Chapter 4 |

Associations between a family history of diabetes mellitus, cardiovascular disease, or kidney disease and disease progression in pre-dialysis patients

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Submitted

Abstract

Background

This study compared the prevalence of a first-degree family history (FH) of diabetes mellitus (DM), cardiovascular disease (CVD), and kidney disease (KD) in pre-dialysis patients and a random sample of the general population. Furthermore, the associations between FH and the decline of kidney function and mortality in the first year of pre-dialysis care were assessed.

Methods

This study included 439 incident pre-dialysis patients (60±15 years; 55% male; $eGFR_{MDRD}$, 13.2±6.3 mL/min/1.73m^2). A random sample of the general population (PREVEND study, N=3,236; 49±12 years; 45% male) was used as reference. Mortality risks were estimated using Cox regression analysis (adjusted for sex and race, HR_{adj}). Differences in the slope of decline of kidney function ($eGFR_{MDRD}$) were estimated using linear mixed effect models, adjusted for sex and race.

Results

The prevalences of FH_{DM}, FH_{CVD}, and FH_{KD} were 18% *vs.* 16%, 29% *vs*. 16%, and 26% *vs*. 3% in first-degree relatives of pre-dialysis patients and the general population, respectively. The sex and race adjusted mortality risk for patients with FH_{DM} (n=103) was HR 2.9 (95% CI 1.3 to 6.7) relative to patients without FH_{DM}. For FH_{CVD} (n=134) HR was 2.4 (95% CI 1.1 to 5.4) relative to patients without FH_{CVD} and in patients with FH_{KD} (n=108) HR was 0.2 (95% CI 0.1 to 1.0) relative to patients without FH_{KD}. The difference in decline of kidney function between patients with and without FH_{DM} was -1.17 mL/min/1.73m^2/year (95% CI -2.59 to 0.25), -0.54 (95% CI -1.91 to 0.83) for FH_{KD}, and 0.77 (95% CI -0.55 to 2.09) for FH_{CVD}.

Conclusion

Patients with FH_{DM} and FH_{CVD} are at increased mortality risk in the first year of pre-dialysis care. Therefore, obtaining information about FH may help to identify pre-dialysis patients at increased risk of adverse outcome.

Introduction

People with a high risk of diabetes mellitus and hypertension have more frequently proteinuria and a lower kidney function.[1] Screening specific high-risk groups of people with diabetes mellitus, hypertension or age 55 years and above is found to be the most effective strategy to detect chronic kidney disease (CKD).[2] Therefore, it can be hypothesized that the presence of specific comorbidities influences the prevalence and possibly the progression of CKD.

An important risk factor for CKD is familial clustering of this disease.[3-6] The prevalence of CKD, a history of hypertension, and diabetes mellitus is higher in first-degree relatives of CKD patients as compared to first-degree relatives of the general population.[7] Surprisingly, first-degree relatives of CKD patients who were under treatment by a nephrologist showed a very low awareness of kidney disease compared to the awareness of other illnesses such as hypertension or diabetes mellitus.[8]

Based on the observation that individuals with familial focal and segmental sclerosis have a poorer prognosis as compared to sporadic cases, it has been hypothesized that the clinical course of patients with sporadic end-stage renal disease (ESRD) in general is better as compared to the clinical course in patients with familial clustering of ESRD. To study this, survival of dialysis patients with familial clustering of ESRD was compared with survival of dialysis patients with sporadic ESRD.[9] It was found that, after adjustment for comorbid conditions, a family history of ESRD in either first- or second-degree relatives did not affect survival in 3,442 incident dialysis patients.

Although no effect of a positive family history on survival during dialysis was found, it might be postulated that a positive family history affects progression of patients not yet on dialysis. Therefore, this study assessed whether the prevalence of diabetes mellitus, cardiovascular disease, and kidney disease was different between first-degree relatives of pre-dialysis patients and first-degree relatives in a random sample of the Dutch general population. In addition, it was studied whether familial clustering of these illnesses in first- and/or second-degree relatives influenced the progression of kidney disease as measured by a faster decline of kidney function and an increased mortality risk in pre-dialysis patients.

Methods

Study Design

PREPARE-1 is a retrospective follow-up study of incident pre-dialysis patients. These patients were treated in eight pre-dialysis outpatient clinics of community and university hospitals in the Netherlands between January 1, 1999 and December 31, 2001. The clinical course during standard treatment of all consecutive patients was followed through medical records until censoring, i.e. the start of dialysis, death, transplantation or end of study (January 1, 2008), whichever occurred first. Predefined data on demography, biometry, clinical symptoms, and comorbidities were collected from written medical records at the start of pre-dialysis care (study inclusion). Data on laboratory measurements were extracted from the Hospital

Information System. The study was approved by the institutions' Medical Ethics Committee's and conducted in accordance with the Good Clinical Practice Guidelines.

Patients

Inclusion criteria for the PREPARE-1 Study were: the patient was at least eighteen years of age and he or she was referred to a pre-dialysis outpatient clinic for specialized pre-dialysis care. In practice, this refers to patients with a creatinine clearance of less than 20 mL/min in whom the need for renal replacement therapy is expected being within one year. Patients with prior renal replacement therapy or a total pre-dialysis follow-up of less than one month were not included in the study.

Data Collection

Primary kidney disease was classified according to the ERA-EDTA coding system.[10] Uncalibrated serum creatinine values were used to estimate the glomerular filtration rate (eGFR) using the 4-variable Modification of Diet in Renal Disease equation.[11]

Reference population

A random sample of the Dutch general population was used as a reference population. This sample is part of the PREvention of Renal Vascular End-stage Diseases (PREVEND) study, a prospective cohort study in inhabitants of the city of Groningen, the Netherlands. The PREVEND study was established in 1997 to investigate the natural course of microalbuminuria and its relation with renal and cardiovascular disease in the general population. The specific random sample (n=3,432) that was used for this analysis was a subsample of the PREVEND study without the enrichment for albuminuria and therefore entirely reflects the general population. Subjects were aged 25-75 years at study inclusion. Study participants were requested to send in a morning urine sample and to fill out a questionnaire on demographic, renal, and cardiovascular history. All patients gave written informed consent prior to study participation. The PREVEND study was approved by the local medical ethics committee and conducted in accordance with the guidelines of the declaration of Helsinki. Further details of the study can be found elsewhere.[12]

Determinants

For pre-dialysis patients family history of specific illnesses, i.e. (a) diabetes mellitus, (b) cardiovascular disease, and (c) kidney disease, was collected from patient-reported information derived from medical records. If positive, it was recorded which of the following first-degree relatives was/were affected: father, mother, brother, sister and/or child. In addition it was assessed which of the following second-degree relatives was/were affected: grandfather, grandmother, grandchild and/or nephew/niece. If family history for a specific disease was not mentioned in the status, it was assumed to be negative. For the reference population family history was recorded by means of questionnaires. Subjects were asked whether father, mother,

brother or sister (a) got medication or a special diet as treatment for diabetes mellitus; (b) had experienced a cerebrovascular accident (except for transient ischemic attack), myocardial infarction or got heart surgery (including angioplasty); and (c) suffered from a kidney disease for which more than six weeks of dialysis was required. In case information for a specific disease was missing, family history for that disease was assumed to be negative.

Endpoints

For the present analyses, two different endpoints were studied. First, the risk (hazard) of death in the first year of pre-dialysis care and during complete pre-dialysis follow-up was estimated. Death during pre-dialysis care was assessed from the medical records and hospital databases. Second, the rate of decline of kidney function in the first year of pre-dialysis care was estimated as the slope (steepness) of the decline of eGFR.

Statistical analyses

Characteristics of all patients at the start of pre-dialysis care as well as characteristics of the reference population were expressed as mean and standard deviation or percentage, as appropriate. The prevalence of diabetes mellitus, cardiovascular disease, and kidney disease in first-degree relatives of pre-dialysis patients was compared to the prevalence of these illnesses in first-degree relatives of the general population. To adjust for age and sex differences between the study population and the reference population, we applied direct standardization using the age- and sex-distribution from the general population (PREVEND subsample) as the reference. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between a first- and/or second-degree family history and mortality in the first year of pre-dialysis care and during total pre-dialysis follow-up. Additional adjustments were made for sex and race. The rate of decline of kidney function was estimated using linear mixed effects models. The models were used to estimate the difference in decline of eGFR (mL/min/1.73m^2/year) between patients with a family history of one or a combination of the abovementioned illnesses and patients with a negative family history. These analyses were also adjusted for sex and race. Under the assumption that the decline of kidney function in a relatively short period is almost linear[13], we restricted follow-up time for this analysis to the first year of pre-dialysis care. Statistical analyses were performed with SPSS statistical software (version 17.0; SPSS, Chicago, IL).

Results

Study population

The retrospective PREdialysis PAtients REcords (PREPARE-1) Study included 547 patients. Of these, 439 (80.3%) patients had data available on family history. Two hundred fifty-four (57.9%) out of these 439 patients had at least one first- or second-degree relative with diabetes mellitus (n=103), cardiovascular disease (n=134) or kidney disease (n=108). Characteristics of these patients are shown in Table 1.

Table 1. Baseline characteristics of PREPARE-1 patients (N=439) grouped by whether their first- and/or second-degree family history of diabetes mellitus, cardiovascular disease, and kidney disease is either positive or negative.

	Family history	
	Positive (n=254)	Negative (n=185)
Age *years*	58.5 (14.8)	59.7 (16.0)
Sex *% male*	52.4	59.5
Race *%*		
Caucasian	91.7	89.7
Blacks	2.8	3.8
Asian	2.0	2.2
Other	3.5	4.3
Primary renal disease *%*		
Diabetes mellitus	18.1	15.7
Glomerulonephritis/sclerosis	8.7	12.4
Hypertension	7.5	11.4
Pyelonephritis	8.7	11.4
Polycystic kidneys, adult type	13.8	1.6
Renal vascular disease	6.3	8.6
Miscellaneous	26.4	24.9
Unknown	10.6	14.1
Body mass index kg/m^2 [n=403]	25.9 (4.8)	25.7 (4.6)
Current smoker % [n=434]	25.1	22.4
Khan comorbidity score *%*		
Low	35.8	31.9
Medium	24.4	31.4
High	39.8	36.8
Systolic BP *mmHg* [n=425]	150.7 (26.6)	153.7 (29.2)
Diastolic BP *mmHg* [n=425]	83.2 (12.8)	83.7 (13.4)
eGFR $mL/min/1.73m^2$ [n=396]	13.4 (6.1)	12.9 (6.5)

Values indicate mean (standard deviation) or percentage, as appropriate; values between square brackets indicate the number of patients for whom information was available on that particular parameter; DM: diabetes mellitus; CVD: cardiovascular disease; KD: kidney disease; BP: blood pressure; eGFR: estimated glomerular filtration rate.

Prevalence

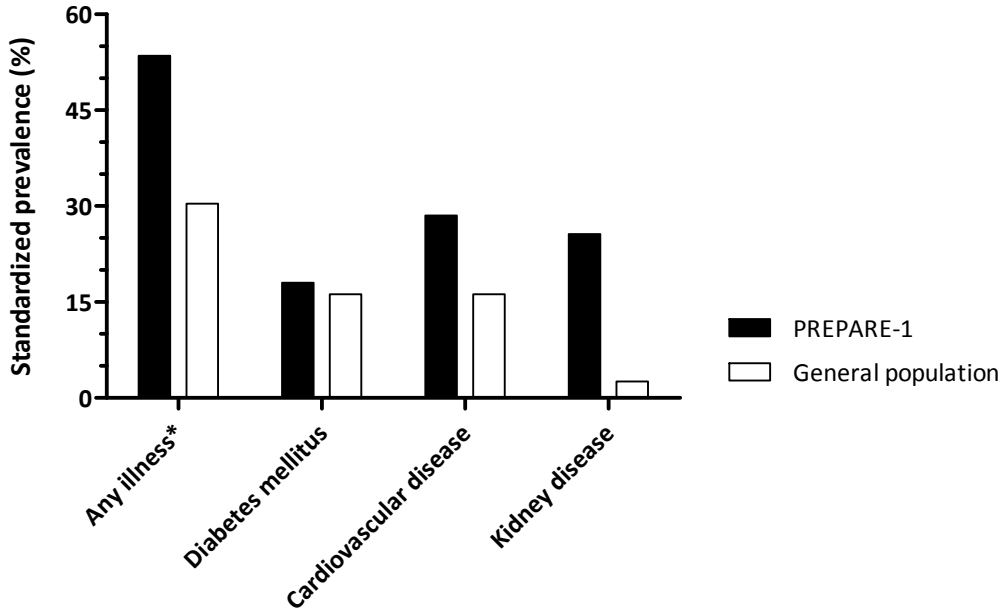
The age- and sex-adjusted prevalence of diabetes mellitus, cardiovascular disease, and kidney disease in first-degree relatives was compared between pre-dialysis patients and a random sample of the Dutch general population. Baseline characteristics of the 3,236 (94.3%) members of a sample of the general population (N=3,432) with available family history are shown in Table 2. The age- and sex-standardized prevalences of diabetes mellitus (18% *versus* 16%), cardiovascular disease (29% *versus* 16%), and kidney disease (26% *versus* 3%) were higher in first-degree relatives of pre-dialysis patients as compared to the general population. (Figure 1)

Table 2. Baseline characteristics of a random sample of the Dutch general population (N=3,236), grouped by whether their first-degree family history of diabetes mellitus, cardiovascular disease, and kidney disease is either positive or negative.

	Family history	
	Positive (n=1,023)	Negative (n=2,213)
Age *years*	52.3 (12.0)	48.0 (12.4)
Sex *% male*	44.2	45.4

Values indicate mean (standard deviation) or percentage, as appropriate; DM: diabetes mellitus; CVD: cardiovascular disease; KD: kidney disease.

Figure 1. Age- and sex-standardized prevalence of diabetes mellitus, cardiovascular disease, and kidney disease in first-degree relatives of pre-dialysis patients (N=439) and in a random sample of the Dutch general population (N=3,236). [a]First-degree relatives with at least one of the following illnesses: diabetes mellitus, cardiovascular disease, and kidney disease.



Mortality

During follow-up 51 pre-dialysis patients died (mortality rate 8.6/100 person-years, py; [95% confidence interval, CI 6.2 to 11.0]) of whom 34 patients (5.7/100py [95% CI 3.8 to 7.7]) had first- and/or second-degree relatives with diabetes mellitus, cardiovascular disease, and/or kidney disease, and 17 patients (2.9/100py [95% CI 1.8 to 4.6]) had a negative family history of these illnesses. Mortality rates for patients with a family history of diabetes mellitus, cardiovascular disease, and/or kidney disease were 2.9/100py (95% CI 1.8 to 4.6), 3.7/100py (95% CI 2.4 to 5.6), and 0.8/100py (95% CI 0.4 to 2.0), respectively. In the first year of pre-dialysis care, the mortality risks in patients with a family history of diabetes mellitus (HR 2.9 [95% CI 1.3 to 6.7]) or cardiovascular disease (HR 2.4 [95% CI 1.1 to 5.4]) were increased as

compared to patients without such family histories. The strength of these associations diminished when referring to complete follow-up during pre-dialysis care. (Table 3)

Table 3. Univariate and multivariate relative mortality risks for mortality associated with a positive family history in 439 pre-dialysis patients during the first year of pre-dialysis care and during the total pre-dialysis follow-up.

	Any illness[a]	Diabetes mellitus	Cardiovascular disease	Kidney disease
First year				
FH+ (events/N)	18/254	11/103	12/134	2/108
FH- (events/N)	5/185	12/336	11/305	21/331
Crude HR (95% CI)	2.45 (0.91; 6.60)	2.96 (1.31; 6.71)	2.44 (1.08; 5.54)	0.25 (0.06; 1.07)
Adjusted HR (95% CI)[b]	2.35 (0.87; 6.34)	2.92 (1.28; 6.66)	2.39 (1.05; 5.42)	0.24 (0.06; 1.04)
Total follow-up				
FH+ (events/N)	34/254	17/103	22/134	5/108
FH- (events/N)	17/185	34/336	29/305	46/331
Crude HR (95% CI)	1.31 (0.73; 2.34)	1.55 (0.87; 2.79)	1.53 (0.88; 2.67)	0.27 (0.11; 0.68)
Adjusted HR (95% CI)[b]	1.29 (0.72; 2.32)	1.63 (0.90; 2.93)	1.46 (0.84; 2.55)	0.28 (0.11; 0.72)

FH+: positive family history; FH-: negative family history; HR: hazard ratio; CI: confidence interval; [a]At least one of the following family histories: diabetes mellitus, cardiovascular disease, kidney disease or a combination of these; [b]Adjusted for sex and race.

Decline of eGFR

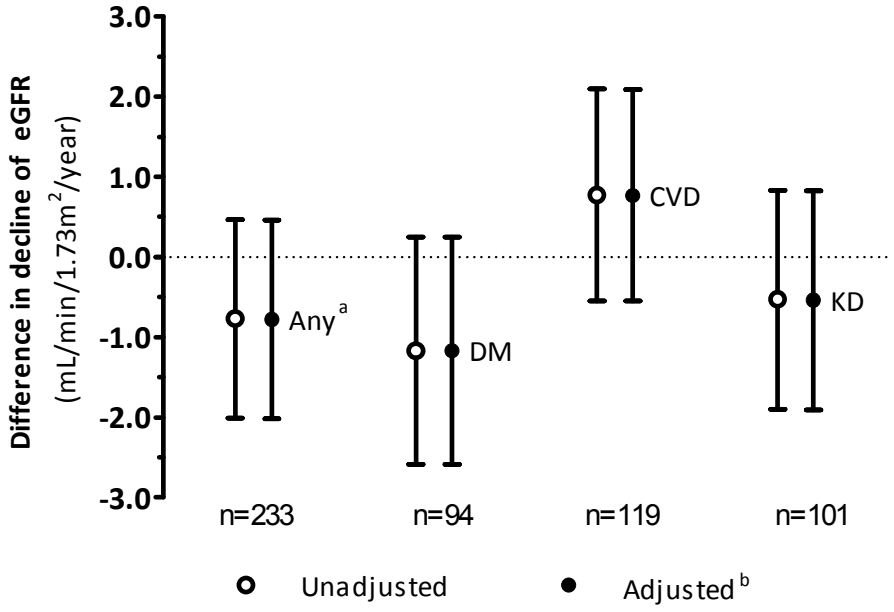
Decline of eGFR in the first year of pre-dialysis care was estimated as the slope of decline of eGFR using linear mixed effect models. In patients with a complete negative family history of diabetes mellitus, cardiovascular disease and kidney disease the mean sex and race adjusted rate of decline of eGFR in this period was -3.65 mL/min/1.73m^2/year (95% CI -4.26 to -3.04). The crude and adjusted differences in the decline of kidney function between patients with and without a family history of diabetes mellitus, cardiovascular disease, and kidney disease in the first year of pre-dialysis care as well as during total follow-up are shown in Figure 2.

Post-hoc analyses

To test the robustness of the results, it was investigated whether the increased mortality risk and the trend for a faster decline of kidney function in patients with a family history of diabetes mellitus could be explained by the presence of diabetes mellitus in the pre-dialysis patients themselves. To that end additional analyses were performed with further adjustment for having diabetes mellitus as comorbidity at baseline. These analyses showed a mortality risk of 2.66 (95% CI 1.13 to 6.29) and a difference in the rate decline of kidney function of -1.15 mL/min/1.73m^2 (95% CI -2.58 to 0.27) in the first year of pre-dialysis care. These results indicate that there is an association between a positive family history of diabetes mellitus and mortality, which is independent of whether the patient has diabetes mellitus. Similarly, it was

tested whether the increased mortality risk in patients with a family history of cardiovascular disease could be explained by the presence of cardiovascular comorbidity in the patients. After additional adjustment for the presence of cardiovascular comorbidities at baseline, the hazard ratio for mortality was 2.32 (95% CI 1.02 to 5.28). Furthermore, it was tested whether patients with multiple affected relatives with diabetes mellitus and/or cardiovascular disease have an even poorer prognosis as compared to patients with only one affected relative. This analysis showed that for every extra relative with a positive family history of diabetes or cardiovascular disease the mortality risk was 1.34 (95% CI 1.09 to 1.66) as compared to patients without a positive family history.

Figure 2. Decline of kidney function in the first year of pre-dialysis care in 396 incident pre-dialysis patients with a family history of diabetes mellitus (DM), cardiovascular disease (CVD), or kidney disease (KD). [a]First-degree relatives with at least one of the following illnesses: diabetes mellitus, cardiovascular disease, and kidney disease; [b]Adjusted for sex and race.



Discussion

This study shows that cardiovascular disease and kidney disease are both more prevalent in first-degree relatives of pre-dialysis patients as compared to the general population. Diabetes mellitus is slightly more prevalent in relatives of pre-dialysis patients as compared to the general population. In addition, a family history of diabetes mellitus (HR 2.9; 95% CI 1.3 to 6.7) and cardiovascular disease (HR 2.4; 95% CI 1.1 to 5.4) is associated with an increased mortality risk in the first year of pre-dialysis care. These results underline the importance of obtaining

family history data from patients with CKD (pre-dialysis) as this may help to identify patients at risk of accelerated disease progression.

To our knowledge, this is the first study focusing on the impact of family history on the progression of CKD as measured by decline of kidney function and mortality during pre-dialysis. It has been shown previously that in dialysis patients a family history of ESRD is not associated with the duration of dialytic survival.[9] The present results add that in pre-dialysis patients a positive family history of diabetes mellitus is associated with a three times increased mortality risk in the first year of pre-dialysis care. Previous studies showed indications for familial clustering of diabetic-associated ESRD.[3-6] In the joint presence of diabetes mellitus and ESRD, mortality risks are shown to be further increased,[1] because diabetes mellitus is characterized by vascular damage that leads eventually to mortality. In the present analysis we also show that a family history of diabetes mellitus is associated with a trend for a faster decline of kidney function in the first year after the start of pre-dialysis care, likely through the same mechanism. The difference in the yearly decline of kidney function in patients with a family history of diabetes mellitus compared to patients without relatives having diabetes mellitus was -1.17 mL/min/1.73m^2 (95% CI -2.59 to 0.25). Although this may seem a minor difference, this decline adds to the 'usual' decline of kidney function of about 4.5 mL/min/1.73m^2/year in these patients.[14] Especially in view of the low mean kidney function at start of pre-dialysis care (mean eGFR approximately 13 mL/min/1.73m^2), this difference is clinically relevant.

The present study also shows that patients with a family history of cardiovascular disease have a two times increased mortality risk in the first year of pre-dialysis care. Our findings extend earlier studies, which showed that the presence of cardiovascular comorbidity in pre-dialysis patients is associated with an increased mortality risk.[15] Furthermore, it has been described that pre-dialysis patients with cardiovascular comorbidities have a faster decline of kidney function as compared to patients without these comorbidities.[16;17] The present results add that such an association is not attributable to a family history of cardiovascular disease. We also show that a family history of kidney disease is associated with a trend for lower mortality risk in pre-dialysis patients, without an association with the rate of decline of kidney function in the first year of pre-dialysis care. To our knowledge, no previous study has focused on this topic before.

Finally, we found that the association between a family history of diabetes mellitus or cardiovascular disease is independent of whether the patient has diabetes mellitus or cardiovascular disease. In addition, we showed that patients with multiple affected relatives with diabetes mellitus and/or cardiovascular disease have an even poorer prognosis as compared to patients with only one affected relative. Taken together, these results give strong indications for a hereditary component which might play a role in faster disease progression in pre-dialysis patients.

When interpreting the present results several points need to be considered. First, family history in pre-dialysis patients (PREPARE-1) was assessed based on available data in patients' medical records, while in healthy subjects (PREVEND) family history was assessed by

questionnaires. Both sources of information might be influenced by underreporting, possibly resulting in biased results due to misclassification. However, in view of the large prevalence differences observed, we expect comparable results even if misclassification might have occurred. Second, in the present study we found that patients with a family history of diabetes or kidney disease have a significantly increased mortality risk in the first year of pre-dialysis care. However, when referring to complete follow-up the association disappeared. This may be explained as follows: patients with a positive family history may be inclined to attend a nephrologist when they get complaints, which clearly might be earlier as compared to patients with a negative family history. Therefore, patients with a negative family history might have died even before their first visit to a nephrologist. Alternatively, patients with a positive family history of diabetes or cardiovascular disease have a largely increased mortality risk and die early in the course of pre-dialysis care or even before the start of pre-dialysis care. The patients who still survive a few years after the start of pre-dialysis are the relatively strong patients. Consequently, the association between a positive family history and mortality on the long-term decreases. Third, the decline of eGFR in the first year of pre-dialysis care was estimated using the MDRD equation[11]. When we would have used the CKD-EPI equation[18] instead, similar results would have been found (results not shown). We also chose to analyze the combined effect of first- and/or second-degree relatives affected with disease. When we restricted our analysis to patients with affected first-degree relatives only, we found similar or even stronger associations with the mortality risk and decline of kidney function, but with slightly wider confidence intervals due to less power (results not shown). Finally, based on the assumption that possible effects of family history are mainly due to genetic differences, the present analyses were adjusted for sex and race only. Other parameters, such as the presence of proteinuria and serum albumin levels, were assumed to be within the causal pathway between family history and the outcomes under study.

Our data have clinical implications. A family history of diabetes mellitus or cardiovascular diseases is associated with a two to three times increased mortality risk. The present study thus provides a strong indication for a hereditary component which might play a role in the faster progression of kidney disease in pre-dialysis patients. In the light of the frequently observed familial clustering of illnesses such as diabetes mellitus, the results of the present study underline the importance of proper identification of high-risk populations. Identification of high-risk populations is not only important for people who might be unaware of their severe disease state, but the present results also highlight the influence of family history on prognosis in patients who were already identified. Furthermore, our results implicate that awareness of family medical history may be helpful in the identification of CKD patients at risk for disease progression in an early stage. It remains to be studied whether timely and more aggressive treatment of pre-dialysis patients with a positive family history is beneficial in decreasing their mortality risk.

In conclusion, a family history of diabetes mellitus and cardiovascular disease is associated with an increased mortality risk in the first year of pre-dialysis care. Therefore, obtaining information about FH may help to identify pre-dialysis patients at increased mortality risk.

Acknowledgement

Trial nurses and data managers from the Hans Mak Institute are gratefully acknowledged for their assistance in data collection. Furthermore, we thank all the laboratory information system managers who invested time and effort to supply laboratory data, and all supporting staff who helped tracing records of (eventually) every patient.

Disclosure

The PREPARE-1 Study is an independent academic study designed and conducted by the Department of Clinical Epidemiology from the Leiden University Medical Center in collaboration with the Hans Mak Institute (Naarden) and the participating hospitals. This study was funded by an unrestricted grant from Amgen BV (The Netherlands and Switzerland). The sponsor of the study was not involved in study design, collection of data, statistical analysis, interpretation of data, writing of the manuscript or in the decision to submit the paper for publication. None of the authors have declared a conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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