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Original Article

Title:

Prevalence of earlobe creases and their association with history of cardiovascular disease in patients undergoing hemodialysis: a cross-sectional study

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Running Head: Earlobe creases in hemodialysis patients

Abstract

Introduction

Earlobe creases are surrogate markers for high risk of cardiovascular disease. There is no data concerning earlobe creases among hemodialysis patients, who have an increased risk of cardiovascular disease. A cross-sectional study was conducted to determine the prevalence of earlobe creases and their association with prevalent cardiovascular disease among hemodialysis patients.

Methods

Patients undergoing hemodialysis were recruited from five outpatient hemodialysis centers. Both earlobes were photographed during a dialysis session with the patient in a supine position and the photos evaluated independently by two experienced nephrologists blinded to the participants' clinical characteristics. Prevalent cardiovascular diseases were defined as a history of myocardial infarction, cerebrovascular accident, or peripheral vascular disease. Sensitivity, specificity, and positive and negative predictive values for detection of prevalent cardiovascular disease were calculated. Logistic analysis was used to examine the association between earlobe creases and prevalent cardiovascular disease.

Findings

Earlobe creases were identified in 24.5% of 330 hemodialysis patients (200 men; mean age, 67.8 years). The prevalence of earlobe creases increased with age for men (*P* for trend < 0.0001), but not for women (*P* for trend = 0.07). Sensitivity, specificity, and positive and negative predictive values were 30.9% (95% confidence interval, 21.9–41.6), 77.5% (71.9–82.3), 30.9% (21.9–41.6), and 77.5% (71.9–82.3), respectively. Multivariate logistic analyses indicated the prevalence of earlobe crease was not

associated with prevalent cardiovascular diseases.

Discussion

The prevalence is similar to that previously reported for Japanese individuals not undergoing dialysis. No association between earlobe creases and prevalent cardiovascular diseases was identified.

Key words: cardiovascular diseases, earlobe crease, epidemiology, hemodialysis patients.

Introduction

Earlobe creases (ELCs), also called Frank's sign, are diagonal folds or wrinkles in the skin of the earlobe. They have been identified as surrogate markers for individuals at high risk of cardiovascular disease (CVD).[1] ELCs were first reported to be associated with coronary artery disease in 1973.[2] Since then, ELCs have been found to be markers not only for coronary artery disease but also for generalized atherosclerosis.[3, 4] Some studies have found no independent association between ELCs and CVD and suggested they are simply markers of advanced age[5]; however, ELCs may have still have potential as clinically useful predictors of CVD because independent association is not necessary to predict risks.

To our knowledge, no studies have documented the prevalence of ELCs and the utility of checking for them among individuals undergoing hemodialysis, despite their higher risk of developing CVD. The cardiovascular death rate is 5 to 500 times higher depending on the age group than that of the general population in both the USA and Japan.[6, 7]

Using baseline data collected from our ongoing prospective study, we conducted a cross-sectional analysis to determine the prevalence of ELCs and evaluate the relationship between them and prevalent CVD. We also calculated sensitivity, specificity, and positive and negative predictive values for detection of prevalent CVD.

Materials and Methods

Study participants

Individuals undergoing hemodialysis were recruited from five outpatient hemodialysis centers in Niigata, Japan, between February and November 2012. Eligibility criteria comprised receiving maintenance hemodialysis three times a week and capable of understanding and signing written informed consent to participate in the study. Potential participants were excluded if they had ear piercings. All participants gave written informed consent to participate in the study. This study was conducted in compliance with the 'Declaration of Helsinki' and approved by the Ethics Committee of the Institutional Review Board at Niigata University Graduate School of Medicine.

Assessment of Outcomes

The primary outcome was prevalent CVD, which was defined as a history of a clinically or electrocardiographically proven myocardial infarction, cerebrovascular accident, or peripheral vascular disease requiring aortic or peripheral vascular bypass surgery or a below- or above-the knee amputation. Information about prevalent CVD was obtained by examining the participants' medical charts.

Presence of ELCs and Covariates

Both earlobes of each individual were photographed in a supine position during a dialysis session using a digital camera (Olympus E-PL2, Olympus Imaging, Tokyo, Japan) by one researcher (M.W.). The presence of ELCs was determined by two independent observers (J.K. and K.K.) who were blinded to the clinical characteristics of the participants and reviewed the photos independently. In cases of disagreement, consensus was established with a third observer (S.Y.). ELCs were defined as total ELC score for both ears ≥3 according to a previously reported grading method.[3, 8] In brief, a deep, clear-cut ELC that extends across the entire earlobe scored two points, an ELC that is superficial or does not extend all the way across the earlobe scores one point, and no ELC scores zero. Photos of typical examples of each grade are shown in Figure 1.

Clinical data such as cause of end-stage kidney disease (ESKD) and medical histories were obtained from the patient medical records. Smoking was defined as the current daily use of cigarettes. Dialysis vintage was calculated from the time of first-ever dialysis to the day when the earlobes were digitally photographed. Diabetes mellitus was defined as having a diabetes diagnosis or filling a prescription for a diabetes medication. Laboratory data, which were measured at the first dialysis session in a week, were obtained from the patient medical records. Non-high-density lipoprotein (HDL) cholesterol was calculated as total cholesterol concentration minus

HDL-cholesterol concentration and dyslipidemia was defined as serum non–HDL-C <130 mg/dL (<3.36 mmol/L) in accordance with Kidney Disease Outcome Qualities Initiative (K/DOQI) guidelines[9].

Statistical Analysis

First, to assess the interobserver reliability for identifying ELCs, percent and the kappa statistic, which is the commonly used statistic for evaluating agreement between two or more observations,[10] were calculated and categorized as slight (κ = 0.00 to 0.20), fair (κ = 0.21 to 0.40), moderate (κ = 0.41 to 0.60), substantial (κ = 0.61 to 0.80), and almost perfect ($\kappa > 0.80$).[11] The 95% confidence intervals (CIs) for the agreement were calculated with exact computation from the binomial distribution and those for kappa with the customary normal approximation.[12] When there were fewer than three positive or negative findings with either method, kappa or CIs for the agreement were not calculated.[13]

Next, the prevalence of ELC stratified by sex and age categories was calculated. These are reported as percentages; with 95% CIs computed using the Poisson approximation. Age was categorized into five groups: <50, 50–59, 60–69, 70–79, and ≥80 years. The prevalence of ELCs stratified by the age categories was evaluated using

a nonparametric test of trend for the ranks across ordered groups (using nptrend Stata command).

Finally, the association between the prevalence of ELC and prevalent CVD was assessed and sensitivity, specificity, and positive and negative predictive values for detection of the prevalence of CVD calculated. The 95% CIs were calculated using Wilson's method.[14] Characteristics stratified by presence or absence of ELCs were compared using either the χ^2-test, analysis of variance (ANOVA), or the Mann–Whitney U test, as appropriate. Multivariate logistic analysis was used to examine the association between the prevalence of ELC and prevalent CVD. Sequential multivariate modeling was performed in which crude estimates were initially adjusted for age and sex (Model 1), then adjusted for dialysis vintage and cause of ESKD (Model 2), and then adjusted for the variables in Model 1 plus serum albumin concentrations, dyslipidemia, and C-reactive protein (CRP) concentrations (Model 3). Skewed data, such as dialysis vintage and CRP, were transformed into natural logarithmic or square root values as appropriate. A P value of <0.05 was considered to indicate statistical significance and all tests were two-tailed. All statistical analyses were performed with SPSS for Windows statistical package (Version 18.0; SPSS, Chicago, IL, USA) and Stata/MP software (Version 12.1; Stata, College Station, TX, USA).

Results

Three hundred and thirty-six of the 354 hemodialysis patients whom we asked to participate gave their consent (Figure 2). We excluded six of them because they had ear piercings. The remaining 330 patients were included in this analysis (participation rate, 93.2%).

Our study participants were similar in age to all dialysis patients as of 31 December 2012 in Japan, [15, 16] with the exceptions of including a lower proportion of men and having a longer dialysis vintage. Additionally, chronic glomerulonephritis was more common as primary cause of ESKD and prevalences of prior cerebral infarction and cerebral bleeding were lower in our study (Table 1).

Interobserver reliability for identifying ELCs

The interobserver agreement for identifying ELCs was 86% and the kappa statistic 0.67 (95% CI, 0.56–0.78). We considered this κ statistic to represent moderate agreement in accordance with the interpretation of the κ statistic reported by Landis and Koch.[11]

Prevalence of ELCs

Eighty-one of the 330 participants (24.5%) had ELCs. The prevalence increased significantly with age in men ($P < 0.0001$) but not in women ($P = 0.07$) (Figure 3).

Associations between ELCs and CVD

Table 2 shows the participants' clinical characteristics stratified by presence or absence of ELCs. Patients with ELCs were more likely to be older, male, and to have a

shorter dialysis vintage and lower serum albumin and HDL cholesterol concentrations. Diabetes and nephrosclerosis were more common as primary causes of ESKD.

Of the 330 individuals undergoing hemodialysis, 81 (24.5%) had a history of CVD. The sensitivity, specificity, and positive and negative predictive values for prevalence of CVD were 30.9% (95% CI, 21.9–41.6), 77.5% (95% CI, 71.9–82.3), 30.9% (95% CI, 21.9–41.6), and 77.5% (95% CI, 71.9–82.3), respectively. When stratified by sex, the sensitivity, specificity, and positive and negative predictive values for male and female patients were 41.5% (95% CI, 29.3–54.9) and 10.7% (95% CI, 3.7–27.2), 74.1% (95% CI, 66.5–80.5) and 82.4% (95% CI, 73.8–88.5), 36.7% (95% CI, 25.6–49.3) and 14.3% (95% CI, 5.0–34.6), and 77.9% (95% CI, 70.3–83.9) and 77.1% (95% CI, 68.3–84.0), respectively.

Both unadjusted and multivariate adjusted logistic regression models showed that the prevalence of ELC was not significantly associated with prevalent CVD (Table 3).

Discussion

In this study, we examined the prevalence of ELCs and its relationship with prevalent CVD in individuals undergoing hemodialysis, who are known to be high-risk patients for CVD. This study provides two new insights. First, the prevalence of ELC among Japanese individuals undergoing hemodialysis was 24.5%. Second, ELCs were not associated with higher risk of prevalent CVD in our cohort.

The first important finding of this study is that 24.5% of Japanese individuals undergoing hemodialysis have ELCs, which is a similar prevalence to that reported for Japanese individuals not undergoing dialysis. The prevalence of ELC was reportedly 32.8% in 100 forensic autopsies of men aged from 50 to 79 years who died free of vascular diseases or related conditions.[3] In another study, the prevalence of ELCs on pre-operative assessment was 23.2% in 530 patients aged 40 years or older who were undergoing elective surgery, excluding coronary artery bypass grafting.[17] A cross-sectional study of 212 consecutive patients (mean age 67±12 years, 48.1% male) who underwent clinically indicated ultrasonographic examination of the extracranial carotid artery systems reported a prevalence of ELC of 28.8%. [18] Although the age and sex distribution of the participants and the methods for evaluating ELCs differed between these studies, these findings suggest that despite their higher risks of developing CVD, the prevalence of ELC would likely not be significantly higher in individuals undergoing hemodialysis than in those not undergoing dialysis. It is possible that survivor bias reduced the prevalence of ELCs in our cohort; if individuals with ELCs are at higher risk of CVD than those without them, those with ELC would also be at higher risk of mortality, which would decrease their prevalence.

The second important finding of this study is that individuals with ELCs undergoing hemodialysis are not at higher risk of prevalent CVD than those without ELCs. Furthermore, sensitivity and positive predictive value for detection of prevalent CVD were low, suggesting that ELC is not a good surrogate marker for identifying individuals at high risk of having occult atherosclerosis in a cohort of persons undergoing hemodialysis.

Why is there no association between ELCs and prevalent CVD in individuals undergoing hemodialysis? There are several possible explanations. First, survivor bias may have affected the results of this cross-sectional study. As stated earlier, if patients with ELCs are at higher risks of CVD than those without ELCs, those with ELCs would also be at higher risk of mortality, which would decrease their prevalence. Second, although the mechanisms leading to the concurrent development of ELC and CVD are uncertain,[5, 19] substantial differences in risk factors for CVD between individuals undergoing hemodialysis and the general population may have affected this association. While some traditional risk factors in the general population, such as obesity and high serum cholesterol concentrations, are not especially relevant for individuals undergoing hemodialysis, non-traditional risk factors specific to ESKD patients, such as disturbed mineral–bone homeostasis, uremic toxins, anemia, oxidative stress, and protein energy wasting, are strongly relevant to these individuals.[20] A previous study showed that traditional risk factors explain only half of all-cause and cardiovascular mortality variations in individuals with ESKD.[21] Traditional risk factors rather than non-traditional factors may be closely associated with development of ELC, which would explain why the association between ELCs and prevalent CVD was not significant in this study.

The present study has several limitations. First, we evaluated ELC in the supine position because all dialysis patients in this study received hemodialysis in bed, which is preferred over being in chair in Japanese dialysis facilities. Because the appearance of ELCs can change markedly with position,[22] the prevalence of ELCs may change according to position. Second, we did not evaluate possible differences, which remain controversial,[23] between unilateral and bilateral ELCs, depth of creases, and ratio of ELC to earlobe length. However, our definition of ELC has moderate kappa statistics.

Despite these limitations, this study has several strengths. First, to our knowledge, this is the first report concerning the prevalence of ELC in individuals with ESKD. Addition, we believe we are the first to examine the association between ELCs and prevalent CVD in individuals with ESKD. Although we found no significant association between ELC and history of CVD, this easily detectable sign may be useful in clinical practice, possibly enabling clinician to add new and valuable information to their patients' risk profiles in other countries, given that the prevalence of ELC differs by race. A previous cross-sectional study using Mag shot demonstrated that Chinese individuals had a lower prevalence of ELCs than White, Black, or Latin-American participants.[24] Thus, the prevalence of ELC and its associations may differ in other cohorts of individuals undergoing dialysis. Because ELCs are easily detectable, their prevalence and associations among such individuals should be evaluated in other geographical areas.

Conclusions

This study is the first to report the prevalence of ELCs among individuals undergoing hemodialysis and to fail to identify an association between ELCs and prevalent CVD.

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Conflict of Interest

All authors declare they have no competing interests.

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Figure Legends

Figure 1. Photos of typical examples of each grade of ear lobe crease

A, B, and C show representative examples of 0, 1, 2 scores, respectively, in ear lobe crease (ELC) grading. A: no points, no ELC observed. B: one point, superficial ELC or one that does not extend all the way across the earlobe. C: two points, a deep, clear-cut ELC extending across the entire earlobe.

Figure 2. Flow chart showing selection of study participants

Three hundred and thirty-six of the 354 individuals undergoing hemodialysis whom we asked to participate consented. After excluding six of them because of ear piercings, 330 patients were eligible for this analysis (participation rate, 93.2%).

Figure 3. Prevalence of earlobe creases stratified by age and sex

Trends are significant for men (■; $P < 0.0001$) but not women (□; $P = 0.07$).

Table 1. Clinical characteristics of study versus all patients undergoing hemodialysis as of 31 December 2012 in Japan

Characteristic	Study participants (N=330)	All hemodialysis patients in Japan[†] (N=268,275)
Age, years	67.8 (11.0)	67.3 (12.4)
Male sex, %	60.6	63.4
Duration of dialysis, years	10.1 (9.4)	6.83 (6.93)
Cause of end-stage kidney disease		
Glomerulonephritis, %	43.3	32.4
Diabetes, %	28.2	38.4
Nephrosclerosis, %	13.6	8.4
Polycystic kidneys, %	3.3	3.5
Prior ischemic heart disease, %	9.4	NA
Prior myocardial infarction, %	NA	9.5
Prior cerebral infarction, %	12.8	18.4
Prior cerebral bleeding, %	3.7	6.0

Values are presented as mean (standard deviation) for continuous variables and percentage for categorical variables.

NA = not available.

[†] Derived from data provided in References 15 and 16.

Table 2. Clinical characteristics of 330 individuals undergoing hemodialysis stratified by presence or absence of earlobe creases

	Earlobe crease		
Characteristics	Present (*n*=81 [24.5%])	Absent (*n*=249 [75.5%])	*P* value
Age, years	73.6 (7.9)	66.0 (11.3)	<0.0001
Male, *n* (%)	60 (74.1)	140 (56.2)	0.004
Current smoker, *n* (%)	14 (17.3)	37 (14.9)	0.60
Body mass index, kg/m^2	22.1 (3.5)	22.4 (4.0)	0.67
Duration of dialysis, years	5.0 (2.9, 9.3)	7.6 (3.1, 15.9)	0.01
Cause of end-stage kidney disease			0.002
Glomerulonephritis, *n* (%)	26 (32.1)	117 (47.0)	
Diabetes, *n* (%)	29 (35.8)	64 (25.7)	
Nephrosclerosis, *n* (%)	18 (22.2)	27 (10.8)	
Polycystic kidneys, *n* (%)	4 (4.9)	7 (2.8)	
Medical history			
Cardiovascular disease, *n* (%)	25 (30.9)	56 (22.5)	0.14
Diabetes, *n* (%)	30 (37.0)	69 (27.7)	0.13
Laboratory variables			
Hemoglobin, g/dL	10.2 (1.2)	10.4 (1.2)	0.23
Serum albumin, g/dL	3.6 (0.5)	3.8 (0.5)	0.01
HDL cholesterol, mg/dl	44 (14)	48 (16)	0.03
Non-HDL cholesterol, mg/dl	99 (81, 126)	114 (90, 131)	0.05
C-reactive protein, mg/dL	0.10 (0.03, 0.35)	0.69 (0.03, 0.75)	0.15

Data are presented as number (%), mean (SD) or median (25th, 75th percentiles) as appropriate.

HDL = high-density lipoprotein.

Table 3. Multivariate analysis of the relation between presence of earlobe creases and history of cardiovascular disease

Variable	Unadjusted	Model 1 Odds ratio (95% CI)	Model 2 Odds ratio (95% CI)	Model 3 Odds ratio (95%CI)
Presence of earlobe crease	1.53 (0.88, 2.67)	1.08 (0.59, 1.98)	0.97 (0.52, 1.82)	1.18 (0.63, 2.20)
Age		1.04 (1.01, 1.07)*	1.05 (1.02, 1.08)*	1.05 (1.01, 1.09)*
Male sex		1.45 (0.83, 2.51)	1.60 (0.90, 2.52)	1.51 (0.82, 2.76)
Square root of dialysis vintage			1.36 (1.08, 1.72)*	
Cause of end-stage kidney disease				
Glomerulonephritis			1.00	
Diabetes			3.65 (1.72, 7.74)*	
Nephrosclerosis			2.17 (0.90, 5.23)	
Polycystic kidneys			3.48 (0.88, 13.7)	
Serum albumin				1.61(0.87, 2.98)
Dyslipidemia				0.99 (0.83, 1.20)
Natural log C-reactive protein				1.09 (0.90, 1.32)

Model 1 adjusted for age and sex.

Model 2 further adjusted for by dialysis vintage and cause of end-stage kidney disease.

Model 3: Model 1 further adjusted for serum albumin, dyslipidemia, and C-reactive protein.

Skewed data, such as dialysis vintage and C-reactive protein, were transformed into natural logarithmic or square root values as appropriate.

*$P < 0.01$.