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Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients

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Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients.

Background. Cardiovascular diseases are the most common causes of death among chronic hemodialysis patients, yet the risk factors for these events have not been well established.

Methods. In this cross-sectional study, we examined the relationship between several traditional cardiovascular disease risk factors and the presence or history of cardiovascular events in 936 hemodialysis patients enrolled in the baseline phase of the Hemodialysis Study sponsored by the U.S. National Institutes of Health. The adjusted odds ratios for each of the selected risk factors were estimated using a multivariable logistic regression model, controlling for the remaining risk factors, clinical center, and years on dialysis.

Results. Forty percent of the patients had coronary heart disease. Nineteen percent had cerebrovascular disease, and 23% had peripheral vascular disease. As expected, diabetes and smoking were strongly associated with cardiovascular diseases. Increasing age was also an important contributor, especially in the group less than 55 years and in nondiabetic patients. Black race was associated with a lower risk of cardiovascular diseases than non-blacks. Interestingly, neither serum total cholesterol nor predialysis systolic blood pressure was associated with coronary heart disease, cerebrovascular disease, or peripheral vascular disease. Further estimation of the coronary risks in our cohort using the Framingham coronary point score suggests that traditional risk factors are inadequate predictors of coronary heart disease in hemodialysis patients.

Conclusions. Some of the traditional coronary risk factors in the general population appear to be also applicable to the hemodialysis population, while other factors did not correlate with atherosclerotic cardiovascular diseases in this cross-sectional study. Nontraditional risk factors, including the uremic milieu and perhaps the hemodialysis procedure itself, are likely to be contributory. Further studies are necessary to define the cardiovascular risk factors in order to devise preventive and interventional strategies for the chronic hemodialysis population.

Key words: coronary risk factors, uremia, blood pressure, dialysis, serum total cholesterol, vascular disease.

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Cardiovascular events are the leading cause of death in chronic hemodialysis patients [1]. Identification of their risk factors is important in order to devise preventive and interventional strategies. Intuitively, it appears reasonable to assume that the traditional cardiovascular risk factors for the general population are also applicable to the hemodialysis patients, and that hemodialysis patients suffer more cardiovascular diseases because these risk factors are present to a greater extent. For example, hypertension is especially prevalent in this population [2]. Against this hypothesis are the observations that the other traditional risk factors, such as hypercholesterolemia, may not be present to a greater extent in the hemodialysis population compared with the general population [3, 4].

Limited available data further suggest that some of the traditional cardiovascular risk factors are not applicable to the hemodialysis patients. For example, in a cross-sectional study, Lowrie and Lew reported that the overall mortality in chronic hemodialysis patients increased exponentially when serum total cholesterol decreased from the range of 200 to 250 mg/dL to less than 100 mg/dL [5]. More recently, Zager et al reported a "U"-shaped curve in the relationship between predialysis systolic blood pressure and mortality, with the lowest mortality observed in the group with blood pressure between 160 and 179 mm Hg [6]. These observations raise questions as to whether the traditional cardiovascular risk factors are applicable to the chronic hemodialysis population.

Many outcome studies in the chronic hemodialysis population, including those addressing risk factors for cardiovascular diseases, have used overall mortality and hospitalization as their outcome measures. Very few, in fact, examined the association of potential risk factors with the cardiovascular events themselves.

The goal of the present study was to evaluate the prevalence and severity of atherosclerotic cardiovascular diseases in a representative chronic hemodialysis population. In addition, we examined the presence of traditional

cardiovascular risk factors and the relationship of these putative risk factors to clinical atherosclerotic cardiovascular diseases in this population, using a cross-sectional design. Since risk factors might differ among various end organs, we examined coronary heart disease, cerebrovascular disease, and peripheral vascular disease individually in this study.

METHODS

Study design

The data analysis on cardiovascular risks was based on a cross-sectional study of the first 1000 patients recruited into the baseline phase of the Hemodialysis (HEMO) Study. The HEMO Study is sponsored by the U.S. National Institute of Diabetes, Digestive, and Kidney Diseases; the full-scale trial began in 1995. Details regarding the design of the HEMO Study have been published elsewhere [7]. In brief, the study is a multicenter, prospective, randomized, clinical trial designed to evaluate the effect of dialyzer urea and β_2-microglobulin clearances on the morbidity and mortality of patients.

Patients were eligible for inclusion into the HEMO Study if they were between the ages of 18 and 80 years, had been receiving chronic hemodialysis three times per week, and had residual renal clearance of urea that was less than 1.5 mL/min/35 L of urea distribution volume. Among the exclusion criteria were unstable angina, New York Heart Association Class IV congestive heart failure despite medical management, and predialysis serum albumin < 3.0 g/dL.

Data procurement

Demographic, medical, and socioeconomic information were obtained once patients were enrolled into the baseline phase of the study. Information that was obtained included age, race, gender, height, predialysis and prescribed dry weight, predialysis and postdialysis sitting blood pressures (single measurements), primary renal diagnosis, duration of end-stage renal disease (ESRD), diabetic status (based on past or current use of hypoglycemic agents), previous extremity amputation, and history of cigarette smoking.

During the fifth week of the study, while the patients were still in the baseline phase, their comorbid medical conditions were assessed and recorded on a standardized form. The form was completed at each clinical center by specially trained study coordinators. The information available for the completion of the form included chart progress notes, list of current medications, and the most recent laboratory data, chest x-ray report, electrocardiogram, and hospital discharge summary and was supplemented by interviews of the patients, family members, primary nephrologists, and dialysis staff as necessary.

The comorbidities were catalogued using the Index of Co-Existing Diseases (ICED), a coding system that classifies the presence and severity of 19 different diseases and 11 physical impairments [8]. The comorbidity index of individual patients is scored with a value ranging from 0 to 3, with 0 indicating the absence of disease and increasing values indicating increasing severity of the disease. The focus of the present report is on atherosclerotic events, namely, coronary heart disease, cerebrovascular disease, and peripheral vascular disease. The scoring system for each of these diseases is described in Table 1.

Table 1. Definitions of the index of co-existing diseases (ICED) for atherosclerotic cardiovascular diseases

Score	Definition
Coronary heart disease	
0	Absence of disease in past or present
1	Diagnosis of coronary heart disease in the past
	Ischemia on electrocardiogram or other diagnostic tests
	Stable or exertional angina or angina during hemodialysis
2	History of myocardial infarction
	Evidence of myocardial infarction on electrocardiogram
	History of coronary revascularization procedures
3	Angina at rest
	Acute myocardial infarction within the past 3 months
Cerebrovascular disease	
0	Absence of disease in past or present
1	Diagnosis of cerebrovascular disease in the past
	Asymptomatic carotid stenosis or history of transient ischemic attacks (TIAs)
	History of carotid endarterectomy
2	Multiple TIAs in the past
	Current usage of anticoagulants for cerebrovascular disease
	History of stroke with no or mild residual neurological deficits
3	History of stroke with major residual neurological deficits
Peripheral vascular disease	
0	Absence of disease in past or present
1	Diagnosis of peripheral vascular disease or aortic aneurysm in the past
2	History of amputation of digits or extremities secondary to vascular disease
	History of peripheral arterial bypass or aortic aneurysm repair
	Intermittent claudication
	Recurrent cellulitis, skin infections, or toe gangrenes secondary to vascular disease
	Vascular disease currently requiring anticoagulants
3	History of knee amputation
	Pain at rest secondary to peripheral vascular disease
	Inoperable vascular disease

Blood samples for total cholesterol were obtained predialysis, as part of the routine clinical protocol, within one month of enrollment without specific instructions to the patients. Serum cholesterol concentrations were measured by the clinical laboratories associated with individual dialysis centers. Fractionation of serum cholesterol and triglyceride determination were not performed.

Statistical analyses

Of the initial 1000 patients enrolled in the baseline phase of the HEMO Study, 64 of them did not have complete information for analyses of cardiovascular risks

described herein. Therefore, only the remaining 936 patients are included hereafter in our report.

Unadjusted and adjusted odds ratios describing the association of selected cardiovascular risk factors with each of three disease categories (coronary heart disease, cerebrovascular disease, and peripheral vascular disease) were obtained by univariable and multivariable logistic regression, respectively. Odds ratio is expressed as the ratio of the odds of having any level of disease between the indicated levels of the risk factor. The cardiovascular risk factors included in the multivariable logistic regressions were those commonly used in the Framingham Study for the general population, namely, age, gender, race, presence or absence of diabetes mellitus, history or current smoking status, and serum total cholesterol, with the addition of predialysis systolic and diastolic blood pressures. Clinical center and total number of years on dialysis were also included as predictor variables in the multivariable logistic regressions, so that the adjusted odds ratios for each of the selected cardiovascular risk factors are controlled for the remaining cardiovascular risk factors, clinical center, and years of dialysis.

For graphical presentation, nonparametric logistic regression analysis with cubic smoothing splines [9] was used to relate the probability of the three disease outcomes to the quantitative risk factors age, blood pressure, and total cholesterol, while controlling for clinical centers, years on dialysis, and the remaining cardiovascular risk factors examined. These analyses indicated a significant nonlinear relationship between age and the logarithm of the odds of coronary heart disease ($P = 0.02$). There was also a trend for a nonlinear relationship between age and the logarithm of the odds of peripheral vascular disease ($P = 0.10$). Therefore, in the logistic regression analyses, the relationships of the odds ratios of the respective disease categories with age in the entire cohort were modeled with separate terms for age <55 years and age >55 years.

RESULTS

Prevalence and severity of atherosclerotic cardiovascular diseases

As can be seen in Table 2, 40% of the patients had coronary heart disease, 19% had cerebrovascular disease, and 23% had peripheral vascular disease. Among those with coronary heart disease, cerebrovascular disease, and peripheral vascular disease, the most prevalent category was that with a severity score of two.

Framingham risk factors in the present study cohort

The levels of traditional Framingham cardiovascular risk factors were examined in this hemodialysis study cohort. There was a slight preponderance (53%) of females. Sixty-four percent of the patients were black, which was higher than that in the U.S. chronic hemodialysis population [1] and might be related to a preponderance of urban dialysis units in the HEMO Study. Caucasians accounted for 33% of the cohort. The mean (± SD) age of the patients was 58 ± 14 years. The mean duration on dialysis was 4.3 ± 4.5 years.

Table 2. Prevalence and severity of atherosclerotic cardiovascular diseases in the HEMO Study cohort

Score[a]	0	1	2	3
Coronary heart disease	60%	14%	24%	2%
Cerebrovascular disease	81%	4%	14%	1%
Peripheral vascular disease	77%	6%	10%	7%

[a] The scoring system is defined in Table 1

The 42% of patients with diabetes mellitus in this study was similar to that in the U.S. hemodialysis population. Fifty-two percent of the patients either smoked cigarettes at the time of entry to the study or had a previous history of smoking. The number of cigarettes smoked was not quantitated. The mean (± SD) serum total cholesterol concentration was 174 ± 40 mg/dL, which was similar to that previously reported for chronic hemodialysis patients [3, 4]. The mean predialysis systolic and diastolic blood pressures were 152 ± 25 and 82 ± 15 mm Hg, respectively. The distributions of total cholesterol concentration, systolic blood pressure, and diastolic blood pressure are shown in Figure 1. Total cholesterol concentrations and predialysis blood pressures of the study cohort were further classified according to the definitions provided by the National Cholesterol Education Program Adult Treatment Panel II [10] and the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Table 3) [11].

Association between traditional Framingham risk factors and probability of cardiovascular diseases

The association between traditional cardiovascular risk factors and the three forms of cardiovascular diseases (coronary, cerebrovascular, and peripheral) in our patients was first examined using separate univariable logistic regression models. The results are presented in Table 4. In this analysis, increasing age and diabetes were strongly associated with all three types of disease. Smoking was associated with cerebrovascular and peripheral vascular diseases, but not with coronary heart disease. Conversely, serum total cholesterol was associated with coronary heart disease, but not with cerebrovascular and peripheral vascular diseases. Of note is that predialysis systolic blood pressure was not associated with any of the three types of atherosclerotic cardiovascular diseases. In contrast, predialysis diastolic blood pressure and the duration on dialysis were inversely associated with coronary heart disease.

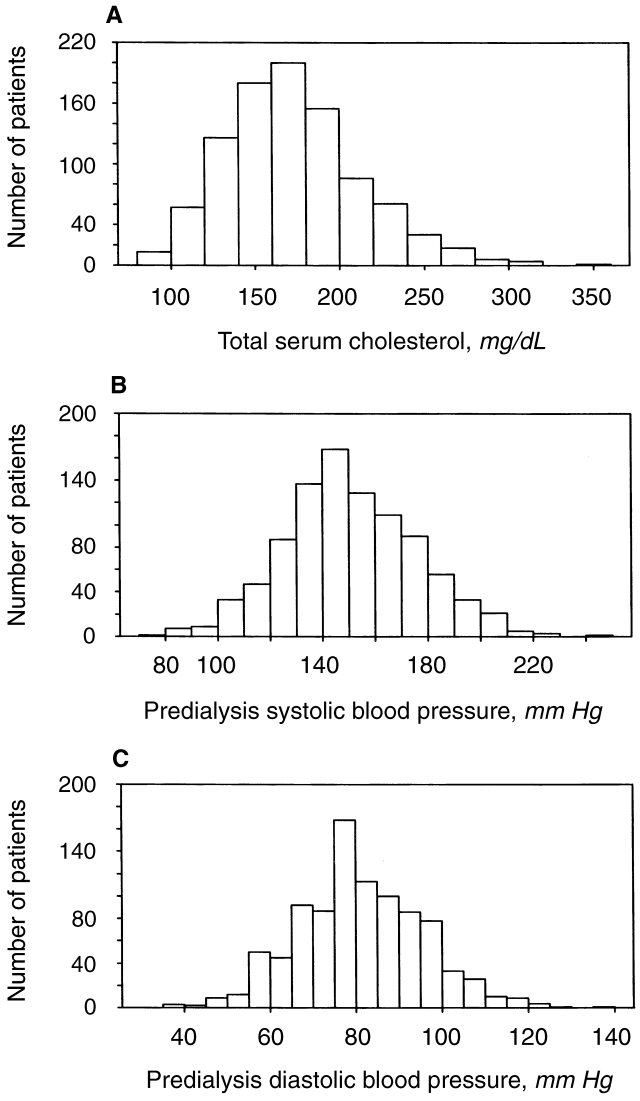

Fig. 1. Distribution of serum total cholesterol levels (*A*) and predialysis systolic (*B*) and predialysis diastolic (*C*) blood pressure values in the HEMO Study cohort.

Results of the multivariable regression model are presented in Table 5. As expected, the presence of diabetes mellitus was associated with a 65% increase ($P = 0.002$) in the odds of having coronary heart disease and a 3.59-fold increase ($P = 0.0$) in peripheral vascular disease. Interestingly, there was no statistically significant association between diabetes and cerebrovascular disease.

As expected, increasing age was strongly associated with atherosclerotic diseases, particularly in the younger age group. In patients below 55 years old, the odds of having coronary heart disease increased by a factor of 2.68 for every 10 year increase in age, while the odds increased by a factor of only 1.47-fold for every 10 years in patients older than 55 years old. The relationship between age and the probability of the various cardiovascular diseases is depicted graphically in Figure 2. The relationship between age and peripheral vascular disease was weaker than that between age and coronary heart disease in general.

There were interactions between age and diabetic status that affected their associations with atherosclerotic cardiovascular diseases. Overall, age had a stronger association with cardiovascular diseases in the absence of diabetes than in the presence of diabetes. In the presence of diabetes, the odds ratio of developing coronary heart disease was 1.48 ($P < 0.0001$) for every 10 year increase in age, while in absence of diabetes, the odds ratio was 2.15 ($P < 0.0001$). In the presence of diabetes, there was no significant linear or nonlinear association between age and cerebrovascular or peripheral vascular disease. In the absence of diabetes, however, the odds ratios of developing cerebrovascular disease and peripheral vascular diseases were 1.96 ($P < 0.0001$) and 1.74 ($P < 0.0001$), respectively, for each 10 year increase in age.

Smoking directly correlated (odds ratio = 1.68, $P = 0.008$) with cerebrovascular disease. Smoking was also associated with peripheral vascular disease (odds ratio = 1.74, $P = 0.003$), but not with coronary heart disease. Black race was associated with a 36% reduction ($P = 0.017$) in the odds of having coronary heart disease and 46% reduction ($P = 0.003$) in peripheral vascular disease, but it had no influence on cerebrovascular disease.

In the multivariable regression model, there was no statistically significant correlation between serum total cholesterol concentration and any of the cardiovascular diseases by either linear regression (Table 5) or nonlinear regression (data not shown) analysis. The relationship between cholesterol concentration and the probability of having the various forms of cardiovascular diseases is depicted graphically in Figure 3. As was the case with total cholesterol, there was no significant linear (Table 5) nor nonlinear (data not shown) association between predialysis systolic blood pressures and any of the cardiovascular diseases. The relationship between predialysis systolic blood pressure and the probability of having the various forms of cardiovascular diseases is depicted graphically in Figure 4.

Association between primary renal diagnosis and cardiovascular diseases

When the patients were categorized based on their primary renal diagnosis, those with diabetic nephropathy had the highest prevalence of atherosclerotic cardiovascular diseases (Table 6). Compared with glomerular diseases, hypertensive nephrosclerosis was associated with a similar or higher prevalence of cardiovascular diseases.

DISCUSSION

Prevalence of cardiovascular diseases

Approximately 40% of the present study cohort had evidence of coronary heart disease, while 19 and 23%

Table 3. Serum total cholesterol concentrations and predialysis blood pressures in the HEMO Study cohort classified according to the definitions of NCEP[a] and JNC VI[b]

				Number of patients	Percentage of population
Serum total cholesterol					
<200 mg/dL				725	77.5
200–239 mg/dL				152	16.2
≥240 mg/dL				59	6.3
Blood pressure	Systolic[c]		Diastolic[c]		
Optimal BP	<120	and	<80	69	7.4
Normal BP	<130	and	<85	77	8.2
High-normal BP	130–139	or	85–89	124	13.3
Stage 1 hypertension	140–159	or	90–99	291	31.2
Stage 2 hypertension	160–179	or	100–109	232	24.8
Stage 3 hypertension	≥180	or	≥110	141	15.1

[a] NCEP, National Cholesterol Education Program Adult Treatment Panel II [10]
[b] JNC VI, Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [11]
[c] When systolic and diastolic blood pressures fall into different categories, the higher category was selected to classify the individual blood pressure status; each patient was classified in only one category

Table 4. Univariable logistic regression analysis of the odds ratio of atherosclerotic cardiovascular diseases for potential risk factors in the HEMO Study cohort

	Coronary heart disease O.R.[a] *P*	Cerebrovascular disease O.R. *P*	Peripheral vascular disease O.R. *P*
Gender *male*	0.89 0.392	1.17 0.354	1.19 0.274
Race *Black*	0.77 0.057	1.06 0.749	0.67 0.011
Age *per 10 year increase*	1.92 0.000	1.56 0.000	1.35 0.000
Presence of diabetes mellitus	2.15 0.000	1.61 0.004	3.17 0.000
Smoking[b]	1.11 0.438	1.79 0.001	1.77 0.000
Cholesterol *per 20 mg/dL increase*	1.10 0.004	1.02 0.609	1.04 0.273
Systolic BP *per 20 mm Hg increase*[c]	1.04 0.424	1.11 0.127	1.03 0.662
Diastolic BP *per 20 mm Hg increase*[c]	0.76 0.004	0.96 0.698	0.83 0.079
Dialysis duration *per 5 year increase*	0.79 0.003	0.90 0.262	0.79 0.017

[a] Odds ratio
[b] History of or current smoking
[c] Predialysis blood pressure

Table 5. Multivariable logistic regression analysis of the odds ratio of atherosclerotic cardiovascular diseases for potential risk factors in the HEMO Study cohort

	Coronary heart disease O.R.[a] *P*	Cerebrovascular disease O.R. *P*	Peripheral vascular disease O.R. *P*
Gender *male*	1.10 0.567	1.18 0.401	1.12 0.539
Race *black*	0.64 0.017	0.97 0.901	0.54 0.003
Age <55 years *per 10 year increase*	2.68 0.000	1.72 0.007	1.44 0.030
Age >55 years *per 10 year increase*	1.47 0.001	1.51 0.003	1.09 0.550
Presence of diabetes mellitus	1.65 0.002	1.41 0.074	3.59 0.000
Smoking[b]	1.08 0.647	1.68 0.008	1.74 0.003
Cholesterol *per 20 mg/dL increase*	1.04 0.343	0.99 0.775	0.99 0.740
Systolic BP *per 20 mm Hg increase*[c]	0.98 0.778	1.09 0.228	0.98 0.750
Dialysis duration *per 5 year increase*	1.02 0.820	1.10 0.385	1.06 0.589

[a] Odds ratio
[b] History of or current smoking
[c] Predialysis blood pressure

had evidence of cerebrovascular disease and peripheral vascular disease, respectively. These prevalence data are very similar to those described in the Dialysis Morbidity and Mortality Wave 2 Study of the United States Renal Data System collected in 1996, which showed 42% coronary heart disease, 16% cerebrovascular disease, and 23% peripheral vascular disease [1]. This prevalence of coronary heart disease in the hemodialysis patients is

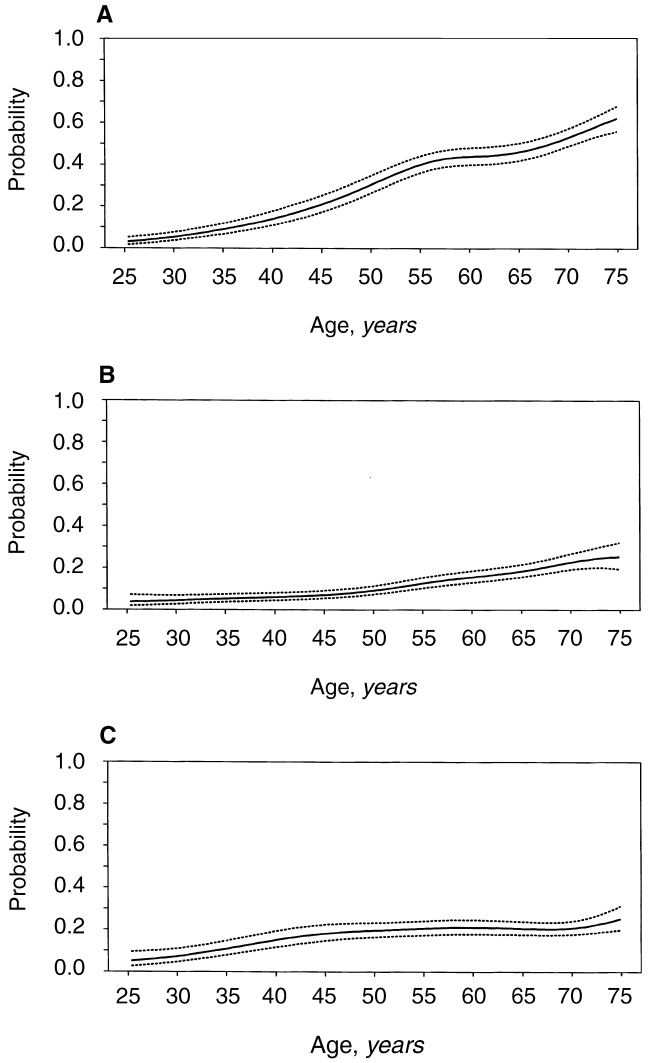

Fig. 2. Relationship between age and probability of having coronary heart disease (*A*), cerebrovascular disease (*B*), and peripheral vascular disease (*C*). The probabilities are adjusted for all other covariates described in the **Methods** section, including duration of dialysis and different dialysis centers. The broken lines represent 95% confidence intervals. There is a significant positive association between each of these disease categories and age. The association of age with the risk of coronary heart disease (expressed as the natural logarithm of the odds) was significantly nonlinear ($P = 0.021$), with a stronger relationship observed at lower ages.

substantially higher than that in the general population, which has been reported to be 2 to 26% depending on age and gender [12].

Traditional risk factors applicable to hemodialysis population

As expected, diabetes was found to be strongly associated with both coronary heart disease and peripheral vascular disease, but interestingly, it was not significantly associated with cerebrovascular disease in the multivariable model. Smoking, on the other hand, was associated with the cerebrovascular and peripheral vascular disease, but not with coronary heart disease. As in the general population, increasing age was associated with the development of all three forms of cardiovascular disease in the entire cohort. This age dependency, however, was lost for cerebrovascular and peripheral vascular diseases in the presence of diabetes, suggesting that diabetes exerts a more powerful influence than age on these disorders. The finding that diabetes, smoking, and age are the most reproducible traditional risk factors associated with cardiovascular diseases is consistent with prior studies in the ESRD population [1, 13, 14].

Racial differences

Multivariable analysis revealed that the black race was associated with a 36% reduction in coronary heart disease and a 46% reduction in peripheral vascular disease, but it was not associated with a reduction in cerebrovascular disease (Table 5). These data on coronary heart disease are consistent with results of prior studies and the lower mortality secondary to all causes as well as cardiovascular disease-specific mortality in the black ESRD population [14, 15]. The reasons for this racial difference, however, remain unknown. One might hypothesize that black patients have a higher percentage of ESRD secondary to hypertension, and hypertensive nephrosclerosis is less likely to be associated with cardiovascular disease than are other causes of renal disease, such as diabetes. While nephrosclerosis as a cause of ESRD was indeed more common in the blacks (42 vs. 17%), diabetic nephropathy was also more common in blacks than in Caucasians (37 vs. 33%). While the prevalence of coronary heart disease in nephrosclerosis was lower than that in diabetic nephropathy, it was greater than that in glomerular diseases (Table 6). Thus, differences in the primary renal diagnosis do not appear to be a satisfactory explanation for the lower coronary risks in blacks. Alternatively, one might speculate that there are factors other than the traditional Framingham risk factors that contribute to atherosclerotic vascular diseases in the chronic hemodialysis patients and that these factors are less common or less severe in the black dialysis patients. For example, homocysteine metabolism has been noted to be more efficient in blacks [16]. Against this hypothesis, however, are the higher lipoprotein(a) levels reported in blacks [17]. It should be noted, however, that these two studies were performed in nonuremic subjects.

Relationship between cholesterol or blood pressure with clinical outcome

The most intriguing results of the multivariable analysis were the lack of association between serum total cholesterol level (Table 5 and Fig. 3) or predialysis sys-

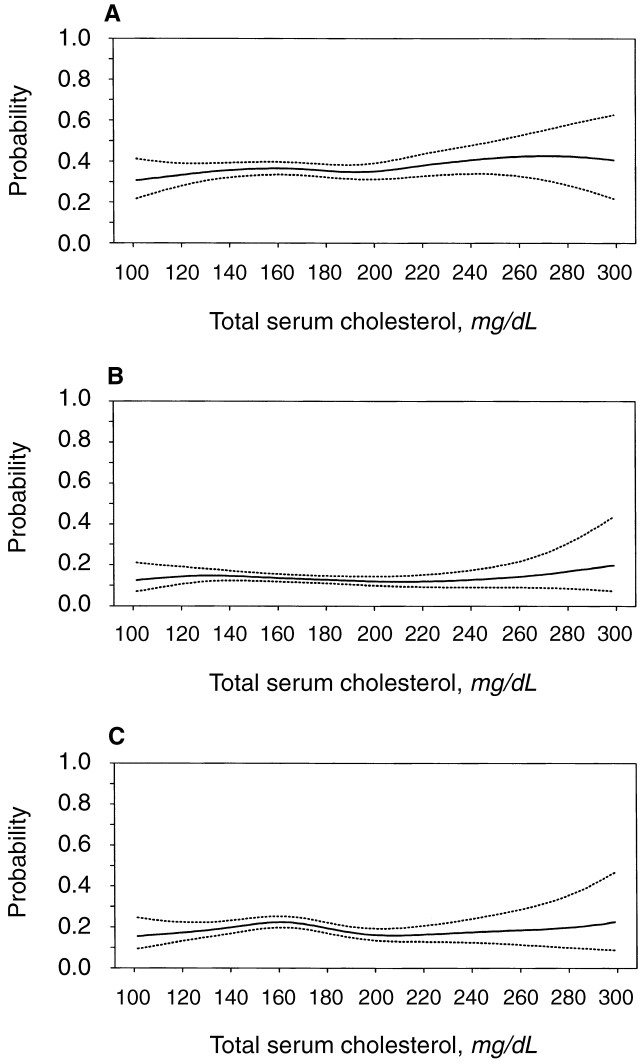

Fig. 3. Relationship between serum total cholesterol concentration and probability of having coronary heart disease (*A*), cerebrovascular disease (*B*), and peripheral vascular disease (*C*). The probabilities are adjusted for all other covariates described in the **Methods** section, including duration of dialysis and different dialysis centers. The broken lines represent 95% confidence intervals. There is no statistically significant linear or nonlinear relationship between serum cholesterol concentration and the natural logarithm of the odds of developing any of the three types of atherosclerotic diseases.

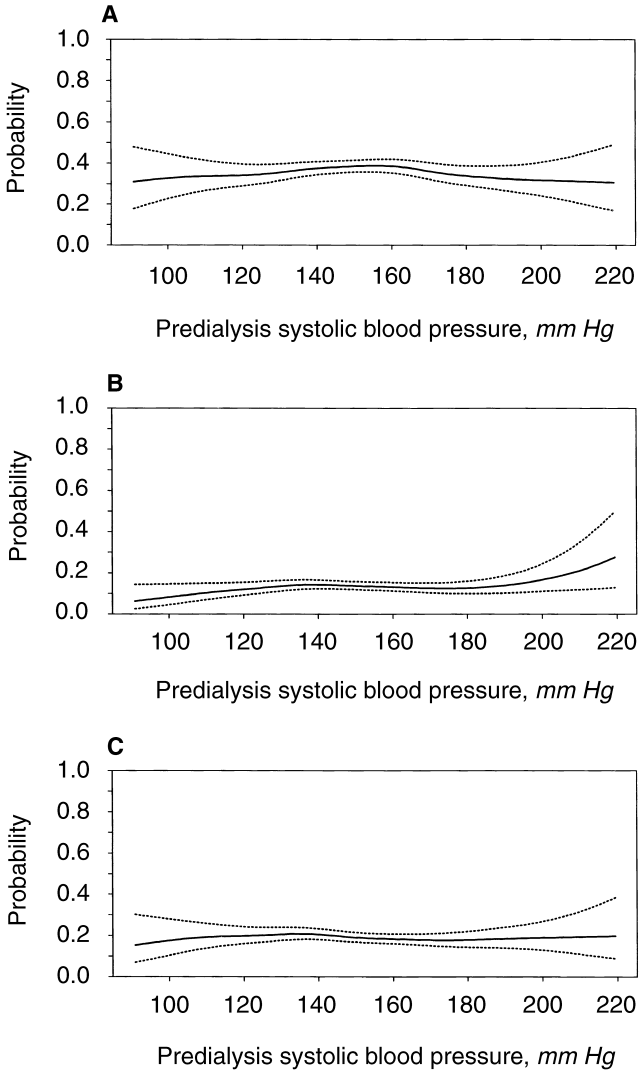

Fig. 4. Relationship between predialysis systolic blood pressure and probability of having coronary heart disease (*A*), cerebrovascular disease (*B*), and peripheral vascular disease (*C*). The probabilities are adjusted for all other covariates described in the **Methods** section, including duration of dialysis and different dialysis centers. The broken lines represent 95% confidence intervals. There is no statistically significant linear or nonlinear relationship between predialysis systolic blood pressure and the natural logarithm of the odds of developing any of the three types of atherosclerotic diseases.

tolic blood pressure (Table 5 and Fig. 4) and the presence of atherosclerotic cardiovascular diseases, despite the well-established effects of serum total cholesterol and systolic blood pressure in the general population [18, 19]. Coincidentally, the results of the present study on cholesterol and blood pressure are not inconsistent with those in other cohort studies. Lowrie and Lew used logistic regression to evaluate the relative risk of hypercholesterolemia in 12,000 hemodialysis patients [5]. They noted a significantly increased overall mortality risk for total serum cholesterol levels at 150 to 200 mg/dL, compared with the risk for cholesterol levels at 200 to 250 mg/dL. The risk continued to increase as the cholesterol levels decreased. This is distinctly different from the relationship in the general population, in which cardiovascular mortality decreases continuously as total cholesterol level decreases from 200 to 240 mg/dL to a level of approximately 140 mg/dL [18]. The argument can be made that a low cholesterol level is an indicator of malnutrition and confounds the risk factor analysis. However, it remains difficult to reconcile the observation that total cholesterol values between 150 and 200 mg/dL (relatively normal values in the general population) should be associated with malnutrition in the hemodialysis population.

Table 6. Prevalence of atherosclerotic cardiovascular diseases according to primary renal diagnosis

	N	Coronary heart disease	Cerebrovascular disease	Peripheral vascular disease
Diabetic nephropathy	326	51%	24%	36%
Hypertensive nephrosclerosis	298	39%	19%	16%
Glomerular diseases	141	27%	18%	13%
Others	143	32%	13%	20%
Overall	908[a]	40%	19%	23%

[a] Of the 936 patients in the study, 908 had a primary renal diagnosis, while 28 were classified as unknown and were excluded from this table

Table 7. Hypothetical risk of development of de novo coronary heart disease in the HEMO Study cohort based on their coronary scores as defined in the Framingham Study[a]

	Male			Female		
	HEMO Study		Framingham	HEMO Study		Framingham
Age group	*N*[b]	Risk[c]	Risk[d]	*N*[b]	Risk[c]	Risk[d]
30–39 years	30	0.9	1.0	28	0.3	NA
40–49 years	56	3.6	4.4	43	1.6	0.9
50–59 years	45	8.3	9.5	40	3.2	3.6
60–69 years	29	13.0	11.6	70	9.0	7.5
70–74 years	13	14.3	NA[e]	17	11.7	NA[e]

[a] By definition, only patients without any evidence of coronary heart disease, cerebrovascular disease, and peripheral vascular disease are included in this analysis. The variables employed to calculate the coronary score in the Framingham Heart Study were age, gender, diabetic status, systolic blood pressure, serum total cholesterol, left ventricular hypertrophy by electrocardiography, and smoking status [24]. The hypothetical risks of developing de novo coronary heart disease over 6 years in the HEMO Study cohort were calculated based on these patients' actual coronary scores. In other words, these were the calculated risks for the HEMO Study patients if they were nonuremic subjects, but not their actual risks. The results show that, based on their coronary scores, HEMO Study patients did not have significantly higher risk of developing coronary heart disease than the general population

[b] Number of patients in the HEMO Study cohort who did not have any evidence of coronary heart disease, cerebrovascular disease, and peripheral vascular disease, categorized according to age

[c] Calculated probabilities of developing de novo coronary heart disease over 6 years in the HEMO Study patients, based on their coronary point scores. These were not their actual probabilities

[d] Probabilities of developing coronary heart disease over 6 years in the Framingham Study estimated from published tables [25]

[e] Data not available

An unconventional relationship between predialysis systolic blood pressure and outcome has also been reported by Port et al [20] and Zager et al [6]. Analyzing data from 4839 chronic hemodialysis patients in the Case Mix Adequacy Study of the U.S. Renal Data System using Cox regression models, Port et al found that higher predialysis systolic blood pressure (from 150 to >180 mm Hg) was not associated with higher mortality risk. When predialysis systolic blood pressure decreased below the reference group (120 to 149 mm Hg), however, relative mortality risk increased and reached statistically significant values at pressures below 110 mm Hg. Using Cox regression analysis with fixed and time-varying covariables, Zager et al found a "U"-shaped relationship between systolic blood pressure and cardiovascular mortality. Of interest was that systolic blood pressure in the range of 160 to 179 mm Hg was associated with the lowest mortality. This is distinctly different from the monophasic curve commonly seen in the general population [21] and nondialysis patients with underlying ischemic heart disease [22]. One may hypothesize that low blood pressure is an indicator of cardiomyopathy, which may confound the risk factor analysis. It remains necessary to reconcile that systolic blood pressure values between 120 and 140 mm Hg (a relatively normal value in the general population) reflect cardiomyopathy in the hemodialysis population. A caveat that should be kept in mind is that the blood pressures reported in the present study and many other studies were predialysis values. Postdialysis and interdialytic blood pressures were likely to be different from predialysis values. Data regarding the impact of blood pressure at these various time points on clinical outcome are limited [6, 20].

It should also be noted that the outcome measure used in the previously mentioned studies varied. Total mortality was the outcome measure in the study of Lowrie and Lew for cholesterol [5] and the study of Port et al for blood pressure [20]. Cardiovascular mortality was the outcome measure in the study of Zager et al for blood pressure [6], while three individual types of nonfatal atherosclerotic cardiovascular events were the outcome measures in the present study.

Cerebrovascular diseases

Studies using cerebrovascular events as clinical outcomes are very limited. Iseki and Fukiyama reported a positive association of predialysis systolic blood pressure, but not age and smoking, with stroke in a Japanese

chronic hemodialysis population [23]. In contrast, we found an association between age or smoking, but not predialysis systolic blood pressure, and cerebrovascular disease (Table 5).

Coronary scores in the HEMO Study cohort and the Framingham cohort

The unconventional associations between serum total cholesterol level or blood pressure and cardiovascular events described previously in this article suggest that traditional coronary risk factors may not be sufficient to explain the extent of cardiovascular diseases in the hemodialysis population. This hypothesis is supported by further analyses in which the coronary point scores in our HEMO Study cohort were compared with those in the Framingham Study cohort (Table 7). The coronary point score was devised to assess the potential risk of nonuremic subjects in developing de novo coronary heart disease [24]. The variables used to generate the score were age, gender, diabetic status, smoking status, serum total cholesterol level, systolic blood pressure, and left ventricular hypertrophy by electrocardiography. Using this scoring system, we computed the projected risk of developing coronary heart disease in a subset of our HEMO Study cohort who did not have a history of any atherosclerotic cardiovascular disease at baseline and compared the results to the published data on the Framingham population.

As seen in Table 7, the risks of developing de novo coronary heart disease in six years for each age group in our HEMO Study subset, as predicted by traditional coronary point scores, were similar to those in the Framingham study participants predicted by the same scoring system [25]. Although longitudinal data on our HEMO Study patients are currently not available, it has been well established that the incidence and prevalence of coronary heart disease in similar populations are at least severalfold greater [12, 26, 27], and the cardiovascular mortality is 10- to 20-fold greater [28] than those in the general population. Taken together, these findings strongly suggest that the traditional coronary risk factors are insufficient to account for the coronary heart diseases in chronic hemodialysis patients. Other factors, such as hyperhomocysteinemia, accumulation of lipoprotein remnants and lipoprotein(a), hyperparathyroidism, yet undefined uremic toxins and other uremic factors, are likely to be significant contributors.

Limitations of the study

Although the results presented herein may lead to various speculations, one should not conclude that high blood pressure or high cholesterol levels are not risk factors for cardiovascular diseases in chronic hemodialysis patients. The present study is cross-sectional in nature, and such studies have several inherent limitations that may bias the results. First, there might be a survival bias, in that the patients with the highest serum total cholesterol levels and highest blood pressure might have already died and therefore could not be enrolled in the study. Second, a cause versus effect bias might exist. In this scenario, hypertension and hypercholesterolemia might have been risk factors for the development of atherosclerotic cardiovascular diseases, but as a result of these diseases, malnutrition and cardiomyopathy developed, which, in turn, lowered the levels of serum cholesterol and blood pressure, respectively. Third, there could have been a treatment effect. According to this hypothesis, modifiable risk factors such as hypercholesterolemia and hypertension could have been treated more aggressively once the diagnosis of cardiovascular diseases had been made. Consequently, at the time of the analysis, these risk factors no longer correlated with the diseases.

It should further be cautioned that even though we label these cardiovascular diseases in the hemodialysis patients as atherosclerotic, the exact histology of the lesions in their blood vessels may be different from those in nonuremic subjects.

Conclusions

In conclusion, we found a high prevalence of atherosclerotic cardiovascular diseases in the chronic hemodialysis patients. Several of the traditional coronary risk factors in the general population appear to be applicable to the hemodialysis population. The levels of serum total cholesterol and systolic blood pressure, however, did not bear the same relationship to atherosclerotic cardiovascular diseases in the hemodialysis population as they do in the general population or as in the two recent reports in chronic hemodialysis patients [5, 6]. The risk factors for coronary heart disease, cerebrovascular disease, and peripheral vascular disease may also differ from each other. Long-term prospective and interventional studies are urgently needed to clarify the impact of serum cholesterol, blood pressure, other traditional risk factors, more recently described risk factors, uremia-related factors, and perhaps hemodialysis-specific risk factors on cardiovascular events in this population.

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