Fatty Acids and Other Risk Factors for Sudden Cardiac Death in Patients Starting Hemodialysis

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Key Words

Omega-3 · Fatty acids · Sudden cardiac death · Hemodialysis · Incident · Risk factors · Nutrition · Cardiovascular disease

Abstract

Background: Little is known about risk factors for sudden cardiac death in hemodialysis patients during the high-risk first year of dialysis. We therefore undertook to identify such risk factors in a nationally representative cohort and were able to include baseline levels of blood fatty acids, some of which influence arrhythmogenicity and sudden cardiac death risk.

Design: The study cohort included 100 patients who died of sudden cardiac death during the first year of hemodialysis and 300 frequency-matched controls. Using the elastic net statistical method, numerous demographic and clinical characteristics were included with baseline total serum levels for 11 major fatty acids (model 1) and with serum phospholipid fractions of these same fatty acids (model 2). Final models included only covariates that had a non-zero coefficient. **Results:** In model 1, serum albumin [odds ratio (95% CI): 0.55 (0.33–0.93); $p = 0.03$] and total serum long-chain $n-3$ docosapentaenoic acid [0.70 (0.51–0.97); $p = 0.03$] were inversely associated with the odds of sudden cardiac death, while the

total serum saturated fatty acid level had a direct association [1.01 (1.00–1.02); $p = 0.03$]. In model 2, serum albumin and docosapentaenoic acid remained inversely associated with sudden cardiac death in a similar manner as in model 1. Pulse pressure also had an inverse association [0.96 (0.93–1.00); $p < 0.05$]. **Conclusions:** Several factors, including blood content of docosapentaenoic acid and saturated fatty acids, were associated with the odds of sudden cardiac death during year one of hemodialysis. These results raise the possibility that dietary modification may reduce sudden death risk.

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Introduction

Sudden cardiac death is the single most common cause of mortality in the hemodialysis population, accounting for approximately one quarter of all deaths [1]. While the rate of sudden cardiac death in hemodialysis patients has slowly fallen in recent years along with overall mortality [1], more substantial reductions remain hampered by our limited understanding of the underlying pathophysiology and need to identify causative factors.

Over the past several years, numerous investigations performed in various dialysis populations have attempted

to identify risk factors for sudden cardiac death [2–11]. Of these, only one [8] focused on the early period after initiation of hemodialysis when mortality risk is highest [12] and none studied a cohort that was representative of the overall US hemodialysis population. In addition, none included dietary factors such as serum fatty acids that could account for risk. This is important because several fatty acids have been associated with sudden cardiac death in the general population, each of which is modifiable by changes in dietary intake. By far the most prominent of these are long-chain n–3 polyunsaturated fatty acids (LCn–3 PUFA) which have been touted for their cardioprotective and anti-arrhythmic benefits. A number of large, well-designed randomized trials have reported that LCn–3 PUFA supplementation lower the risk of cardiovascular events and sudden cardiac death [13–16], though not all studies are in agreement [17–21]. In the first study of its kind, we recently demonstrated that LCn–3 PUFA are strongly, inversely, and independently associated with risk of sudden cardiac death in an incident population of hemodialysis patients [22].

To expand on this work, we endeavored to identify all independent risk factors for sudden cardiac death in a large representative cohort of US hemodialysis patients who were followed over the first year of dialysis. We were able to include blood fatty acid levels in the analysis and hypothesized that LCn–3 PUFA and perhaps other fatty acids would be among the identified associated factors.

Methods

Study Population and Collection of Serum Samples

The complete methods have been published previously [23]. All study subjects participated in the Accelerated Mortality on Renal Replacement (ArMORR) project, a nationally representative prospective cohort study of patients who initiated chronic hemodialysis at any one of over 1,000 US dialysis centers operated by Fresenius Medical Care, North America, between July 1, 2004, and June 30, 2005. 10,044 incident hemodialysis patients representing 1,056 US dialysis units were prospectively enrolled into ArMORR. ArMORR contains detailed demographic and clinical data, including comorbid conditions, laboratory results, and blood samples at the time of dialysis initiation. All clinical data were collected prospectively and entered uniformly into a central database by the patients' practitioners at the point-of-care based on medical records and physical examination. Blood samples collected for clinical care were drawn at individual dialysis units and shipped the same day on ice to Spectra East (Rockland, N.J., USA), a good clinical practice-accredited central laboratory. After blood was extracted for clinical testing, the remaining serum was immediately placed in new tubes, frozen at –80°C, and sent to ArMORR investigators where the samples were aliquotted and immediately stored at –80°C (and subsequently liquid nitrogen). Serum fatty acids

remain stable for years when stored in this manner [24]. This study was approved by the Institutional Review Board of the Massachusetts General Hospital, Boston, Mass., USA, which waived the need for informed consent.

Identification of Patients Dying of Sudden Cardiac Death and Controls

Sudden cardiac death events in ArMORR were defined as deaths occurring (1) out of hospital that were (2) identified by International Classification of Diseases (ICD)-9 diagnosis codes for 'cardiac arrest' (ICD-9: 427.5) and 'sudden death, cause unknown' (ICD-9: 798.1, 798.2, 798.9) [25]. The ICD-9 codes, frequently used to study sudden cardiac death in dialysis patients [8, 26, 27], were documented by the subject's health care providers at the time of death on a dialysis unit mandatory discharge form. The convenience sample we studied included 100 patients who died from sudden cardiac death within 1 year of initiating hemodialysis and 300 hemodialysis patients who survived the first year of dialysis (controls) who were frequency matched by age, gender, and race in a random fashion [23]. Characteristics for each of the case and control cohorts have previously been published [22, 23].

Laboratory Analysis

Biochemical assays were performed at the Spectra East laboratory using standard assays as previously described [28]. Serum was used to determine fatty acid amounts in various lipid fractions in a blinded fashion at the University of Connecticut using gas chromatography and solid-phase extraction techniques [23]. Results of the fatty acid methyl ester analysis were obtained by area percentage reports and reported in weight percent. In addition to individual fatty acids, we also reported composite fatty acids as the following area percent: LCn–3 PUFA included 20:5 n–3 [eicosapentaenoic acid (EPA)] + 22:5 n–3 [docosapentaenoic acid (DPA)] + 22:6 n–3 [docosahexaenoic acid (DHA)]; LCn–6 PUFA included 20:4 n–6 (arachidonic acid) + 22:4 n–6 + 22:5 n–6; saturated fatty acids included 16:0 + 18:0; monounsaturated fatty acids included 16:1 n–7 + 18:1 n–9 + 18:1 n–7, and polyunsaturated fatty acids included LCn–3 PUFA + LCn–6 PUFA.

Statistical Analysis

Patients' characteristics were summarized using mean and standard deviation for continuous variables and frequency and proportion for categorical variables. The weight percentages of fatty acids were summarized using the median (25th, 75th percentile) due to skewed distribution. To identify the risk factors or predictors of sudden cardiac death we used the well-established LASSO (least absolute shrinkage and selection operator) type method (elastic net) [29] for variable selection in a logistic regression model with sudden cardiac death as the response variable. In contrast to the stepwise regression method, the elastic net method does not require a subjectively selected p value threshold and accommodates the selection of correlated covariates. We first ran a model (model 1) with 11 serum total fatty acids [monounsaturated, saturated, *trans*, α -linolenic (18:2 n–6), arachidonic (20:4 n–6), 22:4 n–6, 22:5 n–6, linoleic (18:3 n–3), eicosapentaenoic (20:5 n–3), docosapentaenoic (22:5 n–3), and docosahexaenoic (22:6 n–3)] and the following covariates: demographics (age, gender, race, ethnicity); body mass index; diabetes as cause of end-stage renal disease (yes/no); medical problems (a history of coronary artery disease or myocardial infarction, peripheral vascular disease, stroke,

Table 1. Baseline characteristics

	Study population (n = 400)
Age, years	66.4±14.1
Male	232 (58.0)
Race	
Black	124 (31.0)
White	272 (68.0)
Other	4 (1.0)
Ethnicity	
Non-Hispanic	352 (88)
Hispanic	48 (12)
Body mass index	26.2±6.8
Cause of end-stage renal disease	
Diabetes	186 (46.5)
Other	214 (53.5)
Comorbidities	
Hypertension	149 (37.3)
Coronary artery disease/myocardial infarction	46 (11.5)
Peripheral vascular disease	20 (5.0)
Congestive heart failure	50 (12.5)
Atrial fibrillation	13 (3.3)
Stroke	15 (3.8)
Initial type of vascular access	
First access fistula	120 (31.1)
First access graft	44 (14.3)
First access catheter	211 (54.7)
Systolic blood pressure, mm Hg	142.8±23.0
Diastolic blood pressure, mm Hg	72.6±12.4
Medications	
ACE inhibitor or ARB	169 (42.3)
β-Blocker	243 (60.8)
Aspirin	129 (32.3)
Statin	159 (39.8)
Predialysis laboratory values	
Serum albumin, g/dl	3.5±0.5
Serum cholesterol, mg/dl	150.6±46.0
Serum creatinine, mg/dl	6.1±2.6
Serum ferritin, ng/ml	328.3±583.2
Serum phosphorus, mg/dl	4.6±1.6
Serum potassium, mEq/l	4.3±0.6
Serum calcium, mg/dl	8.4±0.8
Serum PTH, pg/ml	263.1±299.4
Serum alkaline phosphatase, units/l	100.3±71.3
Serum glucose, mg/dl	157.8±78.5
Hemoglobin, g/dl	10.3±1.4
White blood cells (×10 ³ /μl)	8.4±3.3

Figures indicate means ± standard deviations or numbers with percentages in parentheses. Reprinted with permission from reference 23 and S. Karger AG.

Table 2. Serum fatty acid levels in the study cohort

Fatty acid	Total
<i>Saturated</i>	
16:0	20.2 (19.2, 21.4)
18:0	6.8 (6.2, 7.5)
<i>Monounsaturated</i>	
16:1 n-7	2.3 (2.2, 2.6)
18:1 n-9	23.9 (21.7, 26.2)
18:1 n-7	2.3 (2.2, 2.6)
<i>Polyunsaturated</i>	
<i>Omega-6</i>	
18:2 n-6	28.3 (26.4, 30.8)
20:4 n-6	7.5 (6.0, 9.0)
<i>Omega-3</i>	
18:3 n-3	0.5 (0.4, 0.7)
20:5 n-3	0.3 (0.2, 0.4)
22:5 n-3	0.4 (0.3, 0.5)
22:6 n-3	1.3 (1.0, 1.8)
Long chain n-3	2.0 (1.6, 2.5)
Long chain n-6	8.0 (6.5, 9.7)
Long chain n-6/n-3	4.0 (3.3, 4.7)
Saturated fatty acids	28.0 (26.8, 29.2)
Monounsaturated fatty acids	28.2 (25.5, 30.8)
Polyunsaturated fatty acids	40.9 (38.0, 44.3)

Figures are medians (25th, 75th percentiles) of percent weight. Adapted with permission from reference 23 and S. Karger AG.

Table 3. Variables associated with odds of sudden cardiac death in the first year of hemodialysis in a final model^a that included total serum fatty acids

Variable	Coefficient	Odds ratio (95% CI) ^b	p value
Serum albumin, g/dl	-0.5958	0.55 (0.33–0.93)	0.0246
22:5 n-3, weight %	-0.3545	0.70 (0.51–0.97)	0.0334
Total saturated fatty acids, weight %	0.01171	1.01 (1.00–1.02)	0.0258

^a The final model included ethnicity, systolic blood pressure and pulse pressure, serum albumin, creatinine, ferritin, and phosphorus, a history of coronary artery disease or myocardial infarction, stroke, and congestive heart failure, angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, and statin use, and 18:3 n-3, 20:4 n-6, 22:4 n-6, 22:5 n-6, 22:5 n-3, 22:6 n-3, total saturated fatty acids, and total monounsaturated fatty acids.

^b Increase or decrease per unit of the variable. However, for fatty acids the odds ratio reflects 0.1% increases or decreases.

Table 4. Variables associated with odds of sudden cardiac death in the first year of hemodialysis in a final model^a that included serum phospholipid fatty acids

Variable	Coefficient	Odds ratio (95% CI) ^b	p value
Pulse pressure, mm Hg	−0.0358	0.96 (0.93–1.00)	0.0473
Serum albumin, g/dl	−0.5267	0.59 (0.36–0.98)	0.0422
22:5 n–3, weight %	−0.1978	0.82 (0.96–0.98)	0.0254

^a The final model included ethnicity, systolic blood pressure and pulse pressure, serum albumin, cholesterol, ferritin, and phosphorus, a history of coronary artery disease or myocardial infarction, chronic obstructive pulmonary disease, stroke, and congestive heart failure, use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins, diabetes as a cause of end-stage renal disease, and phospholipid fractions of 20:4 n–6, 22:5 n–3, 22:6 n–3, and total monounsaturated fatty acids.

^b Increase or decrease per unit of the variable. However, for fatty acids the odds ratio reflects 0.1% increases or decreases.

congestive heart failure, atrial fibrillation, liver disease, lipid disorders, cancer, anemia, chronic obstructive pulmonary disease); systolic blood pressure and pulse pressure; medication use [angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -blockers, aspirin, and HMG-CoA reductase inhibitors (statins)], and predialysis serum biochemical indices (albumin, creatinine, ferritin, phosphorus, potassium, calcium, glucose, total cholesterol, alkaline phosphatase, parathyroid hormone, hemoglobin, white blood cells). The covariates were chosen either because there is evidence to suggest that they play a role in sudden cardiac death risk or a reasonable clinical concern that they may. We chose to be as comprehensive as possible in terms of including all families of fatty acids while focusing particular attention on the fatty acids that have previously been implicated in cardiovascular and sudden cardiac death events (i.e. polyunsaturated fats). The cross-validation method was used to tune the parameter selections. After running the preliminary variable selection, we then refitted a final logistic model that included only covariates with non-zero coefficients. We also performed a similar model selection with sudden cardiac death as the response variable but replaced the serum total fatty acids with their corresponding serum fatty acid phospholipid fractions (model 2). Descriptive analyses were performed using SAS 9.3 (Cary, N.C., USA). The logistic models with variable selection were performed using GLMNET package (cv.glmnet) in R (2-14-0).

Results

Four hundred patients were available in the complete patient cohort. Clinical characteristics of the combined study cohort are shown on table 1. The cohort was similar to the overall US hemodialysis population in terms of the

following major demographic and clinical characteristics [30]: age (study cohort vs. US population: 66 vs. 63 years), gender (58 vs. 56% male), race (31 vs. 32% black), ethnicity (12 vs. 13% Hispanic), mean body mass index (26 vs. 29), cause of end-stage renal disease (47 vs. 45% due to diabetes), and initial type of vascular access (55 vs. 63% starting with dialysis catheter). Table 2 describes the serum fatty acid profile for the study patients. The most common fatty acids included palmitic acid (16:0), oleic acid (18:1 n–9), and linoleic acid (18:2 n–6), all of which are abundant in the processed foods of the Western diet. The amounts of LCn–3 PUFA were noticeably low compared to other populations [23]. Of note, no *trans* fats were detected in appreciable amounts.

As described in table 3, model 1 identified 3 independent variables that were significantly associated with sudden death risk during the first year of hemodialysis. A 1 g/dl increase in serum albumin was associated with a 45% reduction in the odds of sudden cardiac death and every 0.1% increase in total serum 22:5 n–3 levels was associated with a 30% reduction. In contrast, a 0.1% increase in total serum saturated fatty acid levels was associated with a 1% increase in the odds. In model 2, serum albumin (1 g/dl increase reduced the odds by 41%) and 22:5 n–3 (0.1% increase was associated with 18% reduction in odds) remained as significant variables in the model, with pulse pressure also being inversely associated with sudden cardiac death (1 mm Hg was linked to 4% reduction in odds) (table 4).

Discussion

In this study of a large representative cohort of US incident hemodialysis patients, we identified several variables that were significantly associated with the risk of sudden cardiac death during the high-risk first year period on hemodialysis. These included serum albumin, pulse pressure, as well as the LCn–3 PUFA 22:5 n–3 and total saturated fatty acids. This is the first time that fatty acids have been included in an analysis of this type, and the fact that they were among the very few factors to be associated with the outcome of interest highlights the potential importance of dietary intake on hemodialysis patient outcomes.

Previously identified risk factors for sudden cardiac death in hemodialysis patients include age [5, 7, 8]; race [8]; systolic and diastolic blood pressure [3, 5]; markers of cardiac injury and electrophysiology (brain natriuretic peptide, troponin T, left ventricular ejection fraction,

short TT interval on electrocardiogram) [3, 10]; risk factors for or a history of cardiovascular disease (congestive heart failure, coronary artery disease, diabetes mellitus, peripheral vascular disease, atrial fibrillation) [4, 5, 7, 8, 11]; baseline electrolyte derangements (hypokalemia, hyperkalemia) [4, 8, 11]; aspects of the dialysis procedure (solute clearance, mode of hemodialysis, more aggressive ultrafiltration, timing of dialysis, dialysis catheters, low potassium and calcium dialysate baths) [4–6, 10, 11]; medications (β -blockers, amiodarone) [4, 10], and biochemical markers of illness (serum creatinine, alkaline phosphatase levels, the state of ‘wasting’, C-reactive protein, interleukin-6) [6–9, 11]. All these variables were identified in studies of prevalent hemodialysis patients, with the exception being the study by Parekh et al. [8] which reported that blood inflammatory markers were associated with risk of sudden cardiac death in a cohort of incident peritoneal and hemodialysis patients.

Our analysis involved one model that included individual serum total fatty acids and another that included the serum phospholipid fraction of these fatty acids. We did this because while serum total fatty acids are less cumbersome to measure the serum phospholipid fraction may better reflect the fatty acids in heart cell membranes that mediate ion channels and electrical conduction [31]. In fact, it is not known which fraction of blood fatty acids is the best predictor of patient outcomes, so we presented both models. Our study confirms that serum albumin, a powerful marker of illness and inflammation [32], is also a strong and robust indicator of sudden cardiac death risk as it was significant in both models. Indeed, inflammation is an important component in the pathogenesis of atherosclerotic disease which explains why other markers of inflammation like C-reactive protein have been associated with sudden cardiac death in non-dialysis populations [33].

There exists a large literature on the protective effects of LCn-3 PUFA on sudden cardiac death [34]. Putative mechanisms include effects on cell membrane structure and function, ion channels and electrophysiology, and eicosanoid production. In this study, a higher level of the blood LCn-3 PUFA 22:5 n-3 (DPA) was associated in both models with a markedly lower risk of sudden cardiac death. No association was observed with the two other LCn-3 PUFA, EPA and DHA. In fact, the anti-arrhythmic and other physiologic effects of DPA have been highly understudied relative to EPA and DHA [35]. Since nearly all clinical studies of LCn-3 PUFA with cardiovascular endpoints used fish oil – which is comprised of EPA, DPA, and DHA – it is possible that DPA has ben-

eficial effects independent of EPA and DHA. However, because the metabolism of DPA is closely linked to that of EPA and DHA (i.e. it is partially derived from the same dietary source, partly synthesized from and retroconverted back to EPA via the Sprecher pathway, and partially converted to DHA) [36], it is difficult to clearly differentiate the individual effects of each LCn-3 PUFA on our outcome of interest. In a recent published study, we observed that DPA and DHA, but not EPA, were each independently and inversely associated with risk of sudden cardiac death [22]. Our present findings validate these previous observations by confirming that LCn-3 PUFA are truly independent risk factors for sudden cardiac death. They also expand upon the results by examining the odds of sudden cardiac death for a host of additional risk factors.

Because blood levels of all three LCn-3 PUFA are modifiable by diet in hemodialysis [37] patients, it may be possible to reduce the risk of sudden cardiac death and perhaps other cardiovascular outcomes by supplementing hemodialysis patients with fish oil. Indeed, as we have previously reported, US hemodialysis patients are an especially good population to supplement because their baseline levels are very low [23] and the benefits of supplementation are inversely related to baseline levels [38]. We therefore look forward to this hypothesis being tested in a rigorous manner. Of note, fish is the best dietary source for LCn-3 PUFA, though it contains relatively less DPA than the others [39]. In fact, interconversion from EPA and DHA may play a greater role in determining DPA blood levels than actual dietary intake.

Though models 1 and 2 were generally in agreement, each included one differing variable. An increase in serum total saturated fatty acids was associated with a modest rise in the odds of sudden cardiac death in model 1 but not model 2 likely because very little saturated fat is integrated into phospholipids. Of note, this is the first observation in dialysis patients linking saturated fatty acids with sudden cardiac death though they have been previously demonstrated in murine and primate models to have relatively pro-arrhythmic effects [40, 41]. As suggested by others in the general population [42], confirmation of this finding would support revising current dietary guidelines for dialysis patients by recommending the replacement of saturated fats with LCn-3 PUFAs.

We also found that pulse pressure was a predictive factor in model 2 but not model 1, though the coefficients and odds ratios trended in a similar manner. The reason for this is not clear. In the general population, a greater pulse pressure typically reflects sclerosis of blood vessels

and is therefore an indicator of vascular disease. A higher pulse pressure has also been associated with greater risk in hemodialysis patients [43], in contrast to what we observed where it had a marginally protective effect. We postulate that this is because in our cohort a lower pulse pressure simply represents greater severity of illness. In fact, the relationship appears to be partly dependent on systolic blood pressure because when we remove systolic pressure from the model the pulse pressure becomes non-significant ($p = 0.09$).

Our study has a number of limitations. Not all clinical markers of cardiac function were available nor did we have information on dialysis bath composition, variables that could – but have not yet been proven to – play a role in influencing outcomes. Because it is an observational trial we cannot impute causality. We also cannot exclude the possibility of residual confounding. However, the effects of LCn-3 PUFA on cardiac electrophysiology are well established [44] so our findings are supported by the scientific literature. While there is always a possibility that some of the outcomes were misclassified and not related to sudden cardiac death, this would have supported the null hypothesis and weakened the associations we observed. We cannot exclude the possibility that the non-fasting state in which the blood samples were taken could have influenced the findings. However, the fact that the model including serum phospholipid content – which reflects longer-term dietary intake – had similar findings to the model using total serum content suggests that our findings were not heavily influenced by this factor. Triglyceride levels, which may reflect dietary fat intake, were not available for analysis. Finally, in this analysis fatty ac-

ids were measured in serum and not erythrocytes. Harris [45] derived the omega-3 index, which is the sum of erythrocyte EPA and DHA, to predict cardiovascular outcomes like sudden cardiac death. While we were not able to calculate the omega-3 index, it has never actually been validated in the dialysis population.

Our study also had strengths. It is the first nationally representative cohort of incident patients to be studied for insights into sudden cardiac death. It also included a large array of baseline characteristics and variables and is the first to include blood fatty acid levels.

In conclusion, we observed that baseline serum 22:5 n-3 levels and serum albumin are strongly and inversely related to the odds of sudden cardiac death over the first year of hemodialysis, while serum saturated fatty acid levels and pulse pressure were positively associated with this outcome. Because blood fatty acid levels are modifiable by changes in dietary intake, our findings raise the possibility that dietary interventions may lower sudden cardiac death rates in the hemodialysis population.

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Disclosure Statement

R.T. is a consultant to Fresenius Medical Care North America.

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