Triglycerides and Amputation Risk in Patients With Diabetes

Ten-year follow-up in the DISTANCE study

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OBJECTIVE—To determine the association between triglyceride levels and lower-extremity amputation (LEA) risk in a large diabetic cohort.

RESEARCH DESIGN AND METHODS—This is a 10-year survey follow-up study (from 1995–2006) of 28,701 diabetic patients with a baseline triglyceride measure. All patients were fully insured members of the Kaiser Permanente Medical Care Program and responded to a survey at baseline that included information on ethnicity, socioeconomic status, education, behavioral factors, and information required to determine type of diabetes. The relationship between triglycerides and time to incident nontraumatic LEA, defined by primary hospitalization discharge or procedures, was evaluated using Cox proportional hazards models.

RESULTS—Triglyceride level was an independent, stepwise risk factor for nontraumatic LEAs within this large diabetic cohort: triglycerides 150–199 mg/dL, hazard ratio (HR) 1.10 (95% CI 0.92–1.32); 200–499 mg/dL, 1.27 (1.10–1.47); >500 mg/dL, 1.65 (1.30–2.10) (reference <150 mg/dL).

CONCLUSIONS—Hypertriglyceridemia is a significant risk factor for LEA in diabetic patients even after controlling for known socioeconomic, health behavioral, and clinical factors. This previously unrecognized clinical risk needs to be further investigated to determine if treatment of triglycerides can reduce amputation risk.

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Diabetes is a common condition that damages the blood vessels of patients in a variety of ways. Patients with diabetes suffer from macrovascular complications such as myocardial infarction, stroke, and peripheral vascular disease. Moreover, they also develop microvascular disease that manifests as peripheral neuropathy (one of many mechanisms), retinopathy, and nephropathy. As a result of the of the combination of neuropathy and macroangiopathy in this population, patients with diabetes account for more than half of the nontraumatic lower extremity amputations (LEA) that occur worldwide (1,2). Tight glycemic control has been shown to decrease the number of patients that develop microvascular complications (3,4); however, a significant proportion of diabetic patients continue to develop these complications even with intensive glycemic control (5). Additionally, in the Steno-2 study, patients treated with a multifactorial intervention including aspirin, statins, renin angiotensin blockers, glycemic control, and lifestyle modifications still developed diabetic complications at a high rate (6). These surprising observations are leading investigators to reconsider other potentially modifiable risk factors.

Hypertriglyceridemia has received little attention of late and is typically not considered a primary clinical target. Elevated triglycerides in concert with low HDL is associated with the metabolic syndrome and increased cardiovascular risk in healthy populations (5). However, the relationship between triglycerides and noncardiovascular complications has received less attention. In the EURODIAB cohort study, patients with type 1 diabetes and elevated triglycerides were at an increased risk for the development of peripheral neuropathy in bivariate, but not multivariate analyses (7). Furthermore, elevated triglycerides were recently found to correlate independently with loss of sural nerve myelin fiber density, a marker for progression of diabetic neuropathy (8).

On the other hand, there have only been a few studies that have directly looked into the role of hypertriglyceridemia as a potential risk factor for LEA. In 1996, Humphries et al. (9) followed a cohort of 1,564 Nauruans with diabetes over 12 years to define potential risk factors for nontraumatic LEA. They found that fasting glucose levels, duration of diabetes, and male sex were independent risk factors. Triglyceride levels were higher in patients that sustained amputations, but the result was not statistically significant. In 2006, Davis et al. (10) conducted an observational cohort study, the Fremont Diabetes Study, that followed 1,294 patients with type 2 diabetes. They found that foot ulceration, a low arterial brachial index, elevated hemoglobin A1C level, and neuropathy were all independent predictors of LEA. Again, triglycerides were elevated in those who sustained amputations, but the association was not significant. Previous studies likely lacked sufficient power to detect a significant association of triglyceride level and risk of LEA. Therefore, we decided to investigate the hypothesis that there is a positive correlation between triglyceride and LEA risk in a larger population followed over a longer time frame.

RESEARCH DESIGN AND METHODS—Kaiser Permanente Medical Care Program ("Kaiser Permanente") is a fully integrated, nonprofit, group practice health plan that provides

comprehensive medical services to over ~2.5 million members (January 1995) throughout Northern California (including the San Francisco Bay and Sacramento metropolitan areas) or ~25–30% of the surrounding population. The Kaiser Permanente membership closely approximates the general population ethnically and socioeconomically except for the extreme tails of the income distribution (11).

In 1993, Kaiser Permanente established the Kaiser Permanente Northern California Diabetes Registry. The registry is updated annually by identifying all health plan members with diabetes from automated databases for pharmacy, laboratory, hospitalization records, and outpatient diagnoses (12–14). The registry sensitivity is estimated to be 96% based on chart review (15). During 1994–1996, all noninstitutionalized registry members 19 years or older identified as having diabetes prior to 1 January 1996 (n = 90,302) were selected for participation in a health survey (self-administered questionnaire) or a computer-assisted telephone interview in English or Spanish. Eighty-three percent of eligible members participated in the survey. After removing those denying having diabetes or discontinuing membership, 70,748 respondents with diabetes remained. The survey collected information on, among other things, ethnicity, information needed to classify diabetes type (see Karter et al. for algorithm [16]), family history of diabetes, education, and behavioral risk factors. Survey respondents were ethnically diverse: 14% black, 12% Asian, 10% Latino, and 64% non-Latino White. Of those self-identifying as "Asian," 44% were Filipino, 24% were Chinese, 12% were Japanese, and 19% were Korean, other Asian, or mixed race. We compared the demographic composition (age, sex, socioeconomic status) of diabetes survey responders to nonresponders in a previous study (14) and found no evidence to suggest responder bias. In addition to survey-derived data, we obtained measures of neighborhood-level socioeconomic status by linking each member's address to the 1990 census block group-level average annual 1989 per capita income.

We used a survey follow-up study design to evaluate the incidence density of LEA and its predictors, restricting analysis to the 28,701 survey respondents who had triglyceride data within 1 year of baseline. Initial triglyceride levels were measured after overnight fasting. Baseline was defined as 1 January 1995 for all members surveyed in 1994 and the survey date (January 1995 to March 1997) for those surveyed after that date. The duration of follow-up (person-time) was tabulated through membership records and ended with an event censoring due to dropping of Kaiser Permanente membership for any period greater than 2 months, death, or the end of the study (31 December 2006). We excluded those with a history of prior LEA events noted in hospital discharge records during the 5 years prior to baseline. Prognostic, confounding, and stratifying variables (see below) were ascertained at or prior to baseline from automated records, the diabetes survey, and the 1990 census.

Study end points

Nontraumatic LEA procedures were identified from discharge codes (ICD-9-CM procedure codes 84.10–84.17). We included patients with any amputation of the lower extremity. In two separate validations of amputation procedures (A. Karter, personal communication, n = 109; and J.V. Selby and D. Zhang [17], n = 209), 99% of electronic hospital discharge records were confirmed by chart review.

Statistical analysis

Descriptive and multivariate analysis. Using direct standardization with the entire diabetes cohort as the population standard, we calculated age-adjusted sex- and ethnicity-specific rates for LEA. Proportional hazards regression (Cox) models were then used to calculate adjusted hazard ratios (HRs) as an estimate of the relative risk of elevated triglycerides (<150, 150–199, 200–499, and >500 mg/dL) associated with LEA. After detecting no violations of the proportionality assumption, we specified a series of Cox regression models, including a base demographic model (age-, race-, and sex-adjusted plus an indicator for elevated triglycerides, LDL, and HDL) and specified saturated models that added socioeconomic variables (race, individual-level education, average census block level income, and proportion in working class occupations), health behaviors (smoking status, alcohol intake, self-reported treatments for diabetes including diet and exercise, and frequency of self-monitoring of blood glucose), and clinical factors including type of diabetes, diabetes duration, type of diabetic medications, first-degree family history of diabetes, BMI (underweight, normal, overweight, obese) (18), height quartiles (19,20), hypertension (self-reported and pharmacy records of antihypertensive medication dispensing), peripheral neuropathy (self-report) (17,21), A1C (<7, 7–8, 8–10, >10 g/dL), LDL (<100, 100–129, 130–159, >160 mg/dL), HDL (<40, 40–59, >60 mg/dL), and use of statin or other lipid-lowering agents.

RESULTS—Patients who sustained an LEA were older (61 years [SD 11.2] vs. 59 years [11.2]), had a longer duration of diabetes (14 years [9.7] vs. 9 years [9.5]), and had a higher hemoglobin A1C (9.05 g/dL [2.12] vs. 8.36 g/dL [1.94]) compared with those who did not sustain an LEA (Table 1). The age- and sex-adjusted nontraumatic LEA incidence rate (95% CI) was 2.3 (1.5–3.1) per 1,000 person-years (Table 2). The sex-specific, age-adjusted rates (95% CI) were 1.4 (1.2–1.7) per 1,000 person-years for women and 3.2 (1.6–4.8) for men. The age- and sex-adjusted incidence rates (95% CI) for white, black, Hispanic, and Asians were 2.7 (1.5–4.0), 2.0 (1.6–2.5), 1.4 (1.1–1.8), and 0.9 (0.5–1.3), respectively.

Crude HRs for triglyceride, LDL, and HDL levels revealed a significant, stepwise relationship with triglycerides: 150–199 mg/dL, HR 1.10 (95% CI 0.92–1.32); 200–499 mg/dL, 1.27 (1.10–1.47); and >500 mg/dL, 1.65 (1.30–2.10) (reference <150 mg/dL). There was no significant association for LDL or HDL with amputation risk. Minimally adjusted Cox proportional hazards models including triglyceride, LDL, and HDL levels continued to demonstrate a stepwise association between triglycerides and LEA risk: 150–199 mg/dL, HR 1.07 (95% CI 0.89–1.29); 200–499 mg/dL, 1.20 (1.03–1.40); and >500 mg/dL, 1.39 (1.03–1.88) (reference <150 mg/dL). LDL was again not significantly associated with amputation risk, whereas HDL showed a protective effect between 40–59 mg/dL (HR 0.74 [95% CI 0.64–0.87]) but not at >60 mg/dL (1.21 [0.92–1.60]) (reference HDL <40 mg/dL). A further-adjusted Cox proportional hazards model (model 1 in Table 3) including triglycerides, LDL, HDL, age, sex, and race also revealed a stepwise association of triglycerides and LEA risk.

The stepwise association between triglycerides and LEA persisted despite further adjustment for socioeconomic (individual-level education, average census block level

Table 1—Baseline characteristics for 28,701 members with diabetes experiencing incident nontraumatic LEAs compared with those without incident LEA

	Incident LEA	No LEA	P value
n	981	27,720	
Mean age (years) (SD)	60.8 (10.2)	59.4 (11.2)	<0.0001
Women (%)	35.0	46.5	<0.0001
Race (%)			
White	62.6	58.8	
African American	14.1	11.0	
Asian	5.6	12.5	
Hispanic	10.1	10.5	
Mixed/other	7.7	7.4	<0.0001
Educational attainment (%)			
High school or less	47.9	42.2	0.0031
Some college	27.9	31.8	
College graduate	24.3	26.0	
Lives in working class neighborhood (%)			
(>66% in census block group in working			
class occupation)	47.3	43.5	0.0847
Lives in deprived neighborhood (%)			
(>20% of neighborhood with annual income			
below poverty level)	12.3	9.7	0.0027
Diabetes type (%)			
Type 1	5.7	3.5	
Type 2	94.4	96.5	0.0009
Diabetes therapy (%)			
Insulin only	41.8	24.0	<0.0001
OHA only	44.5	53.0	
Combination	8.7	4.5	
Diet/exercise	4.1	15.2	
No therapy	0.8	3.2	
Other	0.1	0.1	
Reported exercise as part of treatment (%)	45.2	54.4	<0.0001
Daily self-monitoring of blood glucose (%)	47.3	48.2	0.5956
Mean AlC (g/dL) (SD)	9.05 (2.13)	8.36 (1.94)	<0.0001
A1C (g/dL) (%)			
<7	14.6	26.9	<0.0001
7–8	22.1	23.1	
8–10	33.2	29.9	
>10	30.1	19.9	
First-degree family history of diabetes (%)	57.5	57.1	0.8179
Duration of diabetes (<10 years) (%)	38.9	65.5	<0.0001
Uses statin treatment (%)	20.9	16.8	0.0007
Uses fibrates/niacin treatment (%)	9.7	9.3	0.6929
Uses antihypertensive treatment (%)	73.2	60.3	<0.0001
Self-reported hypertension (%)	74.0	64.1	<0.0001
Self-reported peripheral neuropathy (%)	58.1	29.7	<0.0001
LDL (mg/dL) (%)			
<100	12.2	12.6	0.0650
100–129	27.3	27.2	
130–159	28.5	31.9	
>160	32.1	28.3	
HDL (mg/dL) (%)			
<40	67.9	62.1	<0.0001
40–59	25.8	32.7	
>60	6.3	5.3	

income, and proportion in working class occupations), health behavioral (smoking, BMI, drinking, adherence to guidelines for self-monitoring of blood glucose, and exercise), and clinical variables (statin medication, fibrates/niacin medication, family history of diabetes, height, duration of diabetes, A1C, type of diabetes and therapy, hypertension, neuropathy, retinopathy, stroke, heart attack, and end-stage renal disease [ESRD]) (model 2 in Table 3). As expected, duration of diabetes, A1C, height, hypertension, neuropathy, retinopathy, ESRD, stroke, and heart attack were also associated with amputation. Interestingly, statin medication use and fibrates/niacin medication use did not have statistically significant HRs. LDL >160 mg/dL and HDL >60 mg/dL were the only levels of these tests associated with an increased risk of amputation; it appeared to be a threshold effect for LDL, but there was no consistent or stepwise relationship for HDL.

Additionally, the rates of elevated triglycerides did differ substantially by race (21, 40, 46, and 46% among African Americans, Asians, Whites, and Hispanics, respectively; $P < 0.001$). However, we failed to detect a significant interaction between triglyceride level and race ($P = 0.83$), suggesting that the relationship between triglycerides and amputation risk did not differ by race. Furthermore, similar results were seen with triglyceride level and amputation risk using the entire diabetes cohort and utilizing a missing indicator for those who did not have triglyceride levels at baseline. We also found that, as expected, there was a significant, inverse correlation between triglyceride and HDL levels (correlation = −0.24, $P < 0.0001$). However, this modest collinearity was not considered sufficient to distort our triglyceride effect estimates from the Cox regression models.

CONCLUSIONS—In this large, multiethnic cohort of diabetic patients, we found that elevated triglyceride levels are associated with LEA even after adjusting for a host of potential confounders. The consistency of the relationship between triglycerides and LEA across ethnic groups was further supportive. All models revealed a stepwise increase in amputation risk with increasing triglyceride levels. This is in contrast to low HDL, which was not associated with increased amputation risk. The threshold of LDL levels above 160 mg/dL was also associated with increased risk of amputation.

Table 1—Continued

	Incident LEA	No LEA	P value
Triglycerides (mg/dL) (%)			
<150	32.7	37.8	0.0003
150–199	18.9	19.9	
200–499	39.9	36.2	
>500	8.6	6.2	
Mean BMI (kg/m^2) (SD)	29.62 (5.67)	29.99 (6.22)	0.0600
Current drinker (%)	25.7	28.2	0.0028
Current smoker (%)	12.6	11.2	0.0115
Obesity status			
Underweight (BMI <18.5 kg/m^2)	0.4	0.5	0.1143
Normal (BMI 18.5–24.9 kg/m^2)	18.3	17.0	
Overweight (BMI 25.0–29.9 kg/m^2)	38.2	35.4	
Obese (BMI >30.0 kg/m^2)	43.1	47.1	
Height (in quartiles)			
1	13.0	23.7	<0.0001
2	21.8	24.4	
3	30.7	31.1	
4	34.4	20.9	
Patients with ESRD (%)	4.6	0.8	<0.0001
Patients with history of heart attack (%)	17.0	10.9	<0.0001
Patients with history of stroke (%)	8.0	3.7	<0.0001
Patients with retinopathy (%)	1.9	0.6	<0.0001

OHA, oral hypoglycemic agent.

Dyslipidemia has been proposed as a potential risk factor in the development of diabetes complications such as retinopathy and neuropathy based on results utilizing the DCCT/EDIC cohort and the EURODIAB study (7,22). Our results suggest that high triglyceride levels, independent of the other major lipid components, may put patients at risk for one major diabetes complication—LEA. Whether this association applies more widely to other vascular diabetes complications is unknown.

These results add to the finding in prior studies that elevated triglyceride levels may be a risk factor for complications of diabetes (5,7,8), including LEA (9,10). However, the current study involved a larger population and found the association to be statistically significant even after adjusting the models for a multitude of variables that were not assessed in the prior studies.

Given the current state of the literature, the guidelines on triglyceride management do not advocate aggressive treatment. The National Cholesterol Education Program recommends diet and exercise for patients with triglyceride levels between 150–199 mg/dL, to consider treatment in high-risk patients with levels 200–499 mg/dL, and to use pharmacologic treatment when levels are 500 mg/dL or greater to prevent pancreatitis, but not necessarily to prevent microvascular and macrovascular complications

(23). Clearly, further studies are needed to ascertain the role of hypertriglyceridemia in these diabetic sequelae. Our study gives further support to the notion that triglycerides may be one of the key modifiable risk factors in the development of amputations. If this association holds in clinical trials, then clinicians may have a target with the potential to improve important patient outcomes.

One of the main limitations of this study is that a large proportion of our population did not have data on triglyceride, HDL, and LDL levels during the year prior to baseline; at the time, these assessments were not done nearly as frequently or routinely as is common today. However, our sensitivity analysis using missing triglycerides as an indicator and evaluating the entire diabetes cohort suggests that missing data did not substantially bias our findings. Also, observational cohort studies, particularly cross-sectional designs, can make erroneous assumptions between cause and effect when suggestive variables correlate. In our study, the longitudinal study design and exclusion of patients with prevalent amputations at baseline precludes time-ordering violations (i.e., LEA preceding the triglyceride ascertainment). Another limitation is that observational studies are vulnerable to residual confounding; however, we were able to adjust for a wide array of confounders, which should greatly reduce this concern.

The major strengths of this study are its longitudinal cohort design, validated and complete capture of LEA events, and large sample size with rich array of clinical and behavioral data. Additionally, our diabetes registry captures patients who are not treated with diabetes medications (medical nutritional therapy) through laboratory findings and outpatient diagnosis records, providing a more representative diabetic sample than pharmacy-based registries that only capture patients receiving prescriptions or studies from diabetes specialty clinics that typically include patients with more severe disease.

In summary, elevated triglyceride level was associated with subsequent LEA independently of the other lipid components and a wide range of potential confounders in this large, well-characterized diabetic cohort. Though specific guidelines exist for cholesterol (LDL and HDL levels) management in this patient population, only vague guidelines exist for triglyceride management (23). This observational study suggests that triglyceride levels are predictive of amputation risk

Table 2—Incidence rates per 1,000 person-years (95% CIs) for LEA procedures

LEA	Total person-years follow-up	Number of incident events	Age- and sex-adjusted incidence rate per 1,000 person-years (95% CI)	Age-adjusted incidence rate per 100 person-years (95% CI) Women	Age-adjusted incidence rate per 100 person-years (95% CI) Men
Entire cohort	218,027	981	2.3 (1.5–3.1)	1.4 (1.2–1.7)	3.2 (1.6–4.8)
White	127,272	614	2.7 (1.5–4.0)		
African American	24,190	138	2.0 (1.6–2.5)		
Hispanic	23,305	99	1.4 (1.1–1.8)		
Asian	27,795	55	0.9 (0.5–1.3)		
Mixed/other	15,465	75	2.6 (1.3–4.1)		

Table 3—Cox proportional hazards models with HRs (95% CIs) for nontraumatic LEA

	Model 1		Model 2	
	HR	95% CI	HR	95% CI
Triglycerides (mg/dL) (reference: <150)				
150–199	1.16	0.97–1.40	1.29	1.07–1.55
200–499	1.35	1.15–1.58	1.40	1.19–1.65
>500	1.38	1.17–2.14	1.65	1.22–2.24
LDL (mg/dL) (reference: <100)				
100–129	1.05	0.83–1.32	1.10	0.86–1.39
130–159	0.94	0.74–1.19	1.01	0.80–1.80
>160	1.26	1.00–1.59	1.30	1.03–1.64
HDL (mg/dL) (reference: <40)				
40–59	0.87	0.74–1.02	0.88	0.75–1.03
>60	1.53	1.15–2.03	1.37	1.02–1.84
Age (years) (reference: 19–34)				
35–49	1.18	0.62–2.25	1.15	0.60–2.22
50–64	1.48	0.79–2.77	1.31	0.68–2.52
65–79	1.80	0.96–3.39	1.58	082–3.05
80+	0.91	0.35–2.40	0.85	0.32–2.30
Sex				
Male	1.71	1.49–1.97	1.59	1.33–1.90
Race (reference: white)				
African American	1.36	1.12–1.65	1.04	0.85–1.28
Hispanic	0.92	0.75–1.14	0.82	0.66–1.03
Asian	0.44	0.33–0.58	0.51	0.39–0.69
Mixed/Other	1.08	0.85–1.38	0.91	0.71–1.16
Duration of diabetes (years) (reference: <10 years)				
10–19			1.94	1.65–2.28
>20			2.38	1.96–2.88
A1C (g/dL) (reference: <7)				
7–8			1.45	1.16–1.81
8–10			1.51	1.22–1.86
>10			2.18	1.75–2.71
Diabetes type and therapy (reference: diet only)				
Type 1			1.78	1.19–2.65
Type 2 on insulin			2.41	1.88–3.10
Type 2 on OHA			1.62	1.28–2.05
Statin medication			1.02	0.87–1.20
Fibrate/niacin medication			0.85	0.68–1.05
Smoking (reference: never)				
Current			1.24	0.99–1.55
Former			0.98	0.84–1.15
BMI (reference: normal weight)				
Underweight			0.67	0.21–2.11
Overweight			0.86	0.70–1.05
Obese			0.80	0.65–0.98
Height (reference: 1st quartile)				
2nd quartile			1.43	1.09–1.86
3rd quartile			1.34	1.01–1.77
4th quartile			1.98	1.48–2.66
Hypertension			1.51	1.27–1.78
Neuropathy			2.60	2.23–3.04
Retinopathy			1.85	1.15–2.98
Heart attack			1.27	1.06–1.52
Stroke			1.97	1.55–2.50
ESRD			4.29	3.06–6.03

Model 1: Triglycerides, LDL, HDL, age, sex, and race. Model 2: Model 1 + education, income, whether lives in working class neighborhood, smoking, alcohol use, BMI, height, adherence to guidelines for self-monitoring of blood glucose, exercise, statin medication, fibrate/niacin medication, family history of diabetes, duration of diabetes, A1C, type of diabetes and therapy, history of hypertension, neuropathy, retinopathy, ESRD, stroke, and heart attack. OHA, oral hypoglycemic agent.

in a stepwise fashion. Despite standards of glycemic, blood pressure, and cholesterol control, patients continue to develop microvascular and macrovascular complications (combination of neuropathy and macroangiopathy is thought to cause LEAs), and triglyceride control may be an important additional primary prevention effort. More research is necessary to define a causal role of triglyceride levels on amputation risk in diabetic patients. Based on this current robust cohort study, such research should be a priority.

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