*
Roberto Aquilani M.D.
Stefano Murtas M.D.
Chronic Renal Failure Conservative Nutritional Treatment Group, Italian Society of Nephrology, Rome, Italy

Department of Biology and Biotechnology, University of Pavia, Pavia, Italy

Territorial Department of Nephrology and Dialysis, ASSL Cagliari, Cagliari, Italy

E-mail address: pg.bolasco@gmail.com (P. Bolasco).

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