# Scanning the Literature

Steven Granier, MD
Janet Cook, MD

## Add Another to the List of Smoking Risks

Nakanishi N, Nakamura K, Matsuo Y, et al. Cigarette smoking and risk for impaired fasting glucose and type 2 diabetes in middle aged Japanese men. Ann Intern Med 2000; 133:183-191.

**Background:** The contribution of cigarette smoking to development of impaired fasting glucose and type 2 diabetes remains unclear. **Objective:** To investigate the association of cigarette smoking with development of impaired fasting glucose and type 2 diabetes. **Design:** Prospective cohort study. **Setting:** Work site in Osaka, Japan. **Participants:** 1266 Japanese male office workers 35 to 59 years of age who did not have impaired fasting glucose or type 2 diabetes and were not taking medication for hypertension at study entry. **Measurements:** Fasting plasma glucose levels were measured at annual health examinations from May 1994 through May 1999. Impaired fasting glucose was defined as a fasting glucose level of at least 6.1 mmol/L (110 mg/dL) but less than 7.0 mmol/L (126 mg/dL). Type 2 diabetes was defined as a fasting glucose level of 7.0 mmol/L or more or current receipt of hypoglycemic medication. **Results:** 87 and 54 men developed impaired fasting glucose and type 2 diabetes during 5817 and 5937 person-years follow-up, respectively. After controlling for potential predictors of diabetes, the relative risk for impaired fasting glucose compared with never-smokers was 1.62 (95% CI, 0.85 to 3.10) for ever-smokers, 1.14 (CI, 0.58 to 2.25) for persons who smoked 1 to 20 cigarettes/d, 1.33 (CI, 0.63 to 2.80) for those who smoked 21 to 30 cigarettes/d, and 2.56 (CI, 1.32 to 4.95) for those who smoked 31 or more cigarettes/d (*P* for trend for current smokers only = 0.013). The respective multivariate-adjusted relative risks for type 2 diabetes compared with never-smokers were 1.08 (CI, 0.34 to 3.42), 1.88 (CI, 0.71 to 5.00), 3.02 (CI, 1.15 to 7.94), and 4.09 (CI, 1.62 to 10.29) (*P* for trend for current smokers only < 0.001). The number of pack-years of exposure was also positively related to development of impaired fasting glucose and type 2 diabetes (*P* for trend = 0.039 and 0.002, respectively). The relative risk for impaired fasting glucose and type 2 diabetes in current smokers versus never-smokers was stronger among men with a body mass index less than 24.2 kg/m$^2$ than among men with a body mass index of 24.2 kg/m$^2$ or more, although the absolute risk was greater in more obese men. **Conclusion:** The number of cigarettes smoked daily and the number of pack-years of exposure seem to be associated with development of impaired fasting glucose and type 2 diabetes in middle-aged Japanese men.

**Comments:** Primary care physicians usually discuss with their patients the risks associated with smoking. The potential problems include lung cancer and COPD, but could patients also be putting themselves at risk for glucose intolerance or diabetes? This study tried to answer this question in middle-aged Japanese men. They gathered data for 5 years, and the findings were very interesting. After controlling for potential predictors of diabetes, a positive correlation was found. Compared with never-smokers, ever-smokers had a higher relative risk of developing glucose intolerance and diabetes. Also, the risk increased as the number of cigarettes per day increased and as the pack-years of exposure increased. Therefore, physicians should consider including the risk for developing glucose intolerance and diabetes in their litany of problems associated with smoking cigarettes.

## Should Diabetics Double Their Fiber?

Chandalia M, Garg A, Lutjohann D, et al. Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. N Engl J Med 2000; 342:1392-1398.

**Background:** The effect of increasing the intake of dietary fiber on glycemic control in patients with type 2 diabetes mellitus is controversial. **Methods:** In a randomized, crossover study, we assigned 13 patients with type 2 diabetes mellitus to follow two diets, each for six weeks: a diet containing moderate amounts of fiber (total, 24 g; 8 g of soluble fiber and 16 g of insoluble fiber), as recommended by the American Diabetes Association (ADA), and a high-fiber diet (total, 50 g; 25 g of soluble fiber and 25 g of insoluble fiber) containing foods not fortified with fiber (unfortified foods). Both diets, prepared in a research kitchen, had the same macronutrient and energy content. We compared the effects of the two diets on glycemic control and plasma lipid concentrations. **Results:** Compliance with the diets was excellent. During the sixth week of the high-fiber diet, as compared with the sixth week of the ADA diet, mean daily preprandial plasma glucose concentrations were 13 mg per deciliter (0.7 mmol per liter) lower (95 percent confidence interval, 1 to 24 mg per deciliter [0.1 to 1.3 mmol per liter]; P=0.04) and mean daily urinary glucose excretion was 1.3 g lower (median difference, 0.23 g; 95 percent confidence interval, 0.03 to 1.83; P=0.008). The high-fiber diet also lowered the area under the curve for 24-hour plasma glucose and insulin concentrations, which were measured every two hours, by 10 percent (P=0.02) and 12 percent (P=0.05), respectively. The high-fiber diet reduced plasma total cholesterol concentrations by 6.7 percent (P=0.02), triglyceride concentrations by 10.2 percent (P=0.02), and very-low-density lipoprotein cholesterol concentrations by 12.5 percent (P=0.01). **Conclusions:** A high intake of dietary fiber, particularly of the soluble type, above the level recommended by the ADA, improves glycemic control, decreases hyperinsulinemia, and lowers plasma lipid concentrations in patients with type 2 diabetes.

**Comments:** Research is constantly being done on medication used in diabetes, but this study looks at the impact of diet on glycemic control in type 2 diabetes. Investigators specifically evaluated the effect of high dietary fiber intake (instead of the standard fiber intake in the ADA diet) on glucose control. Using a crossover design, both groups followed the diets for 6 weeks each. After the data were analyzed, the diet with higher dietary fiber (double the amount in the ADA diet) resulted in improved glycemic control, lower cholesterol levels, and less hyperinsulinemia. While these diets were prepared in a research kitchen and would be difficult to duplicate at home, these findings may allow for more dietary options in the management of patients with type 2 diabetes.

## Can Hepatitis C Lead to Diabetes?

Mehta SH, Brancati FL, Sulkowski MS, et al. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. Ann Intern Med 2000; 133:592-599.

**Background:** Hepatitis C virus (HCV) infection may contribute to the development of diabetes mellitus. This relationship has not been investigated at the population level, and its biological mechanism remains unknown. **Objective:** To examine the prevalence of type 2 diabetes among persons with HCV infection in a representative sample of the general adult population of the United States. **Design:** Cross-sectional national survey. **Setting:** The Third National Health and Nutrition Examination Survey, 1988-1994. **Participants:** 9841 persons older than 20 years of age for whom data on HCV infection and diabetes were complete. **Measurements:** The presence of diabetes was ascertained by using American Diabetes Association guidelines based on fasting plasma glucose measurement and medication history. Presence of HCV infection was assessed by testing for serum HCV-specific antibodies (anti-HCV). **Results:** Of the 9841 persons evaluated, 8.4% had type 2 diabetes and 2.1% were anti-HCV positive. Type 2 diabetes occurred more often in persons who were older, were nonwhite, had a high body mass index, and had low socioeconomic status. Type 2 diabetes was less common in

persons who acknowledged previous illicit drug use. After adjustment for these factors, persons 40 years of age or older with HCV infection were more than three times more likely than those without HCV infection to have type 2 diabetes (adjusted odds ratio, 3.77 [95% CI, 1.80 to 7.87]). None of the 19 persons with type 1 diabetes were anti-HCV positive. **Conclusion:** In the United States, type 2 diabetes occurs more often in persons with HCV infection who are older than 40 years of age.

**Comments:** Over 2.5 million people in the United States have chronic hepatitis C. As physicians, we discuss associated risks for developing cirrhosis and hepatic carcinoma and many other non-hepatic conditions. Perhaps we should include diabetes as one of the possible complications. This study sought to evaluate the relationship between hepatitis C and type 2 diabetes. After accounting for confounding variables, the final conclusion was that there was an increased prevalence of type 2 diabetes in patients over the age of 40 with hepatitis C. No biologic basis was determined for these findings but possibilities include progressive liver damage with worsening disease, or other time related factors. Interestingly, the same relationship was not found for hepatitis B or other forms of liver disease. Given this relationship, we should counsel our patients with hepatitis C on their risk for developing diabetes and perhaps screen for this more frequently.

*(For a more detailed examination of the relationship between diabetes and hepatitis, see the article by Drs. Mason and Alexander, pp.158-163).*

## Homocystine and Diabetic Retinopathy

Hoogeveen EK, Kostense PJ, Eysink PE, et al. Hyperhomocysteinemia is associated with the presence of retinopathy in type 2 diabetes mellitus: the Hoorn study. Arch Intern Med 2000; 160:2984-2990.

**Background:** Retinopathy is the leading cause of blindness among patients with type 2 diabetes mellitus (DM). Hyperhomocysteinemia is a recently recognized risk factor for cardiovascular disease, independent of established risk factors. **Objective:** To study the association between the homocysteine level and retinopathy among subjects with and without DM. **Methods:** We studied an age-, sex-, and glucose tolerance–stratified random sample of a 50- to 75-year-old general white population in the Hoorn Study (N = 625). Retinal vascular changes (retinopathy) were assessed using ophthalmoscopy and/or fundus photography. Hyperhomocysteinemia was defined as a serum total homocysteine level greater than 16 $\mu$mol/L. **Results:** The prevalence of retinopathy was 9.8% (28/285) in subjects with normal glucose tolerance, 11.8% (20/169) in those with impaired glucose tolerance, 9.4% (10/106) in those with newly diagnosed type 2 DM, and 32.3% (21/65) in those with known type 2 DM. The prevalence of retinopathy was 10.3% (39/380) in subjects without hypertension and 16.3% (40/245) in subjects with hypertension; it was 12.0% (64/534) in subjects with a serum total homocysteine level of 16 $\mu$mol/L or less and 16.5% (15/91) in those with a serum total homocysteine level of more than 16 $\mu$mol/L. After stratification for DM and adjustment for age, sex, glycosylated hemoglobin, and hypertension, the odds ratio (95% confidence interval) for the relation between retinopathy and hyperhomocysteinemia was 0.97 (95% confidence interval, 0.42-2.82) in patients without DM and 3.44 (95% confidence interval, 1.13-10.42) in patients with DM ($P$ = .08 for interaction). **Conclusion:** The findings suggest that hyperhomocysteinemia may be a risk factor for retinopathy in patients with type 2 DM, but probably not in patients without DM.

**Comments:** Diabetic retinopathy is the leading cause of blindness among type 2 diabetics and causes visual impairment in many more. This condition seems to be a vascular, specifically a capillary bed, disorder. Many factors affect one's risk for diabetic retinopathy, including control of the disease and hypertension. Elevated homocystein levels were recently recognized as an independent risk factor for cardiovascular disease. This study sought to investigate whether hyperhomocysteinemia was associated with diabetic retinopathy. The study showed that increased levels of homocystein were associated with diabetic retinopathy (and not nondiabetic retinopathy) independent of known causes like hypertension and glycemic control. While more prospective long-range studies are needed, clinicians should consider screening newly diagnosed type 2 diabetics for hyper-homocysteinemia to assess their risk for diabetic retinopathy. If this is detected, folic acid supplementation may decrease the incidence of diabetic vision loss and impairment.

*Dr. Granier is on staff in Ochsner's Department of Internal Medicine and a member of The Ochsner Journal Editorial Board.*

## Traditional versus Nontraditional

Saito I, Folsom AR, Brancati FL, et al. Nontraditional risk factors for coronary heart disease incidence among persons with diabetes: the atherosclerosis risk in communities (ARIC) study. Ann Intern Med 2000;133:81-91.

**Background:** Major risk factors explain much of the excess risk for coronary heart disease produced by diabetes, but nontraditional factors may also relate to incident coronary heart disease. **Objective:** To examine the association of traditional and nontraditional risk factors with incidence of coronary heart disease in adults with diabetes. **Design:** Prospective cohort study. **Setting:** The Atherosclerosis Risk in Communities (ARIC) Study. **Participants:** 1676 middle-aged persons who had diabetes but no history of prevalent coronary heart disease. **Measurements:** Multiple risk factors were recorded at baseline. Follow-up was from 1987 through 1995. **Results:** 186 participants developed incident coronary heart disease events during follow-up. As expected, the incidence of coronary heart disease in participants with diabetes was associated positively with traditional risk factors (hypertension, smoking, total cholesterol level, and low high-density lipoprotein [HDL] cholesterol level). After adjustment for sex, age, ethnicity, and ARIC field center, incident coronary heart disease was also significantly associated with waist-to-hip ratio; levels of $HDL_3$ cholesterol, apolipoproteins A-1 and B, albumin, fibrinogen, and von Willebrand factor; factor VIII activity; and leukocyte count. However, after adjustment for traditional risk factors for coronary heart disease, only levels of albumin, fibrinogen, and von Willebrand factor; factor VIII activity; and leukocyte count remained independently associated with coronary heart disease ($P<0.03$). The relative risks associated with the highest compared with lowest grouping of albumin, fibrinogen, factor VIII and von Willebrand factor values and leukocyte count were 0.64 (95% CI, 0.44 to 0.92), 1.75 (CI, 1.12 to 2.73), 1.58 (CI, 1.02 to 2.42), 1.71 (CI, 1.11 to 2.63), and 1,90 (CI, 1.16 to 3.13), respectively. Adjustment for diabetes treatment status attenuated these

associations somewhat. **Conclusions:** Levels of albumin, fibrinogen, and von Willebrand factor; factor VIII; and leukocyte count were predictors of coronary heart disease among persons with diabetes. These associations may reflect 1) the underlying inflammatory reaction or microvascular injury related to atherosclerosis and a tendency toward thrombosis or 2) common antecedents for both diabetes and coronary heart disease.

**Comments:** Diabetes increases the risk of coronary heart disease and its manifestations, causing great impacts on morbidity and mortality. Hypertension, smoking, total cholesterol, and low HDL cholesterol levels are traditional risk factors for coronary heart disease in diabetics; however, some nontraditional risk factors have also been associated. This study was intended to examine the association of traditional and nontraditional risk factors with incidence of coronary heart disease in the adult diabetic and concluded that albumin, fibrinogen, von Willebrand factor, factor VIII activity, and leukocyte count were predictors of coronary heart disease among diabetic adults, independent of traditional risk factors. Some limitations of the study were noted. As primary care physicians, we should consider all risk factors for coronary heart disease; but remember, prevention is key.

## Something Other Than Insulin

Langer O, Conway DL, Berkus MD, et al. A comparison of glyburide and insulin in women with gestational diabetes mellitus. N Engl J Med 2000;343:1134-1138.

**Background:** Women with gestational diabetes mellitus are rarely treated with a sulfonylurea drug, because of concern about teratogenicity and neonatal hypoglycemia. There is little information about the efficacy of these drugs in this group of women. **Methods:** We studied 404 women with singleton pregnancies and gestational diabetes that required treatment. Th women were randomly assigned between 11 and 33 weeks of gestation to receive glyburide or insulin according to an intensified treatment protocol. The primary end point was achievement of the desired level of glycemic control. Secondary end points included maternal and neonatal complications. **Results:** The mean (+/-SD) pretreatment blood glucose concentration as measured at home for one week was 114+/-19 mg per deciliter (6.4+/-1.1 mmol per liter) in the glyburide group and 116+/-22 mg per deciliter (6.5+/-1.2 mmol per liter) in the insulin group (P=0.33). The mean concentrations during treatment were 105+/-16 mg per deciliter (5.9+/-0.9 mmol per liter) in the glyburide group and 105+/-18 mg per deciliter (5.9+/-1.0 mmol per liter) in the insulin group (P=0.99). Eight women in the glyburide group (4 percent) required insulin therapy. There were no significant differences between the glyburide and insulin groups in the percentage of infants who were large for gestational age (12 percent and 13 percent, respectively); who had macrosomia, defined as a birth weight of 4000 g or more (7 percent and 4 percent); who had lung complications (8 percent and 6 percent); who had hypoglycemia (9 percent and 6 percent); who were admitted to a neonatal intensive care unit (6 percent and 7 percent); or who had fetal anomalies (2 percent and 2 percent). The cord-serum insulin concentrations were similar in the two groups, and glyburide was not detected in the cord serum of any infant in the glyburide group. **Conclusions:** In women with gestational diabetes, glyburide is a clinically effective alternative to insulin therapy.

**Comments:** The prevalence of gestational diabetes in all pregnancies varies from 1% to 14 %, depending on the population studied and the diagnostic test used. Similar to the nonpregnant diabetic, the principal approach to glycemic control in the pregnant diabetic is dietary therapy, with the addition of a pharmacological agent when diet alone is insufficient. Although insulin has been the main agent used to achieve glycemic control in gestational diabetes, other therapies, if appropriately safe, effective, and available, should be considered. This study was designed to prove the efficacy of glyburide during pregnancy. Glycemic control and perinatal outcomes were similar for patients treated with glyburide or insulin. Therefore, the authors conclude that glyburide is an alternative agent for women with gestational diabetes.

## The Better Diabetic Cocktail

Bastyr EJ III, Stuart CA, Brodows RG, et al. Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA1c. IOEZ Study Group. Diabetes Care 2000; 23:1236-1241.

**Objective:** To compare the overall efficacy of combination therapies focused on fasting or postprandial blood glucose in patients with type 2 diabetes not adequately controlled with oral sulfonylurea agents alone. **Research Design and Methods:** A total of 135 patients were randomly assigned for 3 months to 1 of 3 combination regimens with glyburide (G) that addressed postprandial blood glucose with insulin lispro (L+G), premeal blood glucose with metformin (M+G), or fasting blood glucose (FBG) with bedtime NPH insulin (NPH+G). **Results:** At end point, HbA1c was significantly lower with all therapies (P=0.001) and was significantly lower for L+G (7.68+/-0.88%) compared with either NPH+G (8.51+/-1.38%, P=0.003) or M+G (8.31+/-1.31%, P=0.025). FBG at end point was significantly lower for NPH+G (8.49+/- 2.36 mmol/l) compared with either L+G (10.57+/-1.97 mmol/l, P=0.001) or M+G (9.69+/-2.89 mmol/l, P=0.029). The mean 2-h postprandial glucose after a test meal was significantly lower for L+G (10.87+/-2.88 mmol/l) versus NPH+G (12.21 +/- 3.12 mmol/l, P=0.052) or versus M+G (12.72+/-3.26 mmol/l, P=0.009). The overall rate of hypoglycemia (episodes per 30 days) was low and not statistically significant between groups (P=0.156). **Conclusions**: Adding a second antihyperglycemic agent, regardless of its timing of action, lowers HbA1c and glucose values. However, when insulin lispro was used to focus on postprandial blood glucose, there was greater impact on overall metabolic control. These data support the importance of lowering postprandial blood glucose to optimize overall glycemic control and thus improve long-term outcomes.

**Comments:** Fortunately, several therapeutic options are available to assist our patients with optimizing glycemic control. We should discuss these options with them. This study was designed to compare the efficacy and safety of combination therapies in patients with type 2 diabetes uncontrolled on sulfonylurea agents alone. As shown in the study, we know adding another agent lowers glucose and HbA1c levels. Furthermore, insulin lispro as a second agent for postprandial glucose control showed a greater impact on overall metabolic control. This supports the importance of postprandial glucose control in overall metabolic control. While this study has some limitations, patient satisfaction was improved independent of randomized therapy. Primary care providers should consider all possible therapies and aim for improved overall outcomes.

## Microalbuminuria and Proteinuria as Risks

Valmadrid, CT, Klein, R, Moss, SE, et al. The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. Arch Intern Med 2000;160:1093-1100.

**Background:** Despite the numerous studies on the relation of albuminuria with increased risk of all-cause mortality in type 2 diabetes mellitus, it remains uncertain whether microalbuminuria and/or gross proteinuria are independent risk factors for cardiovascular mortality. Moreover, the association of albuminuria with cardiovascular mortality in people with type 2 diabetes mellitus has not been well described in US populations. **Objective:** To estimate the relative risks (RRs) for the associations of microalbuminuria and gross proteinuria with cardiovascular disease mortality among persons with older-onset diabetes mellitus. **Methods:** We conducted a prospective cohort study of 840 people with older-onset diabetic mellitus who provided urine samples in the 1984-1986 examination of a population-based study of diabetic persons. The presence of microalbuminuria was determined by an agglutination inhibition assay and gross proteinuria by a reagent strip. The main outcome was time to mortality form cardiovascular disease, as determined from death certificates. **Results:** Of the 840 older-onset diabetic persons, 54.8% had normoalbuminuria, while 24.8% had microalbuminuria and 20.5% had gross proteinuria. During the 12-year follow-up (6127 person-years), we identified 364 deaths from cardiovascular disease. Compared with persons with normoalbuminuria, those with microalbuminuria and gross proteinuria had significantly higher risks of cardiovascular mortality. The RR as controlled for age, sex, glycemic control, insulin use, alcohol intake, physical activity, cardiovascular disease history, antihypertensive use, and

retinopathy severity was 1.84 (95% confidence interval [CI], 1.42-2.40) for those with microalbuminuria and 2.61 (95% CI, 1.99-3.43) for those with gross proteinuria. Further adjustment for other factors did not change the relations we found. When the end point used was mortality from coronary heart disease, stroke, or all causes, the increased risks were significant for both microalbuminuria (adjusted RRs [95% CIs], 1.96 [1.42-2.72], 2.20 [1.29-3.75], and 1.68 [1.35-2.09], respectively) and gross proteinuria (adjusted RRs [95% CIs], 2.73 [1.95-3.81], 2.33 [1.28-4.24], and 2.47 [1.97-3.10], respectively). **Conclusions:** Results from our population-based study strongly suggest that both microalbuminuria and gross proteinuria were significantly associated with subsequent mortality from all causes and from cardiovascular, cerebrovascular, and coronary heart diseases. These associations were independent of known cardiovascular risk factors and diabetes-related variables.

*Dr. Cook practices at the Ochsner Clinic in Baton Rouge.*

**Comments:** It is uncertain whether microalbuminuria or gross proteinuria in type 2 diabetics are associated risk factors for cardiovascular mortality. This study involved 840 people with older-onset diabetes mellitus who provided their urine samples for examination. The main outcome was time to mortality from cardiovascular disease, as determined from death certificates. During the 12-year follow-up, 364 deaths were identified from cardiovascular disease. After adjustments for variables, higher relative risks existed among those patients with microalbuminuria (1.84) and gross proteinuria (2.61), strongly suggesting that both are independently associated with mortality from cardiovascular disease.