FIRST YEAR REPORT

PHD PROGRAM IN CLINICAL AND EXPERIMENTAL MEDICINE

XXVII CYCLE

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

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Introduction

The current PhD project entitled "Nutrition and dietary intake and their association with mortality and hospitalization in adults with chronic kidney disease treated with hemodialysis" aims to evaluate the association between exposure to different nutrition and dietary patterns and the risk of mortality (all-cause and cause-specific) and hospital admissions (any, and cause-specific) for adults with end stage kidney disease (ESKD) treated with hemodialysis.

The overall project is based on clinical epidemiology methods and includes multiple sub-projects:

1. Three systematic reviews / meta-analyses
    a. Systematic review / meta-analysis of cohort studies evaluating association between nutritional exposures and the outcomes of interest
    b. Systematic review / meta-analysis of randomized trials evaluating the effects of nutritional interventions on the outcomes of interest
    c. Systematic review / meta-analysis and thematic synthesis of qualitative studies to describe patients' perspectives on dietary management in chronic kidney disease
2. A large scale 'ad hoc designed' prospective cohort study assessing the association between nutritional exposures and the outcomes of interest (first study of its kind ever designed and conducted in this specific population setting).

Adults with chronic kidney failure treated with hemodialysis experience high mortality rates. Effective interventions that improve health outcomes for long-term dialysis patients remain unproven and novel and testable determinants of health in dialysis are needed. Nutrition and dietary patterns are potential factors influencing health in other health settings that warrant exploration in multinational studies in men and women treated with dialysis.

In order to evaluate whether significant equipoise exists to perform an 'ad hoc designed' prospective cohort study in this area, prior to design and conduct of such primary study, a comprehensive review and meta-analysis of the scientific literature has been undertaken both for existing cohort studies, existing randomized trials of interventions, and qualitative research studies.

- This will be now followed by the design and conduct of a large multinational, prospective cohort study to describe nutrition and dietary patterns and the association with major health outcomes for adults treated with dialysis patients in several countries to help in the prioritization and design of robust randomized trials of nutritional strategies in this population.

Rationale

Long-term dialysis treatment for end-stage kidney disease is associated with an annual mortality of between 15% and 20%, a proportion in excess of many cancers.[1] Healthcare interventions have not been generally shown to improve clinical outcomes for adults treated with dialysis and additional testable strategies for improving the health outcomes are needed.

Nutritional intake and dietary patterns are potential determinants of health outcomes in dialysis patients. Malnutrition (commonly referred to as protein-energy wasting[2]) frequently occurs in patients treated with long-term dialysis. The accumulation of uremic metabolites, metabolic acidosis, dietary restrictions, inflammation and additional frequent comorbidities, including cardiac dysfunction, can suppress appetite, decrease protein and energy intake, and increase catabolic processes in this population. [3] Malnutrition affects 20 to 70% of dialysis patients and increases with duration of dialysis treatment;[4,5] approximately 5 to 10% of people treated with dialysis experience severe malnutrition.[6]

Premature death in people with end-stage kidney disease is strongly associated with lower body mass, lower serum cholesterol and other markers of impaired nutrition. Several studies have shown a consistent association between low serum albumin, low height-adjusted body weight and malnutrition (assessed by subjective global assessment) and total and cardiovascular-specific mortality in the dialysis population.[7-9] In addition, protein-energy wasting (incorporating both malnutrition and other metabolic derangements in patients with end-stage kidney disease, such as inflammation) is a strong risk factor for premature death.[3] Other dietary and nutrition factors have potential clinical effects in the setting of end-stage kidney disease. The Mediterranean diet specifically characterized by high intake of olive oil fruit, nuts, vegetables and cereals, more moderate fish and poultry intake and lower consumption of dairy foods, red and processed meats and sweets, prevents cardiovascular events.[10] However, data evaluating the association between dietary composition and clinical outcomes in people treated with dialysis are limited and largely derive from small, single-center, retrospective studies.[11-13]

Therefore, a primary study has been designed to assess the short- and long-term health outcomes associated with dietary intake in adults treated with hemodialysis.

Methods

This will be a multinational, prospective, cohort study designed to evaluate the association between nutrition and dietary patterns and health outcomes in at least 6000 adults treated with long-term hemodialysis treatment at clinics within a multinational collaborative dialysis network in Europe and South America (see Figure 1 for flow diagram). The clinics included in this study will be from dialysis communities in which the local investigators have committed to providing high quality data in Argentina, France, Germany, Hungary, Italy, Poland, Portugal, Romania, Spain, Sweden, and Turkey. These countries also show significantly different rates of overall mortality in end stage kidney disease, which could be (research hypothesis) related to differing dietary patterns.

Participants will be eligible for the study if they meet the following inclusion criteria: (1) have end-stage kidney disease; (2) are treated with long-term hemodialysis for at least the previous 90 days; (3) are 18 years or older; (4) their treating team agrees to the patient's involvement in the study; and (5) the participant is willing to provide written and informed consent. Reasons for exclusion will be: (1) significant neurocognitive disability or medical comorbidity that would preclude them from understanding the dietary questionnaire even if assisted; (2) a life expectancy less than 6 months according to their treating physician; (3) planned kidney transplantation within 6 months of baseline, or (4) anticipated recovery of kidney function.
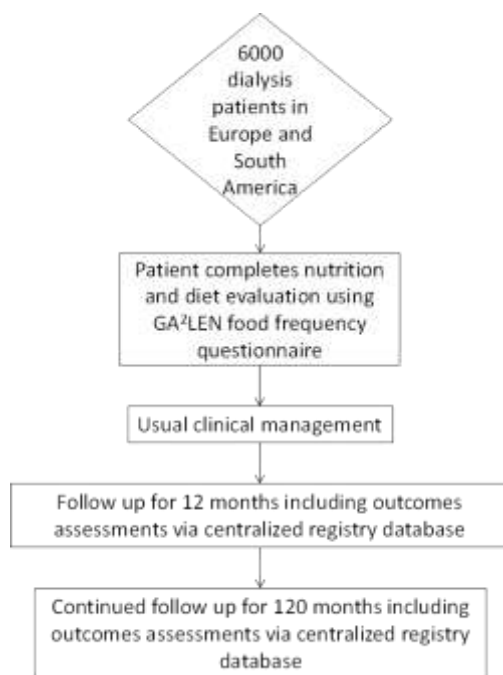
Figure 1 Flow diagram of study activities

Study exposures and outcomes

The primary exposure variables will be dietary consumption of n-3 and n-6 polyunsaturated fatty acids. The primary outcome will be cardiovascular mortality. Secondary exposures will be generalities of nutritional patterns assessed with a specific tool (food frequency questionnaire); key secondary nutritional exposure variables will be dietary total energy, fat (including monounsaturated fatty acids; cholesterol), carbohydrates (including total sugars), protein, fiber, folate, β-carotene, retinol, thiamine, riboflavin, phosphorus, magnesium, calcium, zinc, fluid), and specific food types (fruit, vegetable, nuts, fish, pulses). Secondary outcomes will be all-cause mortality, death due to infection, and all-cause and cause-specific hospitalization.

Assessment of dietary intake (food frequency questionnaire)

Consecutive eligible patients at the selected clinics will be given a food frequency questionnaire to complete during dialysis treatment. The usual dietary intake will be ascertained using the Global Asthma and Allergy Network of Excellence (GA²LEN) food frequency questionnaire (FFQ).[14]
The GA²LEN was initially translated into 12 languages to be used as a single instrument in all the European centers participating in the GA²LEN follow-up survey. The FFQ has been tested in a sub-sample of adults from five European countries and shown to be a reliable instrument to estimate dietary intake in different countries. Nutrient intake will be calculated using the national Food Composition Tables from each participating country. For analyses comprising the entire study sample, a methodological approach will be implemented to describe nutrient composition that includes data from country-specific Food Composition Tables to calculate nutrient estimates of traditional or staple foods of specific countries.
The standard food portion sizes used in the FFQ will be obtained from Food Standard Agency Food Portion Sizes Guidelines in the UK. The frequency of consumption will be converted into grams per day and then into nutrient estimates.
The FFQ is designed to be answered by the participants (self-administered). However, depending on the country and the needs of the research team, as well as of the participants, some centers will prefer to have the FFQ interviewer-administered, when necessary, or have interviewers on hand in the clinics to either

administer the FFQ (for participants who have literacy limitations) or to verify that the FFQ has been answered in full. Participants will complete the dietary questionnaire during a standard hemodialysis treatment. The intake of specific food groups including fruit, vegetable, nuts, fish and pulses will be estimated. Research assistants will be trained using a step-by-step practical overview of the process that is to be followed in administration of the questionnaires, to avoid non-verbal cues indicating surprise or disapproval at the participant's eating patterns.

FFQ responses will be evaluated by members of the research team who are unaware of the participants' identities. All FFQs with missing values will be checked and corrected for any data errors. After data cleaning, if more than 10% of the questionnaire remains incomplete, then the participant will be excluded. In addition, individuals for whom energy intake is in the upper or lower 2% of the intake will then checked for data entry and coding accuracy and errors will be corrected, if identified.

Data from the FFQ will be entered into an electronic database using optical character recognition (OCR) and analyzed using software that facilitates the collection of food recalls in a standardized fashion.

Demographic and clinical data

The collection of demographic, clinical, laboratory and dialysis-related data will be obtained from a patient database within one month of enrolment. Relevant data is obtained from clinical databases linked to the participant via a standardized identification code. Standardized data includes age, gender, race, country of residence, clinic, education, marital and occupational status, family income, financial stress, housing, alcohol intake, smoking history, physical activity, menopausal status, body mass index, protein catabolic rate, cause of kidney disease, existence of cardiovascular comorbidity, diabetes, or hypertension, medication prescription, dialysis prescription, and serum levels of hemoglobin, phosphorus, parathyroid hormone, calcium, ferritin, albumin, and total cholesterol.

After baseline dietary evaluation, clinical outcomes will be measured using linked data at 12 months and thereafter at yearly intervals up to 10 years. Data for total and cause-specific hospitalization and mortality are obtained through data linkages to a centralized database.

Statistical analysis

The initial data analysis will be descriptive. Participants' baseline characteristics (country, clinic, demographics, clinical characteristics, dialysis treatment, etc.) will be described using frequencies for categorical variables and mean, median, range, standard deviation for continuous variables. Characteristics of specific dietary components will also be calculated as mean, median, range, and standard deviation. To evaluate associations between each individual nutrient of interest and the outcomes, multivariate regression analyses using Cox proportional hazards analysis fitted using a shared frailty model to account for clustering within countries will be conducted. Participants will be censored within survival analyses if they emigrate from the dialysis network, are transplanted, or experience recovery of their kidney function. The association between dietary or nutritional exposures (foods, single or grouped or nutritional components) with the outcomes of interest within countries will be explored using logistic or linear regression adjusted by confounding variables) and then combined using meta-analysis. All analyses will be run in STATA (www.stata.com) using existing routines available for the GA^{2}LEN study.

State of the project/Current Activity

The three systematic reviews / meta-analyses are going to be completed or are in the submission phase with peer-reviewed journals. The review of cohort studies is currently at the stage of screening titles and abstracts identified after a systematic search on MEDLINE and EMBASE ; data extraction will follow, and then analysis, once all studies are identified.

The review of randomized trials has already undergone the stage of screening titles and abstracts and 78 eligible randomized trials have been identified. Data extraction is currently ongoing for these 78 studies for the review of RCT, and will be followed by analysis.

The systematic review of qualitative studies has already passed stage of screening of title and abstract to be included and 46 studies (involving 815 patients living in middle- to high-income countries) have been included. Analysis is well advanced, with finding that dietary and fluid restrictions are disorienting and an intense burden for patients with CKD. Many different strategies are suggested to help patients adjust to dietary regimens in order to reduce their impact on quality of life, like patient education. This review is now on peer reviewing for publication on American Journal of Kidney Disease (AJKD).

The protocol of 'ad hoc designed cohort study' has been developed, submitted and approved by all relevant Ethics Committees in Argentina, France, Germany, Hungary, Italy, Poland, Portugal, Romania, Spain, Sweden, and Turkey, and is currently submitted for publication on British Medical Journal (BMJ) Open.

The study enrollment is ongoing among the participating countries, with a conspicuous number of FFQs received (so far n=3580). A database of obtained data is being compiled, awaiting completion of recruitment and in preparation for analysis. The primary analysis will be an ecological study describing dietary patterns in the population, and a subsequent analysis of association with outcomes will be completed at 1 year follow-up.

References

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14. Garcia-Larsen V, Luczynska M, Kowalski ML, et al. Use of a common food frequency questionnaire (FFQ) to assess dietary patterns and their relation to allergy and asthma in Europe: pilot study of the GA2LEN FFQ. *Eur J Clin Nutr.* Jun 2011;65(6):750-756.

Presentations at scientific meetings

51st European Renal Association - European Dialysis and Transplant Association (ERA-EDTA), Amsterdam, May 31- June 3 2014

- Association of periodontitis with all-cause and cardiovascular mortality in adults with end-stage kidney disease: a multinational cohort study
  Suetonia C Palmer, Marinella Ruospo, Germaine Wong, Jonathan C Craig, Massimo Petruzzi, Michele De Benedittis, Pauline Ford, David W Johnson, Marcello Tonelli, Patrizia Natale, Valeria Saglimbene, Fabio Pellegrini, Eduardo Celia, Ruben Gelfman, Miguel R Leal, Marietta Torok, Paul Stroumza, Anna Bednarek-Skublewska, Jan Dulawa, Luc Frantzen, Juan Nin Ferrari, Domingo del Castillo, Amparo G Bernat, Jorgen Hegbrant, Charlotta Wollheim, Letizia Gargano, Casper P. Bots, and Giovanni FM Strippoli on behalf of the ORAL-D Investigators

- Dental health and risk of all-cause and cardiovascular mortality in adults with end-stage kidney disease: a multinational cohort study
  Suetonia C Palmer, Marinella Ruospo, Germaine Wong, Jonathan C Craig, Massimo Petruzzi, Michele De Benedittis, Pauline Ford, David W Johnson, Marcello Tonelli, Patrizia Natale, Valeria Saglimbene, Fabio Pellegrini, Eduardo Celia, Ruben Gelfman, Miguel R Leal, Marietta Torok, Paul Stroumza, Anna Bednarek-Skublewska, Jan Dulawa, Luc Frantzen, Juan Nin Ferrari, Domingo del Castillo, Amparo G Bernat, Jorgen Hegbrant, Charlotta Wollheim, Letizia Gargano, Casper P. Bots, and Giovanni FM Strippoli on behalf of the ORAL-D Investigators

- Interventions for retarding the progression of autosomal dominant polycystic kidney disease (ADPKD): a systematic review and meta-analysis
  Davide Bolignano, Suetonia Palmer, Marinella Ruospo, Carmine Zoccali, Jonathan Craig, Giovanni Strippoli

- Association of surrogate endpoints (serum parathyroid hormone, calcium and phosphorus) with mortality in chronic kidney disease trials: a meta-analysis
  S. Palmer, A. Teixeira-Pinto, V. Saglimbene, M. Ruospo, P. Macaskill, J. Craig, G. Strippoli

Australian and New Zealand Society Of Nephrology (ANZSN) Renal week, Melbourne, August 25-27 2014

- Dental health and risk of all-cause and cardiovascular mortality in adults with end-stage kidney disease: a prospective multinational cohort study
  Suetonia C Palmer, Marinella Ruospo, Germaine Wong, Jonathan C Craig, Massimo Petruzzi, Michele De Benedittis, Pauline Ford, David W Johnson, Marcello Tonelli, Patrizia Natale, Valeria Saglimbene, Fabio Pellegrini, Eduardo Celia, Ruben Gelfman, Miguel R Leal, Marietta Torok, Paul Stroumza, Anna Bednarek-Skublewska, Jan Dulawa, Luc Frantzen, Juan Nin Ferrari, Domingo del Castillo, Amparo G Bernat, Jorgen Hegbrant, Charlotta Wollheim, Letizia Gargano, Casper P. Bots, and Giovanni FM Strippoli

55th Italian Society of Nephrology (SIN), Catania, October 8-11 2014

- Salute dentale e rischio di morte per tutte le cause e per cause cardiovascolari in adulti con insufficienza renale terminale: studio di coorte prospettico multinazionale
  Ruospo M, Palmer S, Saglimbene, Natale P, Sciancalepore M, Gargano L, Petruzzi M, De Benedittis M, Gelfman R, Frazão J, Török M, Duława J, Bednarek A, del Castillo D, Stroumza P, Gelfman, Dambrosio N, Sambati M, Cagnazzo VA, Giannoccaro G, Boccia E, Di Toro Mammarella R, Steri PF,

Flammini A, Murgo M, Pagano S, Montalto G, Salamone B, Rallo D, Fici M, Fichera R, Craig JC, Pellegrini F, Strippoli GFM

- Periodontiti e rischio di morte per tutte le cause e per cause cardiovascolari in adulti con insufficienza renale terminale: studio di coorte prospettico multinazionale
  Ruospo M, Palmer S, Saglimbene, Natale P, Sciancalepore M, Gargano L, Petruzzi M, De Benedittis M, Gelfman R, Frazão J, Török M, Duława J, Bednarek A, del Castillo D, Stroumza P, Gelfman, Dambrosio N, Sambati M, Cagnazzo VA, Giannoccaro G, Boccia E, Di Toro Mammarella R, Steri PF, Flammini A, Murgo M, Pagano S, Montalto G, Salamone B, Rallo D, Fici M, Fichera R, Craig JC, Pellegrini F, Strippoli GFM

- Revisione sistematica e meta-analisi sui trattamenti finalizzati a ritardare la progressione del Rene Policistico Autosomico Dominante (ADPKD)
  Davide Bolignano, Suetonia Palmer, Marinella Ruospo, Carmine Zoccali, Jonathan Craig, Giovanni Strippoli

- Efficacia e sicurezza delle epoetine generiche e biosimilari per il trattamento dell'anemia in pazienti con insufficienza renale cronica: network meta-analisi
  V. Saglimbene, S. Palmer, M. Ruospo, D. Mavridis, G. Salanti, M. Tonelli, J. Craig, G. Strippoli

- Associazione tra endpoints surrogati (paratormone sierico, calcio e fosforo) e mortalità nei trials in pazienti con insufficienza renale cronica: meta-analisi
  V. Saglimbene, S. Palmer, A. Teixeira-Pinto, M. Ruospo, P. Macaskill, J. Craig, G. Strippoli

American Society of Nephrology (ASN) Renal Week 2014 Philadelphia, November 11-16 (accepted, to be presented)

- Comparative Efficacy and Safety of Blood Pressure Lowering Drugs in Diabetic Kidney Disease: A Network Meta-Analysis
  Suetonia Palmer, Dimitris Mavridis, Jonathan C. Craig, Georgia Salanti, Eliano Navarese, Marcello Tonelli, Natasha Wiebe, Marinella Ruospo and Giovanni F.M. Strippoli

- The Views of Patients on Dietary and Fluid Restrictions in CKD: A Thematic Synthesis of Qualitative Studies
  Suetonia Palmer, Camilla Sara Hanson, Jonathan C. Craig, Giovanni F.M. Strippoli, Marinella Ruospo, Katrina L. Campbel, David W. Johnson and Allison Tong

Publications during the PhD program

- Effects of vitamin D on parathyroid hormone and clinical outcomes inperitoneal dialysis: a narrative review.
  Russo R, Ruospo M, Cozzolino M, De Nicola L, Icardi A, Paoletti E, Mazzaferro S. J Nephrol. 2014 Jul 11. [Epub ahead ofprint]

- Dietary and Fluid Restrictions in CKD: A Thematic Synthesis of Patient Views From Qualitative Studies Suetonia C. Palmer, Camilla S. Hanson, Jonathan C. Craig, Giovanni F.M. Strippoli, Marinella Ruospo, Katrina Campbell, David W. Johnson, Allison Tong [accepted, tbp on AJKD]

- 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 Suetonia C Palmer, Marinella Ruospo, Katrina L Campbell, Vanessa Garcia Larsen, Valeria Saglimbene, Patrizia Natale, Letizia Gargano, Jonathan C Craig, David W Johnson, Marcello Tonelli, John Knight, Anna Bednarek-Skublewska, Eduardo Celia, Domingo del Castillo, Jan Dulawa, Tevfik Ecder, Elisabeth Fabricius, João Miguel Frazão, Ruben Gelfman, Susanne Hildegard Hoischen, Staffan Schön, Paul Stroumza, Delia Timofte, Marietta Török, Jörgen Hegbrant, Charlotta Wollheim, Luc Frantzen, and GFM Strippoli*on behalf of DIET-HD Study investigators [submitted to BMJ Open]

- Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: A network meta-analysis
  Suetonia C. Palmer, Dimitris Mavridis, Eliano Navarese, Jonathan C. Craig, Marcello Tonelli, Georgia Salanti, Natasha Wiebe MMath, Marinella Ruospo, David C. Wheeler, Giovanni F.M. Strippoli [submitted to Lancet]

- 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
  Suetonia Palmer, Armando Teixeira-Pinto, Valeria Saglimbene, Jonathan C. Craig, Petra Macaskill, Marcello Tonelli, Giorgia de Berardis, Marinella Ruospo, Giovanni FM Strippoli [submitted to Annals of Internal Medicine]

Educational activities attended during the PhD program

- The Borghese Sessions, Prof. Steven R Ellis - Novara, September 8-22
- Gene Therapy application, Prof. Follenzi – Novara, July 15
- Metformin rewires the signaling network of breast cancer cells and changes their sensitivity to growth and apoptotic stimuli, Prof. Gianni Cesareni – Novara, June 12
- Ribosome alteration in cancer: effect or cause? Prof. Fabrizio Loreni – Novara, June 11