

## ERA Long-Term Research Fellowship Project

### ERN

#### Project's key info

<b>Title of the project</b>	Food as medicine in chronic kidney disease
<b>Working Group and ERA Committee involved in the project</b>	ERN (European Renal Nutrition) Working Group
<b>Principal Investigator(s) of the project</b>	Carla Maria Avesani
<b>Duration</b>	12 months
<b>Fellowship Grant</b>	35.275,00 €
<b>Start of the fellowship</b>	Within 6 months after notification of the grant award to the fellow.

#### Receiving Institute

<b>Name of receiving institute</b>	Karolinska Institute (SWEDEN)
<b>Supervisor's name</b>	Carla Maria Avesani
<b>Supervisor's e-mail address</b>	<a href="mailto:carla.avesani@ki.se">carla.avesani@ki.se</a>

#### Project's detailed description

<p><b>Project description</b></p> <p>Nutrition is one of the cornerstones in the treatment of patients with chronic kidney disease (CKD). It includes assessing the nutritional status, planning the individualized dietary counseling, and following the patient after the nutritional intervention. The aim of the nutritional treatment is to mitigate the metabolic disturbances developed as kidney function decreases, avoid the development of malnutrition, and treat nutritional abnormalities if needed (1).</p> <p>For that, the Nutrition guidelines for patients with CKD recommend a diet where the amount of energy, nutrients, minerals and micronutrients are individualized according to the CKD stage or dialysis treatment, food habits and preferences and socioeconomic conditions. In general, for patients with CKD stages 3 to 5 not on dialysis (estimated glomerular filtration rate (eGFR) &lt; 59 ml/min/1.73 m<sup>2</sup>) a low protein diet with controlled content of phosphorus and sodium is recommended. For patients on dialysis, the protein content increases but the phosphorus and sodium intake remain controlled, in addition to the follow-up on the liquid/fluid intake. The dietary potassium may also need to be adjusted if hyperkalemia is present regardless of the need or not of dialysis treatment (1).</p> <p>Studies have shown that patients that adhere to these dietary recommendations show clinic benefits such as presenting adequate nutritional status, delaying the start of dialysis, decreasing the number of uremic symptoms, presenting a better control of net endogenous acid production (NEAT), better control of phosphate levels (2-5). All these clinical benefits result in a better quality of life and lower mortality rates.</p> <p>However, if the nutritional plan is not carefully designed, the diet may instead become restrictive, insufficient in energy and nutrients and with poor quality. Such diets can be harmful and predispose to the development of comorbidities such as malnutrition, dysbiosis, intestinal</p>
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constipation and others, losing therefore, the benefits that are primarily aimed with the nutritional intervention.

Considering the above said, for the ERA Long-Term fellowship project, the research line “Food as medicine in CKD” will be used. This research line was initiated at the Nephrology of Karolinska Institute in 2020 and has the ambition to add knowledge on the benefits of adequate nutrition to CKD patients. For that there are two ongoing projects, one project planned to start in March 2023 and 2 educational projects from ERASMUS+ that covers four areas of nutrition in CKD: a. How to best evaluate the nutritional status; b. exploring clinical treatments to allow a healthy diet with higher potassium content for patients with hyperkalemia; c. investigating the use of bioactive components from the food to minimize the metabolic disturbances from CKD and, d. exploring barriers, needs and facilitators for patients in hemodialysis, their caregivers and health care professionals to adhere to best practices in nutrition, physical activity and emotional cognitive wellbeing.

All projects are developed at Karolinska Hospital (Renal Medicine, Theme Inflammation and Aging) and at Karolinska Institute (Division of Nephrology – Baxter Novum). The description of the research projects integrating this research line follows below.

**Study 1. Effect of broccoli sprout extract in patients with chronic kidney disease with diabetes type 2 (INITIATE)**

Foods with bioactive components can be an alternative to mitigate the metabolic disturbances present in patients with type 2-diabetes and CKD. Previous research on experimental animals and type 2-DM patients has shown that a substance in broccoli sprouts, called sulforaphane, improves insulin sensitivity (especially in the liver) and glucose control, possibly by its properties as an antioxidant. We here hypothesize that sulforaphane given as a broccoli sprout extract (BSE) can ameliorate glucose control in patients with type 2-DM and CKD with estimated glomerular filtration rate (eGFR)  $> 15 < 45$  ml/min/1.73 m<sup>2</sup>.

This is an ongoing multicentre randomized double-blinded controlled trial including 11 centres in Sweden. The primary outcome will be amelioration in glucose control. The glucose control will be evaluated by the oral glucose tolerance test (OGTT). As a secondary aim, we will investigate the role of BSE in improving other signs of metabolic derangements present in this group of patients, including oxidative stress, proteinuria, inflammation and a decrease in the production of uremic toxins from the gut microbiota.

The novelty and clinical relevance of this study will be to investigate whether BSE is able to improve glucose control of CKD patients with type 2-DM. With this, we hope to contribute to the development of new functional foods to be used in the treatment of this group aiming to reduce the risk factor for cardiovascular disease.

The principal investigator is Peter Stenvinkel and Carla Maria Avesani (the applicant for this grant) is the Research Coordinator.

**Study 2. Healthy diet rich in Potassium containing Fruits, vegetables and nuts to chronic kidney disease patients through the Use of sodium zirconium cyclosilicate: a Feasibility Study (HELPFUL)**

Hyperkalemia is often present in patients with CKD. In this condition, the recommendation is to decrease the intake of fruit sources of potassium, which include fruits, vegetables, nuts, legumes and whole cereals. Since these are healthy foods from the diet, when dietary restriction of potassium is recommended, the overall diet becomes monotonous and of poor quality and may worsen the patient's quality of life. Medications used to decrease plasma potassium, like the sodium zirconium cyclosilicate (SZC), might constitute a clinical option to allow a healthy diet for patients with hyperkalemia. The aim of this study is to investigate the use of the potassium-lowering medication SZC to treat hyperkalemia and allow the intake of a healthy plant-based diet.

The novelty and clinical relevance of this project is to investigate treatment strategies allowing a healthy plant-based diet to patients with CKD that developed hyperkalemia. Since a diet restricted in potassium limits the intake of healthy foods, the results of this project open possibilities to provide better treatment for patients, in addition to facilitating their diet and improving quality of life with a less restrictive diet. Other benefits of plant-based diet include promoting a healthy gut microbiota, ameliorating dysbiosis and intestinal constipation and decreasing inflammation and oxidative stress.

**Study 3. Effect of healthy vs ultra-processed meal with potassium additives on plasma potassium in patients with CKD**

The use of potassium additives in processed foods is increasing in the last two decades. These food additives are used by the food industry to increase the product's shelf-life, change food texture and colour and make products more attractive to the consumer. Currently, 14 potassium-based food additives are registered in the CODEX. The problem with the use of potassium additives is that it becomes a hidden source of potassium in the diet. In addition, potassium food additives may potentially promote a higher increase in plasma potassium because the bioavailability of potassium additives is of about 90% to 100%, while the potassium bioavailability from fruits, vegetables, nuts, legumes and whole cereals is about 40% to 60%.

Therefore, we aim to investigate if meals containing potassium additives can promote a higher acute increase in plasma potassium when compared to a meal with the same potassium content, but without potassium additives. The primary outcome will be changes in plasma potassium from baseline to 240 minutes after the ingestion of two meals with the same potassium content, but one with a healthy meal and another with ultraprocessed meal containing potassium food additives. This project received a grant in August 2022 and we are planning to start in march 2023.

**ERA COOKBOOK project**

In addition to three research projects described above, the fellowship program will include activities to organize the cookbook project already present in the ERA webpage. The aim is to review the adequacy of the recipes already published and create a flow of assessment for new submitted recipes. The assessment and adequacy of the recipes will be based on its nutrient composition according to recommendations to patients with CKD.

The recipes posted in the Cookbook project should follow guideline recommendations for patients with CKD.

Therefore, the following criteria will be used prior to acceptance of the recipe.

- A recipe that supports a healthy diet. For that no ultra-processed food or seasonings should be used in the ingredient list. The classification of ultra-processed food is the one proposed by the NOVA Classification according to the extent of food processing. The NutriScore system can also be used to classify products using the label of processed items

(<https://nutriscore.colruytgroup.com/colruytgroup/en>).

- Preferably, the recipes will use minimally processed or non-processed ingredients, with herbs and natural seasonings to minimize or to replace the use of salt and decrease sodium content.

- The recipes are preferable with controlled content of sodium, potassium, phosphate and liquids.

There is no strict threshold for each of these minerals in the recipe, but we recommend that for potassium up to 800 mg (20 mEq), for phosphate up to 400 mg, sodium up to 1 g / recipe. The recipes should describe the sodium content instead of salt.

- The recipes should describe how many servings it yields and the amount of energy, macronutrients, potassium, phosphate and sodium present in each serving.

- Preferably, the recipes should be colorful and use fresh ingredients.

- Recipes must be submitted in English and in the country's original language with a mention of which the country the recipe is originated.

#### Main references

1. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, et al. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. *Am J Kidney Dis.* 2020;76(3S1):S1-S107.
2. Rhee CM, Ahmadi SF, Kovesdy CP, Kalantar-Zadeh K. Low-protein diet for conservative management of chronic kidney disease: a systematic review and meta-analysis of controlled trials. *J Cachexia Sarcopenia Muscle.* 2018;9(2):235-45.
3. Cupisti A, Gallieni M, Avesani CM, D'Alessandro C, Carrero JJ, Piccoli GB. Medical Nutritional Therapy for Patients with Chronic Kidney Disease not on Dialysis: The Low Protein Diet as a Medication. *J Clin Med.* 2020;9(11).
4. Goraya N, Simoni J, Jo CH, Wesson DE. A comparison of treating metabolic acidosis in CKD stage 4 hypertensive kidney disease with fruits and vegetables or sodium bicarbonate. *Clin J Am Soc Nephrol.* 2013;8(3):371-81.
5. Palmer SC, Maggo JK, Campbell KL, Craig JC, Johnson DW, Sutanto B, et al. Dietary interventions for adults with chronic kidney disease. *Cochrane Database Syst Rev.* 2017;4:CD011998.

#### Goals of the project

The goal of this project is to involve the researcher granted with the fellowship in the activities related with the 3 projects from the research line "Food as medicine in CKD" and, to support the ERA COOKBOOK project, as described above.

In the projects HELPFUL and INITIATE which the data collection will be concluded in December 2022 and April 2023, respectively, the person granted with the fellowship will work in analyzing the data, interpreting the findings, and participating in the elaboration of manuscripts. From the study HELPFUL, the granted researcher will be the first author of a manuscript analyzing the impact of the food basket tailored to each patient according to their food preferences on changes in the dietary pattern before and after the intervention. This paper will also describe the food preferences sources of potassium that each patient listed as part of the study.

The fellowship program will also be important to review the adequacy of the recipes submitted to ERA Cookbook and whether nutrient composition adheres with recommendations to patients with CKD, following the criteria described previously. This will increase visibility of ERA Nutrition Workgroup and will enhance the communication between ERA and its members.

Finally, the project also aims to offer an experience to the researcher granted with the fellowship in being in an environment comprised by researchers from different countries and disciplines (nephrologist, pharmacist, biostatistician, dietitian, dentist, and others). This will allow an international and multidisciplinary view of research related with nephrology and that goes beyond to nutrition.

### Qualifications and/or expertise required to the fellow

#### Mandatory requirements

- Dietitian or nutritionist with experience in renal disease.
- Concluded PhD in science when the fellowship begins.

#### Desirable requirements

- Basic knowledge in biostatistics.
- Publications in the field of Nutrition and renal diseases.