Dietary Fat and the Development of Type 2 Diabetes

The recent release of results from the Finnish Diabetes Prevention Study (FDPS) (1) and the Diabetes Prevention Program (DPP) (2) strongly confirm the hypothesis that interventions that alter diet and physical activity to achieve weight loss can prevent or postpone the development of type 2 diabetes in high-risk individuals. The next challenge will be to translate these impressive results into clinical practice. It seems relevant in this context to ask, "What is the best dietary intervention strategy to improve insulin action and prevent diabetes?" In the current issue of *Diabetes Care*, van Dam et al. (3) assess the association between diet and development of diabetes over a 12-year period in the Health Professionals Follow-up Study (HPFS). They find that consumption of a high-fat diet and high intakes of saturated fat are associated with an increased risk of type 2 diabetes. However, this association disappears when they adjust for BMI. They also find that frequent consumption of processed meats is associated with an increased risk for diabetes. Does this study alter the recommendations we make to individuals at risk for developing diabetes?

Controversy over the role of high-fat diets in insulin resistance

A large body of experimental data generated in laboratory animals strongly supports the notion that high-fat diets are associated with impaired insulin action. It appears from animal studies that saturated fats, in particular, have the most detrimental effects. Based on this information, along with the known risks of high saturated fat intake on cardiovascular disease risk, professional organizations such as the American Diabetes Association, the American Heart Association, and the U.S. Department of Agriculture have made recommendations that Americans aim for a total fat intake of no more than 30% of calories and choose foods low in saturated fat. However, some authors have criticized the evidence on which these public health recommendations have been based (4), and it has been argued that total fat as a proportion of total energy is not important in the prevention of type 2 diabetes (5).

The current study adds weight to the longstanding recommendation to restrict total fat and saturated fat. While adjusting for BMI eliminates the effect, this does not mean that dietary fat is not important. It is biologically plausible that high-fat diets promote weight gain, which then promotes insulin resistance. There is a large body of evidence that supports this view. In addition, there is growing evidence that obesity plays a central pathogenic role in the development of diabetes (1,2). This means that any dietary factor that promotes weight gain will likely promote the development of diabetes. The ubiquitous role of fat in fuel metabolism, energy and fat balance, and structure and function of cell membranes and also as a ligand for nuclear receptors that influence gene expression, make it highly plausible that both the total amount and type of dietary fat play an important role in insulin action, weight maintenance, and prevention of diabetes.

Interventional trials

As van Dam et al. acknowledge in the current issue, the strongest evidence about the relations between dietary factors and the development of disease comes from randomized controlled intervention trials (RCTs). This is true when the trials are carefully conducted and are of sufficient size and duration to detect a difference in diabetes incidence. The recent FDPS (1) and DPP (2), along with the Da Qing Impaired Glucose Tolerance (IGT) and Diabetes Study (6), increased study efficiency by enrolling high-risk individuals with detectable IGT at the beginning of the trial. These studies have demonstrated that the use of an intervention strategy including dietary counseling is associated with up to a 50% reduction in the risk of developing type 2 diabetes. All of these trials used an intervention that focused in part on recommending a restriction in total fat and, in particular, saturated fat in the diet. In the FDPS, the DPP, and the Da Qing studies, suggestions to restrict fat/saturated fat were combined with other suggestions, including caloric restriction, increased fiber intake, increased vegetable intake, and in most intervention groups, increased physical activity. The recent follow-up from the Workforce Diabetes Survey in New Zealand (7) demonstrated that a relatively simple message to restrict fat intake, without explicit instructions to restrict calories, can lead to weight loss and sustained improvements in glycemic status over 5 years (8). The combined results from these studies in ethnically and geographically diverse populations provide the strongest evidence to date that a strategy that includes reducing fat in the diet has beneficial effects on insulin action and the prevention of diabetes.

Further large scale randomized controlled trials to prevent diabetes onset in free-living populations will be difficult (DPP has cost $174.3 million to date) to conduct for all dietary components that may be involved and under all conditions that may modify dietary effects (e.g., level of physical activity, age, and disease stage). In the large RCTs like DPP, nonrandomized variation in diet and physical activity will be further studied to shed light on these questions. Observational studies like the HPFS, which take advantage of the variation in diet already occurring in the population, provide another opportunity to further our understanding of dietary effects in the development of insulin resistance and type 2 diabetes.

Strengths and limitations of observational studies

The strengths of the studies from the Harvard School of Public Health, including the Nurses Health Study (NHS) and the HPFS, are their large size, longitudinal design, repeated dietary measures, and relative sophistication of the study population to provide the information needed. The longitudinal design reduces

the chance that those developing diabetes provide systematically different information than those not developing the disease because dietary information was collected before disease diagnosis. Confounding by other independent determinants of diabetes, such as physical activity, have been adjusted for in the analysis, although we must remain cautious about unknown/unmeasured confounding by independent causes of diabetes in both nonrandomized interventions and observational studies.

Additional limitations arise from measurement error, etiological heterogeneity of type 2 diabetes, potential differential effects that depend on disease stage and case definition, unaccounted for modifiers of the dietary effect, and bias introduced in the analysis. These limitations all have the potential to attenuate the estimated strength of association between dietary fat and diabetes. It should also be noted that, with the exception of measurement error, these potential limitations are not unique to observational studies but also occur in RCTs. It is critical to consider factors like these that could be responsible for incorrectly concluding that only a weak effect or no relation exists between dietary fat and diabetes.

Measurement error in the assessment of dietary intake as documented by these authors will attenuate the relative risk (RR) if the error is not related to developing diabetes. Any systematic underreporting of calories among heavier subjects who are at higher risk for developing diabetes should be largely accounted for in these studies, because all results have been adjusted for reported calorie intake. Any systematic underreporting of fat intake in heavier subjects in combination with the positive association between obesity and diabetes would be expected to bias the RR estimates for fat intake and diabetes downward. Unknown systematic measurement error was guarded against by collecting dietary information before a diagnosis of diabetes had been made. The remaining noise in dietary assessments is expected to result in RR estimates that underestimate the true strength of the association between dietary fat and diabetes.

Type 2 diabetes is commonly considered to be a complex disease with multiple etiologies. To the extent that multiple causal pathways lead to the development of diabetes, a case definition that includes cases due to causes not involving dietary fat will reduce the magnitude of the RR for dietary fat. The case definition may also need to consider the disease stage. The pathogenesis of insulin resistance and glucose intolerance is complex, involving signaling proteins communicating across cell membranes and cytoplasm and nuclear receptors in multiple tissues with tissue-specific effects in muscle, adipose, liver, pancreatic β-cells, and the brain. There are a large number of steps in the natural history of type 2 diabetes where nutrient influences might occur, and different nutrients may be important at different steps. In the HPFS, analyses suggested similar dietary effects in subjects coming to clinical diagnosis regardless of whether they had reported symptoms. Studies of hyperinsulinemia in subjects with normal glucose tolerance (9) and studies of cases identified by screening (10,11) are evaluating the role of diet at an earlier disease stage where dietary influences on insulin action may differ from later stages, when β-cell stress is greater. Differences in case definitions may be responsible for some of the apparent inconsistencies in epidemiological studies.

Finally, readers must carefully consider whether all of the variables included in multiple regression analyses are appropriate. Analyses that adjust rather than stratify by factors that modify the role of dietary fat in diabetes etiology (e.g., genetic susceptibility and physical activity) will underestimate the strength of the dietary fat/diabetes association in subgroups at risk for dietary fat–induced diabetes. In the HPFS (3), adjusting for consequences of dietary fat intake (e.g., hypercholesterolemia) or intermediate links in the causal chain (e.g., BMI) all have the potential to attenuate the RR estimates toward the null (12). It is difficult to compare the NHS and HPFS because results presented for the NHS were all adjusted for obesity (discussed above), and diet adjustments included protein intake, which added complexity to the interpretation (13). Perhaps the most difficult confounder to deal with is that of other dietary components that may be independently related to diabetes risk, such as calorie intake or cereal intake. It is important to recognize that adjustment for factors that are correlated with dietary fat may remove or attenuate a real dietary fat effect either due to a strong correlation between dietary factors in the population studied or due to confounding by measurement error (e.g., if cereal intake can be more accurately measured than fat intake, then this could help explain why adjustment for cereal attenuates the RR for dietary fat).

How to translate epidemiology in clinical practice

Clearly, increasing obesity and type 2 diabetes are serious public health problems in the U.S. and around the world. Behavioral interventions focusing on diet and physical activity are attractive because of their low risk and relatively low cost. This makes the question of which diet to recommend a pressing issue. One might ask which nutritional parameter among many should focus be placed on?

The current study did not find adverse effects of *trans*-fatty acids that were seen in the NHS. The association between saturated fat and diabetes risk seen in HPFS was not seen in the NHS. While the Iowa Women's Health Study did have a suggestion that the relative amounts of saturated fat versus polyunsaturated fat (as represented by the Keys score) were associated with diabetes risk, saturated fat alone was not (14). Why isn't there better agreement among the many studies that have looked for relationships between diet and the development of diabetes? These inconsistencies are not all that surprising, given the methodological issues mentioned earlier and the complexity of both diet and type 2 diabetes. Insulin resistance and the development of diabetes are complex processes involving multiple tissues and multiple gene products. It seems likely that dietary components may have varying effects in individuals with different predisposing genes and/or lifestyles and at different stages in the natural history of the disease. The challenge then in clinical practice is to translate these sometimes diverging research results into coherent recommendations for patients. However, we should not be overly discouraged. While epidemiological studies do not agree on all details, many common themes are apparent. A preponderance of evidence supports the beneficial effects of caloric restriction, physical activity, and whole grain, fruit, and vegetable consumption. Most of the available evidence suggests that polyunsaturated fat is either neutral or beneficial. Total fat, saturated fat, and high caloric intakes leading to

obesity appear to have detrimental effects. While there is evidence in favor of each of these nutritional parameters, presumption at this time would rest with the strategy that has been tested in intervention trials in humans, and that includes a low-fat strategy to prevent or delay the onset of type 2 diabetes.

Strategies for achieving dietary change need further study. A recent RCT found that targeting increased consumption of nutrient-dense fruit and vegetables resulted in a significant reduction in fat and sugar intake (15). However, targeting a reduction in less nutrient-dense sources of fat and sugar did not result in increased fruit and vegetable intake. As relations between diet and disease are becoming better defined, the challenge of understanding the complex determinants of eating behavior and consumption patterns is receiving increased attention. The ability to achieve and maintain behavior change in the general population is important to the long-term success of any disease prevention strategy involving dietary change.

JULIE A. MARSHALL, PHD
DANIEL H. BESSESEN, MD

From the University of Colorado Health Sciences Center, Denver, Colorado.

Address correspondence to Julie Marshall, University of Colorado Health Sciences Center, 4200 East Ninth Ave., Campus Box C245, Denver, CO 80262. E-mail: julie.marshall@uchsc.edu.

References

1. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Hanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M, Finnish Diabetes Prevention Study Group: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
2. The Diabetes Prevention Program: HHS news, August 6, 2001 [article online]. Available from http://www.nih.gov/NEWS/PR/AUG2001/NIDDK-08.htm. Accessed 21 January 2002.
3. van Dam RM, Willett WC, Rimm EB, Stampfer MJ, Hu FB: Dietary fat and meat intake in relation to risk of type 2 diabetes in men. *Diabetes Care* 25:417–424, 2002
4. Taubes G: Nutrition: the soft science of dietary fat. *Science* 291:2536–2545, 2001
5. Hu FB, van Dam RM, Liu S: Diet and risk of Type II diabetes: the role of types of fat and carbohydrate. *Diabetologia* 44:805–817, 2001
6. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care* 20:537–544, 1997
7. Swinburn BA, Metcalf PA, Ley SJ: Long-term (5-year) effects of a reduced-fat diet intervention in individuals with glucose intolerance. *Diabetes Care* 24:619–624, 2001
8. Mayer-Davis EJ: Low-fat diets for diabetes prevention. *Diabetes Care* 24:613–614, 2001
9. Marshall JA, Bessesen DH, Hamman RF: High saturated fat and low starch and fibre are associated with hyperinsulinaemia in a non-diabetic population: the San Luis Valley Diabetes Study. *Diabetologia* 40: 430–438, 1997
10. Marshall JA, Hamman RF, Baxter J: High-fat, low-carbohydrate diet and the etiology of non-insulin-dependent diabetes mellitus: the San Luis Valley Diabetes Study. *Am J Epidemiol* 134:590–603, 1991
11. Marshall JA, Hoag S, Shetterly S, Hamman RF: Dietary fat predicts conversion from impaired glucose tolerance to NIDDM: the San Luis Valley Diabetes Study. *Diabetes Care* 17:50–56, 1994
12. Hennekens CH, Buring JE: In *Epidemiology in Medicine*. Boston, Little, Brown and Company 1987, Ch. 12
13. Salmeron J, Hu FB, Manson JE, Stampfer MJ, Golditz GA, Rimm EB, Willett WC: Dietary fat intake and risk of type 2 diabetes in women. *Am J Clin Nutr* 73:1019–1026, 2001
14. Meyer KA, Kushi LH, Jacobs DR Jr, Folsom AR: Dietary fat and incidence of type 2 diabetes in older Iowa women. *Diabetes Care* 24:1528–1535, 2001
15. Epstein LH, Gordy CC, Raynor HA, Beddome M, Kilanowski CK, Paluch R: Increasing fruit and vegetable intake and decreasing fat and sugar in families at risk for childhood obesity. *Obesity Res* 9:171–178, 2001