

SECOND YEAR REPORT**PHD PROGRAM IN MEDICAL SCIENCES AND BIOTECHNOLOGY****XXIX CYCLE**

PhD candidate: Marinella Ruospo

Research topic: Nutrition and dietary intake and their association with mortality and hospitalization in adults with chronic kidney disease treated with hemodialysis

Tutor: Prof. Piero Stratta

Introduction and Rationale

The aim of the current PhD project is to evaluate the association between exposure to different nutrition and dietary patterns and the risk of mortality and hospitalization in adults with end stage kidney disease (ESKD) treated with hemodialysis.

This is an epidemiological research project, based on systematic reviews of the scientific literature (three different meta-analysis, including randomized controlled trials, cohort studies and qualitative research studies) and the design of 'ad hoc' prospective cohort study.

Nutritional intake and dietary patterns are potential determinants of health outcomes in dialysis patients. Chronic kidney disease (CKD) causes water, sodium, potassium, and phosphorus retention, which contributes to cardiovascular events, intradialysis symptoms, breathlessness, and edema. Obesity is a risk factor for end-stage kidney disease¹, while malnutrition (commonly referred to as protein-energy wasting²) is endemic in people with advanced CKD³. While long-term dialysis treatment for end-stage kidney disease is already associated with an annual mortality of between 15% and 20%⁴, malnutrition affects 20–70% of dialysis patients, increases with duration of dialysis treatment⁵⁻⁷, and is associated with increased mortality³.

However, adherence to dietary regimens in CKD is challenging due to the burden of constant choices about food and drink, the adaptation to complex eating patterns, existing cultural practices, and the competing demands of CKD and related illnesses⁸⁻¹¹.

- a. While dietary interventions are considered central to the management of CKD, health professionals cite insufficient time to implement recommendations¹², and inclusion of patient experiences and perceptions of dietary treatment in CKD guidelines is limited¹³. In the thematic synthesis of patient views from qualitative studies, patients' perspectives and choices of dietary and fluid management in CKD provided in existing qualitative studies have been summarized to inform clinical practice and research.
- b. As dietary composition modifies risk of cardiovascular disease and mortality in the general population, but the association between dietary intake and chronic kidney disease incidence or the progression of kidney disease or mortality in people with established chronic kidney disease have not previously been synthesized, a systematic review of cohort studies has been undertaken to assess the evidence for the association between dietary intake and onset and any association

between dietary composition and progression of chronic kidney disease or premature mortality (total and cause-specific) in adults with established chronic kidney disease.

- c. Dietary intake and composition represents a potential preventative factor for developing chronic kidney disease and a modifiable risk factor for premature morbidity and mortality in people who have developed chronic kidney disease. Currently, few treatments show that pharmacological interventions improve outcomes in CKD, thus new modifiable determinants of outcomes are required. To evaluate the effect of dietary interventions on mortality and major cardiovascular outcomes in adults with chronic kidney disease, a systematic review and meta-analysis of RCT has been conducted.

While running these systematic reviews, it emerged that data evaluating the association between diet and clinical outcomes in people treated with dialysis are limited and largely derive from small, single-centre, studies¹⁴⁻¹⁷. A large-scale multinational cohort study has been therefore designed to evaluate the association between nutrition and health outcomes in adults with end-stage kidney disease treated with hemodialysis. The study will assess the short-term and long-term morbidity and mortality associated with dietary intake (total energy, fat, carbohydrates, protein, fibre, folate, β -carotene, retinol, thiamine, riboflavin, phosphorus, magnesium, calcium, zinc, fluid, and specific food types) in adults treated with hemodialysis.

Methods

Systematic reviews

- a. The systematic review of qualitative studies has been published on AJKD¹⁸. Briefly, MEDLINE, EMBASE, PsycINFO, CINAHL, Google Scholar, reference lists, and PhD dissertations were searched to May 2013. We included qualitative data for adults 18 years or older who had CKD and who expressed opinions about diet or fluid management. Two authors screened all records and discarded those that were not eligible. The full text of the remaining citations then was examined to identify qualitative data. We included CKD stages 1 to 5, kidney transplant recipients, and people treated with dialysis. We identified descriptive themes in primary data and used thematic synthesis to generate analytical themes, importing text of each primary source into HyperRESEARCH (ResearchWare Inc.), performed line-by-line coding, conceptualized the data, and inductively identified concepts relating to patient perspectives, experiences, and values. Similar concepts were grouped into themes and subthemes. Conceptual linkages between themes were used to generate a thematic schema. Revisions of the themes and concepts were discussed, and these were incorporated into the final synthesis.
- b. For the systematic review of observational studies, we searched MEDLINE and EMBASE for cohort studies of major dietary factors (fat, cholesterol, omega-3-fatty acids, *trans*-fatty acids, carbohydrates, glycaemic index, fibre, folate, specific foods, electrolytes or micronutrients, and dietary patterns [e.g. DASH diets; Mediterranean diet, American Heart Association diets]) and chronic kidney disease outcomes. We included cohort studies in adults with chronic kidney disease (any stage) or who were at risk of chronic kidney disease (including those with diabetes mellitus, cardiovascular disease and/or hypertension) in which dietary intake has been evaluated at baseline.
- c. For the systematic review of RCT, we searched Electronic databases including MEDLINE, CENTRAL, EMBASE, and the Cochrane Renal Group's Register of Randomized Trials to identify studies that compare two or more different dietary factors (fat, cholesterol, omega-3-fatty acids, *trans*-fatty acids, carbohydrates, glycaemic index, fibre, folate, specific foods, electrolytes or micronutrients, and dietary patterns in adults with chronic kidney disease (any stage) to extract data about study

characteristics, risk of bias, and outcomes (mortality, cardiovascular mortality, infection related mortality, major adverse cardiovascular events, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, adverse events).

Cohort study

The protocol of the large-scale cohort study has been published on BMJ Open¹⁹ and discussed in detail in the first PhD year report. Briefly, the “DIETary intake, death and hospitalization in adults with end-stage kidney disease treated with HemoDialysis (DIET-HD)” study has recruited approximately 10,000 adults who have ESKD treated by clinics administered by a single dialysis provider in Argentina, France, Germany, Hungary, Italy, Poland, Portugal, Romania, Spain, Sweden and Turkey. Recruitment has taken place between March 2014 and May 2015. Nutritional intake and dietary patterns will be measured using the Global Allergy and Asthma European Network (GA²LEN) food frequency questionnaire after completion of data entry by optical character recognition (OCR) scanner. The primary dietary exposures will be n-3 and n-6 polyunsaturated fatty acid consumption. The primary outcome will be cardiovascular mortality and secondary outcomes will be all-cause mortality, infection-related mortality and hospitalization.

Results

Systematic reviews

- a. In the review of qualitative studies, we included 46 studies involving 816 patients living in middle- to high-income countries. Studies involved patients treated with facility-based and home hemodialysis (33 studies; 462 patients), peritoneal dialysis (10 studies; 112 patients), either hemodialysis or peritoneal dialysis (3 studies; 73 patients), kidney transplant recipients (9 studies; 89 patients), and patients with non-dialysis-dependent CKD stages 1 to 5 (5 studies; 80 patients). Five major themes were identified: preserving relationships (interference with roles, social limitations, and being a burden), navigating change (feeling deprived, disrupting held truths, breaking habits and norms, being overwhelmed by information, questioning efficacy, and negotiating priorities), fighting temptation (resisting impositions, experiencing mental invasion, and withstanding physiologic needs), optimizing health (accepting responsibility, valuing self-management, preventing disease progression, and preparing for and protecting a transplant), and becoming empowered (comprehending paradoxes, finding solutions, and mastering change and demands).
- b. The review of cohort studies is currently at the stage of data extraction by two independent investigators for study characteristics, risk of bias, and outcomes (onset of chronic kidney disease as defined by investigators, progression of chronic kidney disease or death in patients with chronic kidney disease (total and cause-specific). Data analysis will follow.
- c. We included 80 studies involving 172 intervention arms comparing dietary management strategies in the review of RCTs. 5591 individuals and 26 clusters (279 participants) were randomized. Three of the 76 included studies evaluated dietary management in people treated with long-term dialysis while the remainder involved people with chronic kidney disease. No RCTs were identified among recipients of a kidney transplant. Nearly all studies (72 studies) evaluated phosphorus and/or protein-based interventions among 5,508 adults, while five studies evaluated other dietary strategies including individualized nutritional counselling, a Mediterranean diet, olive oil supplementation, or a carbohydrate-restriction, low-iron protein source, and polyphenol intake modification and education on dietary phosphorus content. Studies generally reported insufficient details to inform judgments about risks of bias and were generally of short duration (median duration was 9 months, ranging between 1 month and 7 years) and had small sample sizes (median

of 35 participants). The amount of information available to determine dietary effects on mortality, progression to end-stage kidney disease or patient adherence did not indicate that dietary management strategies had different efficacy, although the confidence intervals were very wide. Similarly, most dietary management strategies did not appear to have different effects on body mass or weight, kidney function, serum lipids or albumin, or blood pressure, however confidence intervals frequently included both the possibility of considerable benefit and harm.

Cohort study

Recruitment has been stopped last May 2015. Data from the food frequency questionnaires (FFQs) have been entered from their arrival at the central scientific office into an electronic database using OCR scanner. So far, a total of 6,177 FFQs among the 11 different participating countries have been scanned and are available in the database for preliminary analysis. Specific contributions from each country as follows:

Argentina: 1,477

France: 92

Germany: 221

Hungary: 658

Italy: 602

Poland: 231

Portugal: 1,016

Romania: 1,063

Spain: 448

Sweden: 56

Turkey: 313

Scanning will continue until the end of the year, in order to have the final database to be clean and ready by the beginning of 2016 for descriptive analysis. 12 months of follow up from the end of recruitment will be required to start analysis of mortality and hospitalization (May 2016).

Conclusions

Data from our systematic review of qualitative studies pointed out that dietary and fluid restrictions are disorienting and an intense burden for patients with CKD. Patient-prioritized education strategies, harnessing patients' motivation to stay well for a transplant or to avoid dialysis, and viewing adaptation to restrictions as a collaborative journey are suggested strategies to help patients to adjust dietary regimens in order to reduce their impact on quality of life.

Despite the importance of dietary management to patients with chronic kidney disease, there is a critical evidence gap for people with chronic kidney disease, such that it is currently not possible to determine the long-term effects of dietary strategies on mortality, cardiovascular events, and progression to end-stage kidney disease. Information is particularly sparse for patient adherence, those treated with dialysis or kidney transplantation, and dietary strategies such as a Mediterranean approach, low fat consumption, or personalized nutritional education or counselling.

We expect that the results of the DIET-HD study will inform large pragmatic trials of nutrition or dietary interventions in the setting of advanced kidney disease.

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Presentations at scientific meetings

World Congress of Nephrology (WCN), Cape Town, March 13-17, 2015

- Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: A network meta-analysis. Palmer S, Navarese E, Craig J, Tonelli M, Salanti G, Wiebe N, **Ruospo M**, Wheeler D, Strippoli GFM.
- Association of drug effects on biochemical endpoints (serum parathyroid hormone, phosphorus, and calcium) with all-cause and cardiovascular mortality in chronic kidney disease trials: A meta-analysis. Palmer S, Teixeira-Pinto A, Saglimbene V, Craig J, Macaskill P, Tonelli M, De Berardis G, **Ruospo M**, Strippoli GFM.
- Comparative effectiveness and safety of phosphate binding agents in adults with chronic kidney disease: A network meta-analysis. Palmer S, Gardner S, Craig J, Tonelli M, Mavridis D, Salanti G, French R, **Ruospo M**, Strippoli GFM.
- No association of periodontitis with all cause and cardiovascular mortality in hemodialysis: A prospective cohort study. Palmer S, **Ruospo M**, Wong G, Craig JC, Petruzzi M, De Benedittis M, Ford P, Johnson D, Tonelli M, Natale P, Saglimbene V, Pellegrini, F, Hegbrant J, Strippoli GFM on behalf of the ORALD Investigators.
- Dental health and mortality in people with end-stage kidney disease treated with hemodialysis: A multinational cohort study. Palmer S, **Ruospo M**, Wong G, Craig JC, Petruzzi M, De Benedittis M, Ford P, Johnson D, Tonelli M, Natale P, Saglimbene V, Pellegrini, F, Hegbrant J, Strippoli GFM on behalf of the ORALD Investigators.
- Depressive symptoms and early all-cause and cardiovascular mortality in hemodialysis patients: A multinational cohort study. Saglimbene V, Palmer S, Scaldapane M, **Ruospo M**, Craig JC, Natale P, Gargano L, Leal M, Bednarek-Skublewska A, Dulawa J, Ecder T, Stroumza P, Murgo AM, Schon S, Wollheim C, Hegbrant J, Strippoli GFM.
- Domains of sexual dysfunction in women with end stage kidney disease treated with hemodialysis: A multinational, cross-sectional study. Saglimbene V, Palmer S, Scaldapane M, **Ruospo M**, Craig JC, Natale P, Gargano L, Leal M, Bednarek-Skublewska A, Dulawa J, Ecder T, Stroumza P, Murgo AM, Schon S, Wollheim C, Hegbrant J, Strippoli GFM.

52nd European Renal Association - European Dialysis and Transplant Association (ERA-EDTA), London, May 28-31, 2015

- Patterns of oral disease in adults with chronic kidney disease treated with long-term haemodialysis: a multinational ecological study. Palmer S, **Ruospo M**, Wong G, Craig JC, Petruzzi M, De Benedittis M, Ford P, Johnson D, Tonelli M, Natale P, Saglimbene V, Pellegrini, F, Hegbrant J, Strippoli GFM on behalf of the ORALD Investigators.
- Periodontitis and early mortality in adults with kidney failure treated with hemodialysis: A multinational observational study. Palmer S, **Ruospo M**, Wong G, Craig JC, Petruzzi M, De Benedittis M, Ford P, Johnson D, Tonelli M, Natale P, Saglimbene V, Pellegrini, F, Hegbrant J, Strippoli GFM on behalf of the ORALD Investigators.
- Pharmacological interventions for depression in adults with end-stage kidney disease. Palmer S, Natale P, **Ruospo M**, Saglimbene V, Rabindranath KS, Craig JC, Strippoli GFM.

- CE-DOSE: effect of erythropoiesis-stimulating agent (ESA) dose on mortality, cardiovascular events and quality of life in end-stage kidney disease. Strippoli GFM, Palmer S, Saglimbene V, **Ruospo M**, on behalf of the CE-DOSE Investigators.
- Depressive symptoms and early all-cause and cardiovascular mortality in hemodialysis patients: A multinational cohort study. Saglimbene V, Palmer S, Scaldapane M, **Ruospo M**, Craig JC, Natale P, Gargano L, Leal M, Bednarek-Skublewska A, Dulawa J, Ecder T, Stroumza P, Murgo AM, Schon S, Wollheim C, Hegbrant J, Strippoli GFM.
- Domains of sexual dysfunction in women with end stage kidney disease treated with hemodialysis: A multinational cross sectional study. Saglimbene V, Natale P, Palmer S, Scaldapane M, **Ruospo M**, Craig JC, Gargano L, Torok M, Celia E, Gelfman R, Bednarek-Skublewska A, Dulawa J, Stroumza P, Leal M, Del Castillo D, Murgo AM, Schon S, Wollheim C, Hegbrant J, Strippoli GFM.

American Society of Nephrology (ASN) Renal Week 2015, San Diego, November 5-8, 2015 (accepted, to be presented)

- Glucose Targets for Preventing Diabetic Kidney Disease and Its Progression: A Meta-Analysis. **Ruospo M**, Saglimbene V, Palmer S, De Cosmo S, Pacilli A, Vecchio M, Craig JC, Strippoli GFM.
- Neurocognitive Functioning and Association with Clinical Outcomes in Adults with End-Stage Kidney Disease: The COGNITIVE-HD Study. Palmer S, **Ruospo M**, Iurillo A, Saglimbene V, Natale P, Barulli MR, Loy CT, van Zwieten A, Wong G, Craig JC, Johnson DW, Tonelli M, Hegbrant J, Wollheim C, Logroscino G, Strippoli GFM on behalf of COGNITIVE-HD study investigators

Publications during the PhD program

- Palmer S, **Ruospo M**, Wong G, Craig JC, Petruzzi M, De Benedittis M, Ford P, Johnson D, Tonelli M, Natale P, Saglimbene V, Pellegrini F, Hegbrant J, Strippoli GFM on behalf of the ORALD Investigators. Patterns of oral disease in adults with chronic kidney disease treated with long-term haemodialysis: a multinational ecological study (submitted to NDT, under recommended revision)
- Palmer S, **Ruospo M**, Iurillo A, Saglimbene V, Natale P, Barulli MR, Loy CT, van Zwieten A, Wong G, Craig JC, Johnson DW, Tonelli M, Hegbrant J, Wollheim C, Logroscino G, Strippoli GFM on behalf of COGNITIVE-HD study investigators. Neurocognitive Functioning and Association with Clinical Outcomes in Adults with End-Stage Kidney Disease: The COGNITIVE-HD Study (submitted to BMJ Open, under recommended revision)
- Vecchio M, Bonerba B, Palmer SC, Craig JC, **Ruospo M**, Samuels JA, Molony DA, Schena FP, Strippoli GF. Immunosuppressive agents for treating IgA nephropathy. *Cochrane Database Syst Rev*. 2015 Aug 3;8:CD003965.
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- Palmer SC, Mavridis D, Navarese E, Craig JC, Tonelli M, Salanti G, Wiebe N, **Ruospo M**, Wheeler DC, Strippoli GF. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. *Lancet*. 2015 May 23;385(9982):2047-56.
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- Kaminski MR, Raspovic A, McMahon LP, Strippoli GF, Palmer SC, **Ruospo M**, Dallimore S, Landorf KB. Risk factors for foot ulceration and lower extremity amputation in adults with end-stage renal disease on dialysis: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2015 May 5.
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J, Wollheim C, Frantzen L, Strippoli GF; DIET-HD Study investigators. Nutrition and dietary intake and their association with mortality and hospitalisation in adults with chronic kidney disease treated with haemodialysis: protocol for DIET-HD, a prospective multinational cohort study. *BMJ Open*. 2015 Mar 20;5(3):e006897.

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Educational activities attended during the PhD program

- Le cellule staminali nel danno renale acuto e nel trapianto di rene, dott. Cantaluppi - Novara, July 28
- Basis of scientific research, Prof. Filigheddu - Novara, June 10
- Ribosomopathies, Prof. Ellis - Novara, May 25
- An Integrated Approach to the Diagnosis and Treatment of Ovarian Cancer, Prof. McDonald - Novara, May 7
- Signal control in iNKT cell development and function, Prof. Zhon - Novara, April 9
- Proof of principle for cell therapy: from autologous transplantation of tissue specific progenitors to gene corrected patient specific injured pluripotent stem cells, Prof. Bosnakovski - Novara, March 11
- Anticancer strategy Targeting cancer cell metabolism in ovarian cancer, Prof. Yong-Sang Song - Novara, January 19
- Targeting the liver to cure myocarditis: a lesson from a model of STAT3-dependent auto-immune myocarditis, Prof. Poli - Novara, January 21