Triglycerides and Amputation Risk in Patients With Diabetes

Ten-year follow-up in the DISTANCE study

BRIAN C. CALLAGHAN, MD 1
EVA FELDMAN, MD, PHD 1
JENNIFER LIU, MPH 2
KEVIN KERBER, MD 1
RODICA POP-BUSUI, MD 1
HOWARD MOFFET, MPH 2
ANDREW J. KARTER, PHD 2

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.

Diabetes Care 34:635–640, 2011

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 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
Triglyceride and amputation risk

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 with diabetes prior to 1 January 1996 were ethnically diverse: 14% black, 12% Hispanic, 6% 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 respondents 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), AL1C (<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 AIC (g/dL) (SD)     | 9.05 (2.13)  | 8.36 (1.94) | <0.0001     |
| AIC (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, AIC, 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, AIC, 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 colinearity 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

| Triglycerides (mg/dL) (%) | Incident LEA | No LEA | P value |
|--------------------------|--------------|--------|---------|
| <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/m²) (SD)    | 29.62 (5.67) | 29.99 (6.22) | 0.0600 |
| Current smoker (%)       | 25.7         | 28.2   | 0.0028  |
| Current drinker (%)      | 12.6         | 11.2   | 0.0115  |
| Obesity status           |              |        |         |
| Underweight (BMI <18.5 kg/m²) | 0.4       | 0.5    | 0.1143  |
| Normal (BMI 18.5–24.9 kg/m²) | 18.3       | 17.0   |         |
| Overweight (BMI 25.0–29.9 kg/m²) | 38.2       | 35.4   |         |
| Obese (BMI >30.0 kg/m²)  | 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 stroke (%) | 17.0 | 10.9 | <0.0001 |
| Patients with history of heart attack (%) | 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.

### 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                                                               | 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)                                                      |                                                          |

(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 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    | 0.82–3.05 |
| >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 | 2.38    | 1.96–2.88 |
| >20                     | 2.24    | 1.91–2.66 | 2.04    | 1.72–2.45 |
| **A1C (g/dL)** (reference: <7) |         |       |         |       |
| 7–8                     | 1.45    | 1.16–1.81 | 1.51    | 1.22–1.86 |
| 8–10                    | 1.51    | 1.27–1.90 | 2.18    | 1.75–2.71 |
| >10                     | 2.18    | 1.84–2.62 | 2.62    | 2.12–3.24 |
| **Diabetes type and therapy** (reference: diet only) |         |       |         |       |
| Type 1                  | 1.78    | 1.19–2.65 | 1.62    | 1.18–2.23 |
| Type 2 on insulin       | 2.41    | 1.88–3.10 | 2.02    | 1.54–2.64 |
| Type 2 on OHA           | 2.02    | 1.54–2.64 | 1.78    | 1.36–2.34 |
| Statin medication       | 1.02    | 0.87–1.19 | 1.02    | 0.87–1.19 |
| Fibrate/niacin medication | 0.85    | 0.68–1.05 | 0.85    | 0.68–1.05 |
| Smoking (reference: never) |         |       |         |       |
| Current                 | 1.24    | 0.99–1.55 | 0.98    | 0.75–1.30 |
| Former                  | 0.98    | 0.84–1.15 | 0.98    | 0.85–1.15 |
| **BMI (reference: normal weight)** |         |       |         |       |
| Underweight             | 0.67    | 0.21–2.11 | 0.67    | 0.21–2.11 |
| Overweight              | 0.86    | 0.70–1.05 | 0.86    | 0.70–1.05 |
| Obese                   | 0.80    | 0.65–0.98 | 0.80    | 0.65–0.98 |
| **Height** (reference: 1st quartile) |         |       |         |       |
| 2nd quartile            | 1.43    | 1.09–1.86 | 1.59    | 1.19–2.10 |
| 3rd quartile            | 1.34    | 1.01–1.77 | 1.51    | 1.21–1.87 |
| 4th quartile            | 1.98    | 1.48–2.66 | 2.60    | 2.23–3.04 |
| **Hypertension**        | 1.51    | 1.27–1.78 | 1.85    | 1.53–2.26 |
| **Neuropathy**          | 2.60    | 2.23–3.04 | 2.60    | 2.23–3.04 |
| **Retinopathy**         | 1.85    | 1.53–2.26 | 1.85    | 1.53–2.26 |
| **Heart attack**        | 1.27    | 1.06–1.52 | 1.27    | 1.06–1.52 |
| **Stroke**              | 1.97    | 1.55–2.50 | 1.97    | 1.55–2.50 |
| **ESRD**                | 4.29    | 3.06–6.03 | 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.
Triglyceride and amputation risk

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.

Acknowledgments—This study was supported by the National Institutes of Health (NIDDK R01-DK056564 and DK081796) and by the Neurology Training Grant Fellowship (T32).

The Program for Neurology Research & Discovery was instrumental in providing salary support for B.C.C.

No potential conflicts of interest relevant to this article were reported.

B.C.C. was involved in interpretation of the statistical analysis and wrote the manuscript. E.F. proposed the hypothesis and helped with the manuscript. J.L. performed the statistical analysis. K.K. helped with statistical interpretation and contributed to the manuscript. R.P.-B. contributed to the manuscript. H.M. reviewed the manuscript. A.J.K. was integrally involved in the creation of the cohort and was significantly involved in analysis and writing the manuscript.

Parts of this study were presented in abstract form at the American Neurologic Association meeting, San Francisco, California, 12–15 September 2010.

References

1. Bouillon AJ. The diabetic foot: grand overview, epidemiology and pathogenesis. Diabetes Metab Res Rev 2008;24(Suppl. 1): S3–S6
2. van Houtum WH. Amputations and ulceration: pitfalls in assessing incidence. Diabetes Metab Res Rev 2008;24(Suppl. 1):S14–S18
3. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329: 977–986
4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352: 837–843
5. Steiner G. How can we improve the management of vascular risk in type 2 diabetes: insights from FIELD. Cardiovasc Drugs Ther 2009;23:403–408
6. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383–393
7. Tesfaye S, Chaturvedi N, Eaton SE, et al.; EURODIAB Prospective Complications Study Group. Vascular risk factors and diabetic neuropathy. N Engl J Med 2005; 352:341–350
8. Wiggins TD, Sullivan KA, Pop-Busui R, Amato A, Sima AA, Feldman EL. Elevated triglycerides correlate with progression of diabetic neuropathy. Diabetes 2009;58: 1634–1640
9. Humphrey AR, Dowse GK, Thoma K, Zimmer PZ. Diabetes and nontraumatic lower extremity amputations. Incidence, risk factors, and prevention—a 12-year follow-up study in Nauru. Diabetes Care 1996;19:710–714
10. Davis WA, Norman PE, Bruce DG, Davis TM. Predictors, consequences and costs of diabetes-related lower extremity amputation complicating type 2 diabetes: the Fremantle Diabetes Study. Diabetologia 2006;49:2634–2641
11. Hiatt RA, Friedman GD. Characteristics of patients referred for treatment of end-stage renal disease in a defined population. Am J Public Health 1992,72:829–833
12. Selby JV. Linking automated databases for research in managed care settings. Ann Intern Med 1997;127:719–724
13. Selby JV, Karter AJ, Ackerson LM, Ferrara A, Liu J. Developing a prediction rule from automated clinical databases to identify high-risk patients in a large population with diabetes. Diabetes Care 2001;24: 1547–1555
14. Karter AJ, Newman B, Rowell S, et al. Large-scale collection of family history data and recruitment of informative families for genetic analysis. J Registry Manag 1998;25:7–12
15. Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV. Ethnic disparities in diabetic complications in an insured population. JAMA 2002,287:2519–2527
16. Karter AJ, Ackerson LM, Darbinian JA, et al. Self-monitoring of blood glucose levels and glycemic control: the Northern California Kaiser Permanente Diabetes registry. Am J Med 2001;111:1–9
17. Selby JV, Zhang D. Risk factors for lower extremity amputation in persons with diabetes. Diabetes Care 1995;18:509–516
18. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Am J Clin Nutr 1998;68: 899–917
19. Adler AI, Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Smith DG. Risk factors for diabetic peripheral sensory neuropathy. Results of the Seattle Prospective Diabetic Foot Study. Diabetes Care 1997;20:1162–1167
20. Christen WG, Manson JE, Bubes V, Glynn RJ; Sorbinil Retinopathy Trial Research Group. Risk factors for progression of distal symmetric polyneuropathy in type 1 diabetes mellitus. Am J Epidemiol 1999; 150:1142–1151
21. Reiber GE, Pecoraro RE, Koepsell TD. Risk factors for amputation in patients with diabetes mellitus: a case-control study. Ann Intern Med 1992;117:97–105
22. Lyons TJ, Jenkins AJ, Zheng D, et al. Diabetic retinopathy and serum lipoprotein subclasses in the DCCT/EDIC cohort. Invest Ophthalmol Vis Sci 2004;45:910–918
23. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285: 2486–2497