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

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ABSTRACT

Introduction: Adults with end-stage kidney disease (ESKD) treated with haemodialysis experience mortality of between 15% and 20% each year. Effective interventions that improve health outcomes for long-term dialysis patients remain unproven. 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. We report the protocol of the “DIETary intake, death and hospitalisation in adults with end-stage kidney disease treated with HaemoDialysis (DIET-HD) study,” a multinational prospective cohort study. DIET-HD will describe associations of nutrition and dietary patterns with major health outcomes for adults treated with dialysis in several countries.

Methods and analysis: DIET-HD will recruit 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 will take place between March 2014 and June 2015. The study has currently recruited 8000 participants who have completed baseline data. Nutritional intake and dietary patterns will be measured using the Global Allergy and Asthma European Network (GA²LEN) food frequency questionnaire. 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 hospitalisation.

Strengths and limitations of this study

- The study includes a large population and comprehensive validated food frequency questionnaire across a diverse range of countries to investigate nutritional patterns and associated outcomes in adults treated with haemodialysis.
- The accumulated data from this study will inform large pragmatic interventional studies.
- Outcome data will be measured using registry linkages, which increases the feasibility of the large sample size but may lead to some limitations in outcome adjudication.
- The observational study design is hypothesis generating due to potential confounding from measured and unmeasured variables.

Ethics and dissemination: The study is approved by the relevant Ethics Committees in participating countries. All participants will provide written informed consent and be free to withdraw their data at any time. The findings of the study will be disseminated through peer-reviewed journals, conference presentations and to participants via regular newsletters. We expect that the DIET-HD study will inform large pragmatic trials of nutrition or dietary interventions in the setting of advanced kidney disease.

BACKGROUND

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. Healthcare interventions have not been generally shown to improve clinical outcomes for adults treated with dialysis and additional testable strategies for improving mortality and morbidity are needed.

Nutritional intake and dietary patterns are potential determinants of health outcomes in dialysis patients. Dietary restrictions aimed at keeping fluid, serum phosphorus and potassium levels within range often result in limited food choices and unappetising meals. The accumulation of uraemic metabolites, metabolic acidosis, inflammation and additional frequent comorbidities, including cardiac dysfunction, can suppress appetite, decrease protein and energy intake and increase catabolic processes in this population. Malnutrition (commonly referred to as protein-energy wasting) affects 20–70% of dialysis patients and increases with duration of dialysis treatment. Approximately 5–10% of people treated with dialysis experience severe protein-energy malnutrition.

Premature death in people with end-stage kidney disease is strongly associated with low body mass, low 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. In addition, protein-energy wasting (incorporating malnutrition and other metabolic derangements in patients with end-stage kidney disease, such as inflammation) is a strong risk factor for premature death. Data for 5058 adults in the US Renal Data System (USRDS) indicated that dialysis patients who were considered malnourished by their physicians had a 27% greater risk of cardiovascular death. Similarly, a Dialysis Outcomes and Practice Patterns Study (DOPPS) cohort study comprising 7719 adult haemodialysis patients reported that severe malnutrition (evaluated by a modified subjective global assessment, recent weight loss, poor dietary intake, gastrointestinal symptoms and visual assessment of subcutaneous fat) was linked to a 33% higher mortality risk.

Serum n-3 and n-6 polyunsaturated fatty acid profiles are additional potential determinants of cardiovascular outcomes in adults treated with haemodialysis. N-3 polyunsaturated fatty acids such as eicosapentaenoic acid and docosahexaenoic acid may favourably influence oxidative stress, inflammation and thrombosis. Dialysis patients have a decreased ratio of n-3 to n-6 PUFAs, which independently predicts accelerated cardiovascular disease. However, data for dietary polyunsaturated fatty acid intake and associations with mortality in this clinical setting are sparse, although n-3 polyunsaturated fatty acid supplementation may lower mortality and hospital admissions in other settings of chronic disease, including earlier stages of chronic kidney disease.

Other dietary and nutrition factors have potential clinical effects in the setting of end-stage kidney disease. The Mediterranean diet, characterised by high intake of olive oil, fruit, nuts, vegetables and cereals, moderate fish and poultry intake and lower consumption of dairy foods, red and processed meats and sweets, prevents cardiovascular events, although prognostic data in the setting of kidney disease are rare. The average blood levels of biologically important trace elements including selenium and zinc (antioxidant molecules) differ in people with end-stage kidney disease. Lower zinc levels in patients with end-stage kidney disease are associated with increased oxidative stress, lipid peroxidation and inflammation. Since deficiency or excess of trace elements is potentially harmful, the hypothesis that trace element supplementation might influence clinical outcomes is worthy of evaluation. Similarly, vitamin C is an antioxidant with several immune and regulatory functions, and levels are often depleted in patients with end-stage kidney disease by up to 50%. A recent Cochrane review of trials investigating the use of antioxidants for people with chronic kidney disease found that antioxidant therapy does not reduce cardiovascular or all-cause death but, due to the suboptimal quality of existing studies, a clinically important benefit cannot be excluded.

The quality and quantity of food intake may play a role in cardiovascular and infection related complications in the dialysis setting. In addition, dietary patterns may have prognostic implications for patients through mechanisms independent of nutritional status. However, data evaluating the association between diet and clinical outcomes in people treated with dialysis are limited and largely derive from small, single-centre, retrospective studies.

The prospective study described in this protocol will be the first large-scale multinational cohort study to evaluate the association between nutrition and health outcomes in adults with end-stage kidney disease treated with haemodialysis. The study will assess the short-term and long-term morbidity and mortality associated with dietary intake (total energy, fat (including monounsaturated and n-3 and n-6 polyunsaturated fatty acids; cholesterol), carbohydrates (including total sugars), protein, fibre, folate, β-carotene, retinol, thiamine, riboflavin, phosphorus, magnesium, calcium, zinc, fluid, and specific food types (fruit, vegetable, nuts, fish, pulses)) in adults treated with haemodialysis. The study will also evaluate nutrient and non-nutrient antioxidants, specific food groups related to Mediterranean or other regionally distinctive diets and the intake of processed food and fresh fruit and vegetables.

**METHODS AND ANALYSIS**

**Study design summary**

The “DIETary intake, death and hospitalisation in adults with end-stage kidney disease treated with HaemoDialysis (DIET-HD) study” is a multinational prospective cohort study.
study designed to evaluate the association between nutrition and dietary patterns and health outcomes in prevalent adult haemodialysis patients in Europe and South America. The study is currently recruiting.

**Target population, setting and inclusion/exclusion criteria**

The DIET-HD population will recruit approximately 10 000 adults treated with long-term haemodialysis treatment at clinics within a multinational collaborative dialysis network administered by Diaverum, a provider of renal services. Recruitment will take place between March 2014 and June 2015. Overall, 8000 participants have been recruited by February 2015. 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.

Participants will be eligible for DIET-HD if they meet the following inclusion criteria: (1) have end-stage kidney disease; (2) are treated with long-term haemodialysis 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. We will exclude potential participants from DIET-HD if they have: (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 or (3) planned kidney transplantation within 6 months of baseline.

**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 outcomes will be all-cause mortality, death due to infection and all-cause and cause-specific hospitalisation. The key secondary nutritional exposure variables will be dietary total energy, fat (including monounsaturated fatty acids; cholesterol), carbohydrates (including total sugars), protein, fibre, folate, β-carotene, retinol, thiamine, riboflavin, phosphorus, magnesium, calcium, zinc, fluid, and specific food types (fruit, vegetable, nuts, fish, pulses).

**Study procedures**

**Assessment of dietary intake (food frequency questionnaire)**

Consecutive eligible patients in a convenient sample of selected clinics will be given a food frequency questionnaire (FFQ) to complete during dialysis treatment. The usual dietary intake will be ascertained using the Global Allergy and Asthma European Network (GA2LEN) FFQ. To estimate dietary intake in different countries, translations of the FFQ have been carried out following the standard operating procedure of the WHO. Forward translation from English into relevant participant languages was carried out by local research team members. Back translation was then carried out by an independent translator who had not seen the original English version. During this stage, local foods were incorporated into each of the FFQs. GA2LEN has been adapted to mirror the local and staple foods of each participant country in this study without affecting the international comparability structure of the FFQ. The FFQ provides information on the frequency of a wide range of foods, which have been classified using the European Food Group Classification Method designed by Ireland et al. This is an international classification based on the European Food Consumption Survey Method (EFCOSUM) designed to “define a minimum set of dietary components which are relevant determinants of health and to define a method for the monitoring of food consumption in national representative samples of all age-gender categories in Europe in a comparable way.”

**Nutrient estimates**

Nutrient intake will be calculated using national Food Composition Tables from each participating country. For analyses comprising the entire study sample, we will implement the methodological approach used by GA2LEN which employed the British Food Composition Table to describe nutrient composition, including data from country-specific Food Composition Tables, to calculate nutrient estimates of traditional or staple foods of specific countries. Current analyses in the GA2LEN Nutrition study show that the British Food Composition Table is the most comprehensive table in terms of number of nutrient data available. We have access to all the latest data within Food Composition Tables in European countries facilitated by EuroFir (European Food Network of Excellence) which, as GA2LEN, was a European Union funded Network. This is now a non-profit consortium that fosters the advancement in the knowledge of food composition in Europe and other 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 centres 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 haemodialysis treatment.
We will calculate intake of the following macronutrients and micronutrients using estimates of the EuroFir Food Composition Tables: energy (kJ/day), fat (including monounsaturated and polyunsaturated fat; n-3 polyunsaturated fatty acids; n-6 polyunsaturated fatty acids; trans fatty acids; cholesterol), carbohydrate, glycaemic index, total sugar, protein (including sources (animal vs vegetable sources)), fibre, folate, β-carotene, retinol, thiamine, riboflavin, phosphorus, magnesium, calcium and zinc. We will also estimate the intake of specific food groups including fruit, vegetable, nuts, fish and pulses. 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. The protocol emphasises the need for assistants 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 be 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 and analysed using software that facilitates the collection of food recalls in a standardised fashion.32

Demographic and clinical data
Demographic, clinical, laboratory and dialysis-related data will be obtained from a patient database within 1 month of enrolment. Relevant data will be obtained from clinical databases linked to the participant via a standardised identification code. Standardised data will include age, gender, race, country of residence, clinic attended, 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, time on dialysis, and serum levels of haemoglobin, phosphorus, parathyroid hormone, calcium, ferritin, albumin and total cholesterol.

Outcomes
Measurement time points
After baseline dietary evaluation, we will measure clinical outcomes using linked data at 12 months and thereafter at yearly intervals up to 10 years. Data for total and cause-specific hospitalisation and mortality are obtained through data linkages to a centralised database administered by Diaverum. In this database, every change in participant status is updated by the managing clinician on a monthly basis, including change in survival status or hospitalisation, with causes of death or hospital admission.

Outcomes
The primary study outcome will be cardiovascular mortality. Secondary outcomes will be all-cause mortality, infection-related mortality and all-cause and cardiovascular-related hospitalisation. A cardiovascular-related death or hospitalisation will include death or hospitalisation attributed to acute myocardial infarction, pericarditis, atherosclerotic heart disease, cardionmyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, pulmonary oedema, congestive cardiac failure, cerebrovascular accident including intracranial haemorrhage, ischaemic brain damage including anoxic encephalopathy, or mesenteric infarction or ischaemic bowel. An infection-related death will include sepsicaemia due to internal vascular access, central nervous system infection (brain abscess, meningitis, encephalitis), sepsicaemia due to peripheral vascular disease or gangrene, cardiac infection (endocarditis), pulmonary infection (pneumonia or influenza), abdominal infection (peritonitis, perforated bowel, diverticular disease, gallbladder infection) or genitourinary infection (urinary tract infection, pyelonephritis, renal abscess).

Sample size
The sample size for this study will be approximately 10 000 participants. On the basis of previous validation data for the FFQ28 and our experience during recruitment of 8000 participants, we anticipate that approximately 10% of participants will not provide a completed survey and that 5% of the patient population will leave the network for reasons other than mortality, transplantation or withdrawal from dialysis, leaving a potential analyzable population of 8500. On the basis of an anticipated mortality of 14–15% each year and a cardiovascular mortality rate of 6% per annum, we anticipate that recruitment and evaluation of at least 6000 participants will allow a study with a type 1 error α=0.05 and power of 80% to detect an HR of at least 1.10 for each 1 SD decrease in n-3 polyunsaturated fatty acid intake. When adjusting for the complete set of potentially confounding variables, assuming an R²=0.30, the same sample size will detect an HR of at least 1.12 for each SD decrease in the primary exposure.

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 and SD for continuous variables. Characteristics of specific dietary components will also be calculated as mean, median, range and SD. To evaluate associations between each individual nutrient of interest and the outcomes, we will conduct multivariate regression analyses using Cox proportional hazards.
analysis fitted using a shared frailty model to account for clustering within countries. Participants will be censored within survival analyses if they emigrate from the dialysis network, are transplanted or experience recovery of their kidney function.

Given the large number of nutritional exposures, we will control for potential false discoveries using the Simes’ procedure allowing for a 5% false discovery rate while controlling for potential confounding variables. Similarly, we will explore associations between groups of foods (eg, vegetables or fruits) and nutrients using similar techniques. We will then explore the association between dietary or nutritional exposures (foods, single or grouped or nutritional components) and the outcomes of interest within countries using logistic or linear regression adjusted by confounding variables and then combine data from all countries using meta-analysis. We will consider the gross national product and income equality in analysis. We will also calculate weighting of the sample to make it representative of the source population within each country. We will conduct analyses in STATA (http://www.stata.com) using existing routines available for the GA2LEN study.

ETHICS AND DISSEMINATION

Ethical approval
The study is based on informed written consent, and participants can withdraw from the study at any point in time. The study is non-invasive and imposes no significant risks to participants. Data material will be managed confidentially and anonymously.

Dissemination
The findings of the study will be disseminated through peer-reviewed journals, national and international conference presentations and to the participants through communication within the dialysis network in which this study is conducted via a regular newsletter.

DISCUSSION

We have designed DIET-HD to evaluate whether dietary patterns and nutritional intake are associated with mortality and hospitalisation in adults with end-stage kidney disease treated with haemodialysis. This study will generate potential testable diet and nutrition targets for evaluation in pragmatic multicentre trials and meta-analyses.

Our study design, while incorporating data from several countries and using validated and robust multinational dietary analysis tools from the GA2LEN network collaboration, has potential limitations. To ensure sufficient data from a broad range of participants, we have used a convenient sample of clinics within the participating countries to maximise recruitment without stratification by key clinic demographic or clinical characteristics. This may limit our ability to provide data representative of source populations but will still be the largest in-depth nutritional survey of adults treated with haemodialysis to date. In addition, as our patient population is >95% European, we will lack generalisable data for non-European ethnicities. Mortality and other endpoint data will be obtained using linkages to a data registry. There will not be adjudication of clinical end points by personnel blinded to exposure and there will be some misclassification of clinical outcomes.

Effective strategies to improve health outcomes in this population are scarce and urgently needed. 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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Contributors SCP conceived and designed this study and drafted the manuscript. KLC contributed to the conception and design of the study and to the drafting of the manuscript. VGL contributed to the conception and design of the study and to the drafting of the manuscript and the GA²LEN material including the translated food frequency questionnaires and statistical analysis models. MR, VS, PN, LG, JCC, DJW, MT, AB-S, EC, Ddc, JD, TE, EF, JMF, RG, SHH, SS, PS, DT, MT, JH, CW, LF and JK contributed to the design of the study and reviewed the manuscript. GFMS conceived and designed this study and assisted with the drafting of the manuscript.

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Competing interests MR, VS, PN, LG, AB-S, EC, Ddc, JD, TE, EF, JMF, RG, SHH, SS, PS, DT, MT, JH, CW, LF and GMFS are employees of Diaverum; no other relationships or activities that could appear to have influenced the submitted work. SCP is a 2014 New Zealand Rutherford Discovery Fellow. JK is employed by the George Institute for Global Health. KLC is funded by fellowships from the Lions Senior Medical Foundation and Queensland Government.

Ethics approval Ethics approval was received from the following human research ethics committees for the DIET-HD study: for France—Comité de Protection des Personne Sud-Méditerranée II (committee reference 214 S01; France)—Regionala Etikprövningsnämnden, Lund (reference number 2013-A01669-36); for Germany—Ethikkommission Landesärztekammer Brandenburg (reference number AS 46 (bB)2014); for Hungary—Égyesüligyű Tudományos Tanács Tudományos és KutatástechnikaiBizottság (ETT TUKEB) (reference number 5458-2013/EKU (43/2014)); for Italy—Azienda Sanitaria Locale Br Comitato Indipendente di Etica Medica. Poland—Komisja Bioetyczna, Śląskiego Uniwersytetu Medycznego w Katowicach (reference number KNW/0022/KB/236/13); for Portugal—Comissão de Ética da DIA/VERUM Romania; Romania—Ministerul Sănătăţii Comisia Naţională de Etică pentru Studiul Clinici al Medicamentelor; Spain—Comité Ético de Investigación Clínica del Hospital Clinic de Barcelona (HCb/2014/ 0309); for Sweden—Regionalt Etikprövningsnämnden, Lund (reference number Dnr 2013/882); Turkey—İstanbul Üniversitesi İstanbul Tip Fakültesi Klinik Araştırmaları Elık Kılulaştı (2014/543). Ethics approval was not required for this type of study in Argentina.

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