ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #609

1. Title:
Relation of Diet to Diabetic Retinopathy

2. Writing Group:
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3. Timeline:
Analyses are planned to be completed between January, 1999 and April, 2000.

4. Rationale:
Diabetic retinopathy is an important cause of visual impairment among people with diabetes in the United States. As the population ages in the next 50 years, there will be more people living with adult-onset diabetes, increasing the economic burden of this condition substantially. Although treatment for this condition using laser photocoagulation is often effective in reducing the progression, a reduction in vision frequently occurs even with treatment, and treatment is costly. Thus, slowing the onset or progression of retinopathy is likely to have a large impact on the health and health care costs of older people who have diabetes.

Glycemic control has been demonstrated to be an important predictor of the development and progression of diabetic retinopathy in both experimental animals and in humans, leading to treatment goals to improve control of blood glucose. Although medical treatments aimed at tight glycemic control in the Diabetes Complications and Control Trial were able to reduce the incidence and progression or retinopathy in people with insulin-dependent diabetes mellitus (IDDM), they did not eliminate it. Diet may provide the means for additional glycemic control beyond that possible by medical means, particularly in people with non-insulin dependent diabetes mellitus (NIDDM). Furthermore, diet may influence other risk factors for the progression of retinopathy that were recently identified in the Early Treatment for Diabetic Retinopathy Study sush as serum triglycerides and hematocrit. Diet may also influence oxidative stress which has been proposed to contribute to microvascular complications like retinopathy.

Diet and Glycemic Control A variety of dietary factors may influence glycemic control by influencing postprandial rises in blood sugar, as well as by influencing insulin sensitivity and glucose utilization by peripheral tissues. High levels of fat in the diet appear to not only contribute to obesity, which reduces insulin sensitivity, bu tmay also reduce insulin sensitivity independent of the effect on weight.
Low-fat/high-carbohydrate diets may improve glycemic control via the high carbohydrate content which has been observed, in a variety of short-term clinical studies, to result in lower incidence of hyperglycemia and decreased mediation for the control of hyperglycemia. The short-term influence of high carbohydrate diets on lowering blood sugar, might also be due to the fact that high carbohydrate diets also often provide higher levels of fibers, which have been shown to reduce the postprandial rise in blood sugar. We will evaluate the relationships of dietary fat, carbohydrate and fiber and the prevalence of retinopathy in the ARIC population.

The type of dietary fat may also influence the development and progression of diabetic complications. There is evidence that diets high in monosaturated fat and fish oils and low in saturated fat and shorter chain polyunsaturated fat may protect against diabetic retinopathy, but these relationships have not been studied over the long-term in populations of people with diabetes. We plan to evaluate relationships between the level of different types of fat in the diet and retinopathy and nephropathy. We will also evealute the relationship between the levels of fatty acids in plasma phospholipids and cholesterol esters and eye and renal diabetic

complications in a subsample of ARIC participants from the Minneapolis center.

High-carbohydrate/high-fiver diets contain high levels of cereal, fruits, and vegetables. Diets high in these foods may also be more likely to provide adequate levels of other micronutrients that may be needed to maintain glucose tolerance. One such nutrient is magnesium. Low serum levels of magnesium have been observed in people with Type 1 and Type 2 diabetes. Preliminary data from the ARIC population also indicate an inverse relationship between serum magnesium and the incidence of diabetes. We will evaluate the relationships between magnesium in the serum and diet and the prevalence of diabetic retinopathy in the ARIC population.

Despite the fact that diets higher in carbohydrates are often related to better control of blood glucose, they may not be beneficial in reducing the overall risk for retinopathy. High carbohydrate diets can also increase the levels of triglycerides in the serum. High levels of serum triglycerides were related to the progression of diabetic retinopathy in the Early Treatment for Diabetic Retinopathy Study (ETDRS) and have been shown to be related to lower levels of insulin receptors in experimental animals. We will evaluate the relationship of very high levels of carbohydrate in the diet, and retinopathy. We will also determine whether these relationships are explained by associations of high levels of serum triglycerides and retinopathy.

Alcohol intake has been correlated with hyperglycemia in large population studies. Observations of higher circulating insulin levels that accompany alcohol intake are consistent with data which indicate that alcohol impairs insulin sensitivity and that it augments insulin release. However, some epidemiologic studies also indicate that moderate alcohol consumption is realted to lower risk for Type 2 diabetes, indicating a possible protective relationship between moderate alcohol consumption and blood glucose control. We plan to investigate the relationship between the history of alcohol intake and the prevalence of diabetic retinopathy.

Other Influences of Diet on the Development of Retinopathy Diet may influence oxidative stress which is thought to contribute to retinopathy. While antioxidants may inhibit retinopathy directly, they might also work through an influence on blood glucose control. In some (but not all) previous studies, the administration of supplements containing the vitamins E or C improved blood glucose control. In the Beaver Dam population, the level of vitamin C in the diet was inversely related to glycosylated hemoglobin in people without diabetes. Similar but non-significant results were observed in the smaller group of people with diabetes in this population. In a more recent study in Beaver Dam, the intake of fruits and vegetables that are important sources of vitamin C were related to lower five-year incidence and progression of retinopathy. These relationships were independent of blood glycosylated hemoglobin levels. We will investigate the relationships of antioxidant nutrients in food and supplements on the prevalence of retinopathy.

In the ETDRS study, the progression of retinopathy was greater in people with low hematocrit at baseline. These investigators speculated that anemia may contribute to the development of retinopathy. We will investigate the relationships of dietary nutrients needed to prevent anemia (iron, folate, vitamin B12) and retinopathy.

5. Main Hypotheses:

1. ARIC participants with diabetes and retinal photographs at Visit 3 (1307 persons) who have dietary intakes:

-in the highest quintile vs lowest quintile for: fat, saturated fat, polyunsaturated fat

-in the lowest vs highest quintile for: fruit, vegetables and grains, vitamin C, vitamin E, magnesium, iron, folate, vitamin B12, monounsaturated fatty acids,
omega-3 fat

will have higher odds ratios for retinopathy.

A. These relationships described aboe will be independent of the (1) the presence of hypertension and atherosclerosis and (2) elevated levels of triglycerides.

B. These associations will strengthen after excluding people whose diets have changed substantially over the six years of follow-up.

2. Among ARIC participants with diabetes, the prevalence of diabetic retinopathy at Visit 3 will be:
lower in long-term users of multivitamin supplements compared to non-users
lower in persons who use vitamin C or E supplements for six or more years compared to non-users

3. The prevalence of retinopathy among ARIC participants at the Minnesota site will be inversely related to the percent of monounsaturated and long-chain polyunsaturated fatty acids in serum cholesterol esters and phospholipids and directly related to the percent of saturated fatty acids in these lipid fractions.

4. The odds for retinopathy will be higher among ARIC participants with diabetes who consumer greater than one alcohol beverage per day at visits 1 and 3 compared with those who consume less.

6. Data:
1. Retinal data required from 1993-5 visits:
level of diabetic retinopathy, number of microaneurisms, number and type of retinal hemorrhage, presence of Hemorrhages or microaneurisms, presence of
hard or soft exudates, macular edema, IRMA, venous beading

2. Dietary Data:
A. Estimates of intake at baseline (1987-89) from foods using updated Willett databases:
energy
macronutrient-related variables:
animal fat, vegetable fat, saturated fat, monounsaturate fat, oleic, polyunsaturated fat, linoleic acid, cholesterol, omega 3 fatty acids, protein,
carbohydrate, sucrose, crude fiber, alcohol
B. Estimates of intake at baseline from foods and supplements (estimate 1987-89 intake using supplement type and duration variables gathered at Visit 3):
minerals: iron, magnesium
vitamins: vitamin C, vitamin E, folate, B12

whole grains
C. Estimates (above) of food and nutrient intake at visit 3 (to assess diet stability)
Years of supplement use:
multivitamins
any supplement providing: vitamin C, vitamin E (these variables are derived by the research team of J. Mares-Perlman from supplement data
collected at Visits 1 through 3)

3. Blood values at baseline and follow-up visits:
Magnesium
Estimates of plasma levels of individual fatty acids in phospholipids (participants at the Minnesota site only)

4. Other variables to evaluate as explanatory variables, confounders or effect modifiers:
Serum values from visit 1:
glucose, insulin, triglycerides, ultrasonigraphically-determined carotid wall thickness, history of cigarette smoking (never, past, current), numbers of
cigarettes/day, average weekly intake of alcoholic beverages (beer, wine, hard liquor), history of past heavy drinking, education, income, race, gender,
height, weight, body mass index, waist-to-hip ratio, physical activity, systolic and diastolic blood pressure measurements, history of hypertension, history
of diabetes with insulin use, history of diabetes without insulin use, and use of diabetic diet and years

on diabetic diet.

7. Analyses and Statistical Power:
The primary outcome variable will be the presence or absence of diabetic retinopathy at Visit 3. Of the 1,307 people with diabetes with retinal photographs, 22% (291 persons) have retinopathy. Associations with types and severity of retinopathy will be evaluated for consistency in relationships with independent variables.

Logistic regression analyses will be employed to evaluate relationships between the existence of diabetic retinopathy and the level of dietary intake or levels of nutrients in the serum. Systematic evaluations of confounders and effect modifiers (see list above) will be undertaken.

Sample Size Calculations The statistical power available to evaluate difference in odds ratios for retinopathy among people in extreme quintiles for level of nutrient intake was computed. We estimate, given the rate for retinopathy, a power of 81% to detect a 60% increase in risk among people in extreme quintiles. The power to detect associations with levels in the lowest quintile (Eg for magnesium) compared to all others is greater; a 50% increase in risk can be detected with 80% power.

The associations between the levels of different fatty acids (in cholesterol esters and phospholipids) and retinopathy will be evaluated among participants at the Minneapolis site only. At this site there were 241 person with diabetes and gradable eye photographs, 32 of whom had retinopathy at Visit 3. The minimum detectable difference between average levels of specific fatty acids among people with and without retinopathy was estimated. For cholesterol esters, the minimum percent difference in saturated fatty acids that could be detected with 90% power is 0.4%. For monounsaturated fatty acids the minimum is 1.1% and for polyunsaturated fatty acids is 1.6%. These values are less than the range of values in the population between the 25th and 50th percentiles. For phospholipid fatty acids, the power is slightly lower for saturated fatty acids (a difference of 0.6% can be detected with 90% power) and higher for monounsaturated fatty acids and polyunsaturated fatty acids (differences of 0.5% for each type can be detected with 90% power.) Thus, there is adequate statistical power to conduct the first epidemiologic evaluation of these associations. The results may form the basis for larger studies in the future in the ARIC population or elsewhere.

Overall, the statistical power that is available to evaluate the relationships between nutritional factors and retinopathy in the ARIC population is considerably greater than that previously available in past studies to evaluate the relationships of diet to retinopathy.