



Present and future in renal nutrition research

Interviewed: Juan Jesus Carrero

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¹ In March 2012, Juan Jesus Carrero visited the Department of Applied Nutrition / Nutrition Institute – Rio de Janeiro State University – as a Guest Professor.

² Carla Maria Avesani is a clinical dietitian and researcher specialized in nutritional aspects of chronic kidney disease. Her doctoral studies were conducted at the Federal University of Sao Paulo. After that she spent 12 months at Karolinska University for her post-doctoral studies, where she worked with Juan Jesus Carrero. Currently she is Adjunct Professor at the Department of Applied Nutrition / Nutrition Institute – UERJ. She is the coordinator of the research group studying nutritional aspects of elderly hemodialysis patients at the Nutrition Institute – UERJ.

Juan Jesus Carrero was graduated as pharmacist by Granada University (Spain), and dedicated his studies and research ever since to the field of nutrition/catabolism. His PhD studies at Granada University, Spain versed on nutritional supplementation strategies in populations with high cardiovascular risk. Various randomized controlled trial designs tested the effects of nutritional supplementation with n-3 fatty acids, oleic acid and vitamins B6, B9 and E.

During his postdoc he joined the Department of Renal Medicine at Karolinska Institutet, Sweden, where he deepened into the field of nutritional aspects of chronic kidney disease, with emphasis on the association between protein energy wasting, inflammation and cardiovascular disease (CVD). Within this context he achieved a second Ph.D. degree at Karolinska University.

He has then developed his research lines at Karolinska Institutet in the areas of body composition derangements, nutritional deficiencies, endocrine disorders and consequences

of systemic inflammation in chronic kidney disease. He already has more than 120 publications in the best Nephrology journals and, in my opinion, he is presently one of the most promising young researchers in the field of nutrition and CKD.

In March 2012, Juan Jesus Carrero visited the Department of Applied Nutrition / Nutrition Institute – Rio de Janeiro State University – as a Guest Professor (granted by UERJ's Graduate Studies and Research Provost). His visit allowed an important interaction with the post-graduate students from the Nutrition, Health and Food post-graduate Program (Master and Doctoral degrees) and vividly discussed his area of expertise and appropriate use of epidemiology/statistics in research. This interview aims to share his opinion about present and future directions on renal nutrition research.

Demetra: *For many years, malnutrition was the main nutritional disturbance discussed in the field of nutrition and chronic kidney disease (CKD). However, after the publication of the reverse epidemiology in hemodialysis (HD) patients in 1998, a change toward the role of obesity on survival of CKD patients (in both pre-dialysis and dialysis stages) started. Many studies have been published regarding this subject. With this in mind, what is your opinion about the role of obesity as protective or non-protective factor on mortality in the population?*

Juan Jesus Carrero: I think that both concepts are not opposed, but complementary. Malnutrition/wasting is a tremendous and devastating condition with rapid impact on both body composition and patient survival. In the context of this accelerated wasting, obese individuals have the capacity to survive slightly longer due to larger energy depots to stand for the body's hyper-catabolism. In this context, obesity is "protective" in the short term, since it allows patients with protein-energy wasting to resist more. However, in the long term obesity is a risk factor associated to hypertension, diabetes, atherosclerosis and inflammation.

Demetra: *This subject also brings upfront the new findings of the metabolic disturbances coming from obesity, the stage of dysmetabolism leading to insulin resistance, low grade inflammation (or subclinical inflammation), hyper-triglyceridemia, which all together increases the chance of CVD. How can one balance these findings with the higher survival rates found in HD patients with higher BMI?*

Juan Jesus Carrero: As I said, it is an issue of competing risks. Malnutrition/wasting is a short-term risk that competes with the problems of obesity. In this competition, malnutrition wins and the patient dies of malnutrition. When malnutrition is not present, the patient may die of the metabolic disturbances linked to obesity.

Demetra: *Body composition methods are also of interest when discussing obesity in CKD patients. For research and clinical purposes, what method would you recommend to assess body composition of CKD patients?*

Juan Jesus Carrero: BMI has problems due to the inability to separate muscle from fat compartments and to the issue of over-hydration in the context of CKD. I think that waist circumference is an easy and reliable estimate of abdominal fat, and handgrip strength is a valid estimate of muscle strength. There are of course much better assessments, but as a screening tool in the clinic these are valid enough.

Demetra: *Also interesting is the finding that obese patients can also have signs of protein malnutrition, characterized by a state of sarcopenia. The co-existence of obesity and sarcopenia has been defined by some as obese sarcopenia. In CKD patients there is not much published so far on this subject. Can you tell us upfront what is your guess about this very particular clinical condition?*

Juan Jesus Carrero: Indeed this issue has never been studied in CKD patients. A pioneer study assessed the prevalence of malnutrition in the context of obesity (Honda AJCN 2006). However, assessment of obese sarcopenia is still lacking. Loss of muscle mass is a prevalent condition in our patients and the best outcome predictor in terms of body composition assessment tools. Overweight, obesity and over-hydration may hide the visual presence of muscle atrophy, and probably remains underdiagnosed. I think this is an exciting and potentially clinically relevant aspect of uremic PEW, especially given the growth of obesity epidemic in the CKD population.

Demetra: *How could sarcopenia be treated? Are you aware of clinical studies aiming to treat sarcopenia (regardless of being obese or not) in CKD patients?*

Juan Jesus Carrero: The treatment would depend on the causes of sarcopenia in this population. Muscle catabolism occurs principally because of persistent inflammation, lack of circulating aminoacids from the diet, metabolic acidosis and ineffective anabolic drives (resistance to GH/IGF-1 or insulin, testosterone deficiency...). Treatments are available for each of these conditions, but few have been appropriately tested in uremic patients so far.

Demetra: *Malnutrition, recently defined as protein energy wasting, is also of high importance due to its close association with increasing mortality rates. How can be protein energy wasting be diagnosed (or assessed) in CKD patients?*

Juan Jesus Carrero: The diagnosis is presently difficult because there is no real consensus on their definition. The International Society of Renal Nutrition and Metabolism has proposed some diagnostic criteria but these have not yet been validated. Measures of food intake, body composition tools, nutritional scoring systems, and laboratory values such as serum

albumin are used to diagnose PEW and to assess the degree of severity of PEW without clearly validated diagnostic criteria. Ongoing debate as to whether such surrogates as serum albumin concentrations are markers of nutritional status, inflammation, comorbidity, or other conditions has led to confusion and diagnostic and therapeutic nihilism. Irrespective of the cause of hypoalbuminemia in dialysis patients, evidence suggests that nutritional interventions can increase serum albumin in dialysis patients. Hence, we should continue assessing serum albumin and other surrogates of nutritional status to risk-stratify patients and to allocate nutritional therapy, while well-designed, large-scale, randomized, controlled trials of the effects of nutritional intake on clinical outcomes are awaited.

One consideration is that it is perhaps difficult to have stringent criteria applicable to all patients, societies and cultures. In addition, characteristics and clinical cut-offs may vary with aging and with the context of the disease. For instance, hypoalbuminemia in the elderly may not be considered with the same cutoff than in young patients. Also, hypoalbuminemia should probably be considered at lower thresholds for patients undergoing peritoneal dialysis than for patients undergoing hemodialysis. In order to make a decision on diagnosis / assessment of PEW, we cannot rely exclusively on these biomarkers. We need to balance patient self-reports, clinical judgment and the information obtained from this assessment tools.

Demetra: *Clinical studies trying to treat protein energy wasting failed to reverse this condition. Why is it so difficult to treat protein energy wasting?*

Juan Jesus Carrero: The main difficulty starts with the fact that it is a truly multifactorial syndrome, where pure malnutrition coexists with inflammation / hyper-catabolism, resistance to anabolic drives and a sedentary lifestyle. Treatment strategies so far have concentrated in targeting one of these components only. The appropriate treatment of a multifactorial syndrome like this one should likely be multifaceted and combine nutritional support with anti-inflammatory strategies, exercise training and anabolic hormones.

Demetra: *In this opposing field: obese vs protein energy wasting, which nutritional disturbance has the worse outcome and lower quality of life? Which one in your opinion should be first target in the research projects?*

Juan Jesus Carrero: Protein-energy wasting without any doubts. Protein-energy wasting also exists in obese people, and it is more difficult to diagnose it in these individuals as we interpret their excess weight as a sign of health. When it becomes evident it may be too late. Therefore nutritional assessment is necessary and required frequently in all CKD patients, irrespective of their body mass index.