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Association between nutritional, inflammatory and oxidative status (NIOS) and risk of adverse outcomes in patients on haemodialysis (HD): the NIOS-HD prospective cohort study protocol

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ABSTRACT

Introduction The mortality of patients on chronic haemodialysis is 10–30 times greater than that of the general population and over 60% of these individuals die within the first 5 years of beginning haemodialysis. Although causes for excessive mortality in haemodialysis patients are not clearly defined, it seems that nutrition, inflammation and oxidative stress play key roles in this regard. Until now, no cohort study has focused on the association between nutritional, inflammatory or oxidative status and risk of complications and adverse outcomes in Iranian haemodialysis patients. Therefore, we sought to fill this gap and designed the Nutritional, Inflammatory, and Oxidative Status in Hemodialysis (NIOS-HD) prospective cohort study to determine the association of dietary factors, malnutrition, anthropometric indices, body composition, inflammation and oxidative stress with quality of life, dialysis access infections, hospitalisation, potential years of life lost and mortality in adults on maintenance haemodialysis in Isfahan, Iran.

Methods and analysis The sample size of this cohort was estimated to be 300 participants. At baseline, demographic, medical and dialysis-related data of eligible patients will be recorded. In addition, participants will undergo anthropometric measurements, malnutrition assessment and body composition analysis. Also, their dietary intake and quality of life will be evaluated through interviewer-administered questionnaires. Moreover, their fasting blood samples will be collected and stored for biochemical assays including transthyretin, albumin, serum amyloid A, pentraxin-3, trimethylamine N-oxide, myeloperoxidase, paraoxonase-1 and superoxide dismutase. After baseline evaluation, patients will be followed up to 3 years to update exposure information (except biochemical assays) and measure adverse outcomes. Finally, collected data will be analysed using descriptive and inferential statistics.

Ethics and dissemination The NIOS-HD is in agreement with the Declaration of Helsinki and has been approved by the Ethics Committee of Isfahan University of Medical Sciences (reference number: IR.MUI.RESEARCH.REC.1399.605). Findings of this study will be published in academic journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Nutritional, Inflammatory, and Oxidative Status in Hemodialysis (NIOS-HD) is a multicentre prospective cohort study which is the gold standard of observational research.
⇒ Many exposures and outcomes of patients on haemodialysis as well as their combined associations will be covered in this study.
⇒ In the NIOS-HD, several quality control measures will be undertaken before, during and after data collection to ensure validity and reliability of data.
⇒ The data of common confounding factors will be collected and statistically controlled in this study.
⇒ Due to financial constraints, biochemical assays will only be performed at baseline.

INTRODUCTION

Chronic kidney disease (CKD) is described as the presence of kidney damage or glomerular filtration rate under 60 mL/min/1.73 m^2 for 90 days or longer, irrespective of its cause. According to the Global Burden of Disease Study, CKD has shifted from the 29th leading cause of mortality in 1990 to the 18th leading cause of mortality in 2019 and represented the fast growing condition worldwide.[1] More than 600 million people are currently estimated to have CKD, of whom >80% are believed to be living in low and middle-income countries such as Iran. Unfortunately, recent epidemiological studies have reported a higher prevalence of CKD in Iran compared with global average (15.4% vs 13.4%).[2]

Haemodialysis is a treatment for patients suffering from the final stages of CKD. There are currently about 2 million individuals on haemodialysis worldwide. This number continues to rise with ageing.[3] Unfortunately, despite technical advances in

haemodialysis, patients on maintenance haemodialysis experience a lower quality of life, increased morbidity (especially infections related to dialysis access), more hospitalisation episodes and higher mortality rate compared with the non-dialysis population.[4 5] Indeed, the mortality of haemodialysis patients is 10–30 times greater than that of the general population and over 60% of these individuals die within the first 5 years of starting haemodialysis.[6 7] These statistics emphasise the need for additional attention of policy makers and researchers to this issue.

Main causes for excessive mortality in patients on maintenance haemodialysis are not clearly determined. Nevertheless, it appears that nutrition, inflammation and oxidative stress play key roles in this regard.[8 9] For instance, a higher consumption of fruits and vegetables has been found to be associated with lower all-cause and non-cardiovascular mortality in adult patients on haemodialysis.[10] In addition, a diet with low acid load has been shown to be beneficial for patients with CKD[11] but a U-shaped association has been observed between dietary acid load and risk of mortality in a general adult population.[12] Furthermore, it has been indicated that obese and overweight haemodialysis patients are at lower risk for death than haemodialysis patients with non-elevated body mass index (BMI).[13] This result is also in contrast to the findings obtained from general population studies.[14] Besides, lower body fat percentage has been associated with greater mortality in haemodialysis patients, whereas lower quality of life has been reported by haemodialysis individuals with higher body fat percentage.[15] Moreover, it has been revealed that pentraxin-3 and serum amyloid A are novel predictors of mortality in haemodialysis.[16 17] Interestingly, both of these biomarkers seem to be better indicators of inflammatory state in haemodialysis patients than C-reactive protein or even high-sensitivity C-reactive protein.[17–19] Also, trimethylamine N-oxide, an inflammatory metabolite derived from gut microbiota, has shown prognostic implications in maintenance haemodialysis.[20 21] Furthermore, low levels of paraoxonase-1 and superoxide dismutase as well as high levels of myeloperoxidase have been associated with increased risk of cardiovascular events in patients on dialysis.[22–24]

Although nutrition, inflammation and oxidative stress appear to be crucial targets in the medical management of haemodialysis patients, few cohort studies have evaluated their roles in quality and quantity of life in these individuals.[25–27] In particular, no cohort study has focused on this issue in Iran. Therefore, we aimed to fill the gap and designed a prospective cohort study to determine the association of dietary factors, malnutrition, anthropometric indices, body composition, inflammation and oxidative stress with quality of life, dialysis access infections, hospitalisation, potential years of life lost and mortality in adult patients on maintenance haemodialysis. This study was called the Nutritional, Inflammatory, and Oxidative Status in Hemodialysis (NIOS-HD).

METHODS AND ANALYSIS

Specific study aims

The specific objectives of the NIOS-HD are as follows:

1. To determine the association between dietary factors (dietary acid load, diet quality, consumption of specific foods, food groups, and nutritional supplements, phosphorus-to-protein ratio, and intake of fluids, energy, and macronutrients and micronutrients) and risk of adverse outcomes (low quality of life, dialysis access infections, hospitalisation, potential years of life lost and all-cause and cause-specific mortality) in patients on haemodialysis.
2. To determine the association between malnutrition (albumin, transthyretin, creatinine index, Subjective Global Assessment-Dialysis Malnutrition Score (SGA-DMS), hand grip strength and normalised protein catabolic rate) and risk of adverse outcomes (low quality of life, dialysis access infections, hospitalisation, potential years of life lost and all-cause and cause-specific mortality) in patients on haemodialysis.
3. To determine the association between anthropometric indices (BMI, mid-upper arm circumference, waist circumference, waist-to-height ratio, hip circumference and waist-to-hip ratio) and risk of adverse outcomes (low quality of life, dialysis access infections, hospitalisation, potential years of life lost and all-cause and cause-specific mortality) in patients on haemodialysis.
4. To determine the association between body composition (fat and muscle mass) and risk of adverse outcomes (low quality of life, dialysis access infections, hospitalisation, potential years of life lost and all-cause and cause-specific mortality) in patients on haemodialysis.
5. To determine the association between inflammation (serum amyloid A, pentraxin-3 and trimethylamine N-oxide) and risk of adverse outcomes (low quality of life, dialysis access infections, hospitalisation, potential years of life lost and all-cause and cause-specific mortality) in patients on haemodialysis.
6. To determine the association between oxidative stress (myeloperoxidase, paraoxonase-1 and superoxide dismutase) and risk of adverse outcomes (low quality of life, dialysis access infections, hospitalisation, potential years of life lost and all-cause and cause-specific mortality) in patients on haemodialysis.

Study design and setting

The NIOS-HD is a multicentre prospective cohort study in adult patients on maintenance haemodialysis. Participants will be recruited from the haemodialysis centres of Farabi Hospital, Amin Hospital, Shariati Hospital, Zahraye Marzieh Hospital and Hojjatieh Hospital in Isfahan, Iran. This study started on 10 April 2022, and participant recruitment is ongoing.

Patient and public involvement

During the feasibility phase of the NIOS-HD, the selection of exposures and outcomes was discussed through semi-structured interviews with 30 patients on maintenance

haemodialysis, and their viewpoints and feedback were obtained. Then, research aims and plans were revised to align with patients' prime concerns. Finally, the results of this study will be summarised and disseminated to haemodialysis patients through brochures. They will also be requested to share the findings with their families and friends.

Sample size and sampling method

The sample size calculation was done based on all-cause mortality as the primary endpoint using free power and sample size calculator (available at: http://powerandsamplesize.com). Assuming that 12% of patients can meet the primary endpoint,[27 28] 267 haemodialysis patients need to be recruited to yield 90% power to detect a significant association for a relative risk of 3.14 for transthyretin.[28] Based on consultation with haemodialysis research experts in Iran, the attrition rate is anticipated to be about 10%. Therefore, the recruitment target of the NIOS-HD is 300 patients. The purposive convenience sampling method will be used for the selection of participants.

Inclusion and exclusion criteria

Individuals will be included in the NIOS-HD if (1) they have been undergoing maintenance haemodialysis for at least the previous 90 days, (2) they are 18 years or older, (3) they have no residual renal function, and (4) they have the ability and willingness to participate in the study. Haemodialysis patients will be not included in the NIOS-HD if (1) they were hospitalised or infected within the previous month, (2) they have an anticipated life expectancy of less than 6 months according to their physician, (3) they are scheduled to have kidney transplantation within 6 months of baseline, or (4) they are participating in clinical studies that may impact the outcomes of interest. Subjects will be excluded if they lose their ability and willingness to participate in the study.

Study description

The research team will visit the mentioned haemodialysis centres, screen eligibility criteria of patients attending there, inform them of the importance, objectives, methods and timeline (table 1) of the NIOS-HD and invite them to participate in it. Oral and written informed consent will be obtained from participants before the enrolment. At baseline, demographic, medical and dialysis-related data of each eligible patient will be recorded. Also, participants will undergo malnutrition assessment, anthropometric measurements and body composition analysis. In addition, their dietary intake and quality of life will be investigated through interviewer-administered questionnaires during haemodialysis sessions. Furthermore, their fasting blood samples will be collected and stored for biochemical assays. After baseline assessment, all patients will be followed up to 3 years to measure adverse outcomes. These outcomes include low quality of life, dialysis access infections, hospitalisation, potential years of life lost and all-cause and cause-specific mortality. In this cohort, quality of life will be assessed at yearly intervals and compared with baseline. Other outcomes will be assessed at 3-month intervals through medical records and caregiver or patient reports. During the follow-up period, all exposure data except biochemical assays will also be updated at yearly intervals. Biochemical assays will be only performed at baseline due to their expensive cost. Data collection tools and methods are detailed below.

Demographic, medical and dialysis-related data

Demographic, medical and dialysis-related data will be obtained from medical records and caregiver or patient reports through face-to-face interviews. These data will include gender, age, educational level, place of residence, employment status, marital status, family income, alcohol and drug intake, smoking history, menopausal status, cause of renal failure, existence of comorbidities such as

Table 1 The timeline of assessments in the NIOS-HD prospective cohort study

	Timepoint (months)												
Assessments	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**
Demographic, medical and dialysis-related data	X				X				X				X
Malnutrition assessment	X				X				X				X
Anthropometric measurements	X				X				X				X
Body composition analysis	X				X				X				X
Dietary intake	X				X				X				X
Biochemical assays	X												
Quality of life	X				X				X				X
Dialysis access infections		X	X	X	X	X	X	X	X	X	X	X	X
Hospitalisation		X	X	X	X	X	X	X	X	X	X	X	X
Potential years of life lost		X	X	X	X	X	X	X	X	X	X	X	X
All-cause and cause-specific mortality		X	X	X	X	X	X	X	X	X	X	X	X

NIOS-HD, Nutritional, Inflammatory, and Oxidative Status in Hemodialysis.

cardiovascular diseases, diabetes, dyslipidaemia and hypertension, medication prescription, haemodialysis prescription, time on haemodialysis and recent (within 3 months) laboratory tests including blood urea nitrogen, creatinine, 24-hour urine volume, fasting blood sugar, lipid profile, phosphorus, potassium and complete blood count.

Malnutrition assessment

SGA-DMS, hand grip strength, creatinine index and normalised protein catabolic rate will be used to assess malnutrition. The reliability and validity of these tools have been previously tested and found to be acceptable in haemodialysis patients.[29–31] SGA-DMS consists of seven features: dietary intake, dry weight change, signs of muscle wasting, subcutaneous fat, functional capacity, gastrointestinal symptoms and comorbidities. Each component has a score from 1 (ie, normal) to 5 (ie, very severe).[32] Hand grip strength is a measure of the maximum static force that the left or right hand is able to compress using a dynamometer.[33] Creatinine index is known as normalised creatinine production rate, which is equivalent to the sum of creatinine excretion rate and metabolic degradation rate in the steady state.[34] Normalised protein catabolic rate shows the daily dietary protein intake in stable haemodialysis patients and is calculated from measuring predialysis and postdialysis blood urea nitrogen.[35]

Anthropometric measurements

Height will be measured with 0.1 cm precision by means of a stadiometer while patients will be standing upright against a stadiometer in bare feet. Dry weight will be measured to the nearest 0.1 kg using a calibrated digital medical scale while patients will be wearing light clothing without shoes. BMI will be calculated by dividing dry weight in kilograms by height in metre squared. Waist circumference will be measured in the standing position at the level of the umbilicus to the nearest 0.1 cm using a constant tension tape. Hip circumference will also be measured with the same tape to the nearest 0.1 cm at the maximum circumference over the buttocks. Waist-to-height ratio will be calculated as waist circumference in centimetres divided by height in centimetres. Waist-to-hip ratio will be calculated as waist circumference divided by hip circumference. Mid-upper arm circumference will be measured at the midpoint between the inferior border of the acromion process and the tip of the olecranon process to the nearest 0.1 cm on the bare left arm using a flexible non-stretchable tape measure.

Body composition analysis

Body composition including fat mass and muscle mass will be measured using bioelectrical impedance analysis. This measurement will be performed in the morning, in a fasting state and after emptying the bladder.[36] Bioelectrical impedance analysis has been found to be a reliable and valid instrument for body composition assessment in Iranian haemodialysis patients.[37]

Dietary intake

A semiquantitative Food Frequency Questionnaire that contained 168 food items will be used to assess the consumption of specific foods and food groups. The reliability and validity of this questionnaire have been previously evaluated and found to be acceptable in Iranians.[38] Energy and macronutrient and micronutrient intake and dietary phosphorus-to-protein ratio will be calculated using Nutritionist IV software. Diet quality will be assessed according to energy density and nutrient adequacy ratios.[39] To calculate energy density, daily energy intake will be divided by the total weight of consumed foods (excluding beverages).[40] Nutrient adequacy ratio will be calculated by dividing the daily intake of each nutrient by its dietary recommended intake.[41] Dietary acid load will be calculated using the following formula: Dietary acid load (mEq/day)=potential renal acid load+(body surface area [m^2]×41 [mEq/day]/1.73 m^2).[42] Potential renal acid load will be determined using dietary intakes of five key nutrients according to the next formula: Potential renal acid load (mEq/day)=(0.49×protein [g/day])+(0.037×phosphorus [mg/day])−(0.021×potassium [mg/day])−(0.026×magnesium [mg/day])−(0.013×calcium [mg/day]).[43] Body surface area will be calculated by the Du Bois formula using the measured height and dry weight.[44] Fluid intake will be assessed through questions on the consumption of water, yoghurt drink (doogh), soft drinks and other beverages during both dialysis and non-dialysis days. Supplement intake of vitamins, minerals and herbal products will be assessed through questions on the type and dosage of supplementation.

Biochemical assays

At baseline, antecubital venous fasting blood samples will be taken from participants in the predialysis period at the end of the week in the laboratories of Farabi Hospital, Amin Hospital, Shariati Hospital, Zahraye Marzieh Hospital and Hojjatieh Hospital. Serums will be immediately separated, frozen and kept at −80°C in the above laboratories. It is worth mentioning that each serum will be divided into four samples. As soon as possible, these samples will be transferred to the Biobank Center of the School of Health by cool box and stored at −80°C until the time of assay. Subsequently, serum levels of transthyretin, albumin, serum amyloid A, pentraxin-3, trimethylamine N-oxide, myeloperoxidase, paraoxonase-1 and superoxide dismutase will be measured using appropriate commercial kits according to the manufacturer's instructions.

Quality of life

Kidney Disease Quality of Life-Short Form, Version 1.3 (KDQOL-SF 1/3) will be used to evaluate the quality of life in haemodialysis patients. KDQOL-SF 1/3 is a questionnaire developed for patients suffering from kidney disease and those on dialysis treatment. It includes 43 kidney disease-targeted items, such as the impacts of the disease on daily living activities, social interaction and working status, and 36 items that yield a measure of mental

and physical health, and one general health rating item that ranges from 0 (the worst health status) to 10 (the best health status).[45] The reliability and validity of this questionnaire have been previously assessed and found to be acceptable in Iranian patients on haemodialysis.[46]

Main study outcomes

The primary outcome of the NIOS-HD is all-cause mortality. The secondary outcomes of the NIOS-HD are low quality of life, dialysis access infections, hospitalisation, potential years of life lost and cause-specific mortality. In this cohort study, all outcomes of interest will be investigated for 3 years from the beginning of the study. As mentioned earlier, quality of life will be evaluated using the KDQOL-SF 1/3 questionnaire at yearly intervals and compared with baseline values. Causes of dialysis access infections, hospital admissions and deaths will be collected through medical records as well as caregiver or patient reports at three monthly intervals. Potential years of life lost are an indicator of the average number of years a person would have lived if she or he had not died prematurely.[47] In this study, it will be calculated for each patient who will die before age 75 using the formula described by the Association of Public Health Epidemiologists in Ontario.[48]

Quality assurance procedures

In cohort studies, the quality of data collection is very important. Therefore, several quality control measures will be undertaken before, during and after data collection to ensure validity and reliability of data. Before data collection, collectors will follow extensive training on study procedures, minimisation of interviewer bias and standardisation of data collection. During data collection, identical data collection instruments will be used in all centres. Besides, these instruments will be regularly calibrated. After data collection, quality checks will be routinely performed for entered data by trained research assistants and one statistician to find outliers and missing values.

Statistical analysis

Qualitative variables will be expressed as number (percentage). Quantitative variables will be reported as mean±SD or median (IQR), as appropriate. The Kolmogorov-Smirnov test will be applied to determine the normal distribution of variables. Comparisons between groups will be performed using independent samples t-test, analysis of variance (ANOVA), or non-parametric equivalents and also χ^2 test, as appropriate. The repeated measurements of variables that will be obtained during different periods will be analysed using repeated measures ANOVA and mixed models. Logistic regression as well as Cox proportional hazards models will be used to investigate the association between different predictors and adverse outcomes. HRs and 95% CIs will also be reported. The Kaplan-Meier curves and log-rank test will be used to elucidate the survival probability by different predictors. In the above analyses, potential confounding factors will be statistically controlled. Statistical significance will be defined as $p<0.05$. All statistical analyses will be performed using SPSS (version 21) and Stata software.

ETHICS AND DISSEMINATION

The NIOS-HD study is in agreement with the Declaration of Helsinki and has been approved by the Ethics Committee of Isfahan University of Medical Sciences (reference number: IR.MUI.RESEARCH.REC.1399.605). Findings of this study will be published in academic journals. The following ethical considerations will be taken into account in the study:

1. Participation in this study will be optional, and participants will be given the opportunity to leave the study at any time and for any reason.
2. The necessary information about this study including its objectives, methods and possible risks will be provided to participants in both oral and written forms.
3. Before the enrolment, written informed consent will be obtained from participants.
4. Standard procedures will be used to evaluate dietary intakes, malnutrition, anthropometric indices, body composition indicators, biological markers and complications and outcomes of patients on maintenance haemodialysis.
5. All involved personnel will be adequately trained to keep the personal information of each participant strictly confidential.
6. Collected data will be stored in a secure and lock-protected location until data entry.
7. During the data entry phase, the collected data will be coded with serial numbers instead of names to maintain the anonymity of participants.

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Contributors MHR conceptualised the study. SF and MHR designed the study and wrote its protocol. GA, MB, MM, FM, ST and ZH critically revised the study design and its protocol. All authors read and approved the final manuscript.

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