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1. Title:
Relation of Diet to Diabetic Nephropathy

2. Writing Group:
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3. Timeline:
Analyses are planned to be completed between January, 2000 and April, 2001.

4. Rationale:
More than one-third of people with diabetes mellitus develop diabetic nephropathy. It is the single, most common cause of end-stage renal disease in the United States. The Diabetes Control and Complications Trial has demonstrated that glycemic control achieved with intensive insulin treatment results in a substantial reduction in the incidence and progression of nephropathy. However, epidemiologic studies indicate that tight glycemic control is only achieved by a small percentage of the population. Aggressive management of hypertension and the use of ACE inhibitors have also been shown to slow the progression of nephropathy. However, these approaches do not prevent it. There is a need to identify modifiable factors to prevent and slow the development of nephropathy among people with diabetes. This will become even more important as the population ages in the next fifty years, when even greater numbers of older adults develop Type 2 diabetes are at risk for developing renal complications.

Dietary factors which improve the control of blood glucose may slow the development of nephropathy. Diet levels of macronutrients, vitamins and minerals could influence glycemic control by influencing postprandial rises in blood sugar, as well as by influencing insulin sensitivity and glucose utilization by peripheral tissues. Higher levels of fat in the diet are thought to contribute to obesity, which, in turn lowers insulin sensitivity. Epidemiological studies also indicate that diets high in fat may reduce insulin sensitivity, independent of weight. Other dietary patterns associated with high-fat diets, such as the low dietary content of carbohydrate and fiber, may be responsible for poorer blood glucose control or higher rates of diabetes that are sometimes associated with high-fat diets. Diets high in carbohydrates or dietary fiber have been observed to improve blood glucose control in short-term clinical studies. Diets that are higher in fat are also generally lower in fruits and vegetables. Lower intake of these foods may provide fewer micronutrients that may be important in the maintenance of blood glucose control such as magnesium, and vitamins C and E. We plan to study the relationship between levels of macronutrients and micronutrients in the diet and the incidence of early renal disease in the ARIC population. We will also determine whether these relationships are attenuated by markers of blood glucose control (fasting glucose), insulin sensitivity (fasting serum insulin values), physical activity and obesity.

Excessive protein intake has been implicated in the pathogenesis of diabetic nephropathy. However, there is limited scientific data upon which to establish from nutrition recommendations for protein intake in diabetes. Some clinical trials indicate a beneficial effect of protein restriction on progression from early to later stages of renal disease in patients with diabetes. However, it is unclear whether the protein composition of the diet will influence the onset of early renal disease. We will evaluate the relationship of protein intake to the incidence of early renal disease in the ARIC population.

5. Main Hypothesis:
1. ARIC participants with diabetes at visit four (we estimate 1,258 persons) who have dietary intakes:
   A. in the highest quintile vs all other quintiles for: protein, fat saturated fat, polyunsaturated fat
   B. in the lowest versus all other quintiles for: fruit, vegetables and grains, monounsaturated fatty acids, carbohydrates, magnesium in the serum, magnesium in the diet, vitamin C, vitamin E
   C. will have higher odds ratios for the nine-year incidence or early renal dysfunction (change in serum creatinine of 0.4 mg/dL or greater) after controlling for the duration of diabetes, use of insulin, and hypertension.
2. These associations will strengthen after excluding people whose diets have changed substantially between Visits 1 and 3.
3. These associations will not be attenuated by further controlling for obesity, physical activity, fasting blood glucose or fasting insulin.
4. Among ARIC participants with diabetes, those that have a change in serum creatinine of 0.4 mg/dl or greater will:
   A. be less likely to be long-term users of multivitamin supplements
   B. be less likely to use vitamin C or E supplements for six or more years.
5. Serum magnesium at baseline will be inversely related to the nine-year incidence of early renal dysfunction.
6. Data:
   1. Renal data: serum creatinine (visits 1, 2, and 4)
   2. Dietary data:
      A. Estimates of intake at baseline (1987-89) from food using updated Willett databases:
         - energy
         - macronutrient-related variables: animal fat, vegetable fat, saturated fat, monounsaturated fat, oleic, polyunsaturated fat, linoleic acid, cholesterol, omega 3 fatty acids, protein, carbohydrate, sucrose, crude fiber, alcohol
      3. Estimates of intake at baseline from foods and supplements (estimate 1987-89 intake using supplement type and duration variables gathered at visit 3):
         A. minerals: magnesium
         B. vitamins: vitamin C, vitamin #
         C. servings of: fruits and vegetables; fruits; vegetables; whole grains; nuts; fruits, vegetables, nuts and whole grains
      4. Estimates (above) of food and nutrient intake at Visit 3 (to assess diet stability)
      5. Years of supplement use:
         A. multivitamins
         B. any supplement providing: vitamin C, vitamin 3 (these variables are derived by the research team of J. Mares-Perlman from supplement data collected at Visits 1 through 3)
   6. Blood values at baseline and follow-up visits: magnesium
   7. Other variables to evaluate as explanatory variables, confounders or effect modifiers:
      A. Serum values from Visit 1: glucose, insulin, triglycerides, HDL and LDL cholesterol, ultrasonographically 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, use of diabetic diet and years on diabetic diet
6. Analyses and Statistical Power:
   Logistic regression will be used to evaluate relationships of nutritional variables to early renal disease. The
main outcome measure to reflect early renal disease will be a change in serum creatinine of 0.4 mg/dL between Visit 1 and Visit 4 (after correcting for any analytic drift in creatinine values and excluding persons with baseline serum creatinine values over 1.5 mg/dL). Based on the incidence of serum creatinine between visit one and two, we estimate 180 people to have developed an increase in serum creatinine of this magnitude between visits one and four. This will result in the ability to detect odds ratios of 1.5 among people in high or low quintiles versus all other quintiles for dietary macronutrients and micronutrients at 80% power. The power to detect statistically significant odds ratios between high and low quintiles is somewhat less (1.75).

If values for microalbuminuria become available, relationships of diet to this separate indicator of early diabetic nephropathy may be explored, as well.