Topics in Type 2 Diabetes and Insulin Resistance

ZACHARY T. BLOOMGARDEN, MD

This is the second of six articles based on presentations at the American Diabetes Association Scientific Sessions held 6–10 June 2008 in San Francisco, California.

Predicting diabetes

Frederick Brancati (Baltimore, MD) discussed diabetes screening. Approaches using age, sex, BMI, family history, hypertension, and lifestyle as predictive measures have shown good performance in cross-sectional and prospective studies, and capillary glucose measurement adds further value, although the public health impact of such approaches has not been determined. In the Diabetes Prevention Program (DPP), 158,177 individuals were screened, with 3,819 randomized. Those whose fasting capillary glucose was 90–115 mg/dl had increased risk of impaired glucose tolerance (IGT); levels ≥130 mg/dl were 250 times as likely as levels <90 mg/dl to be associated with IGT. Patrick O'Connor (Minneapolis, MN) pointed out that health plans have become very interested in identifying and treating diabetes and addressed the question of whether systematic identification of pre-diabetes by screening leads to better health outcomes than would occur without screening. Developing an approach to identification and subsequent interventions that would be cost-effective is an important priority. O'Connor reviewed responses to a survey of medical directors of 35 plans, caring for a total of 47 million individuals, focused on awareness of cardiometabolic risk. At-risk enrollees can be identified by age, BMI, sex, race, laboratory test results, physician diagnoses, smoking history, and prescription data based on pharmacy claims, although lack of electronic medical records is "a weak link." Duration of treatment and of illnesses (including diabetes) and other aspects of medical history are not readily available.

Nonetheless, using all the available information, it certainly is possible to identify individuals at increased diabetes risk. Two approaches are taken: *1*) direct outreach to large numbers of people for prevention of adverse outcome or *2*) case management of smaller numbers of people at much higher risk. In large-group outreach approaches, smoking cessation, healthy eating, and physical activity are typically recommended and the importance of lipid and blood pressure management is emphasized, but glucose measurement and approaches to reduction of glucose intolerance and insulin resistance are not currently recommended by the majority of managed-care programs. In disease management approaches, measures to improve insulin sensitivity and glycemia are limited to management of individuals with existing diabetes. Cardiometabolic risk information is, however, being given to participants in many plans, with priorities for health coaching, health risk appraisal, and incentives, such as discounts on health club membership. Use of case management to oversee treatment plans is less frequently being pursued than what is termed the "medical home" primary care approach of treatment managed and coordinated by an individual physician. Health care providers are offered lipid, blood pressure, and preventative health service guidelines, but the American Diabetes Association (ADA) guidelines are not typically stressed, and O'Connor suggested that "guidelines are increasingly being viewed as irrelevant." Rather, "payment for performance" initiatives are more "front and center," he said, and assistance in coordination of care infrequently addresses pre-diabetes. Medical directors feel that they do not have sufficient resources for such efforts and believe that "there is an evidence problem" and are hampered by limited information systems, although O'Conor suggested that once diabetes is diagnosed, obesity, A1C, blood pressure, LDL cholesterol, and aspirin use all improve, "so when you activate these systems . . . you can get a lot done." A missing tool is the electronic medical record, which could be readily used to identify individuals at high risk and could incorporate linked patient "portals" or proactive "e-visits," for which providers could be offered reimbursement, and either simple alerts or more complex decision-support tools to allow physician-directed interventions. The surveyed health plan directors indicated that complicated screening tests (which they apparently consider to include glucose tolerance testing) are less likely to be used.

Paul Franks (Umeå, Sweden) discussed genetic aspects of diabetes risk prediction, particularly "context-dependent genetic effects" that may be used to enhance risk prediction. He contrasted genetic and familial risk, the former representing the disease risk attributable to carrying one or two copies of a specific risk allele. These include polymorphisms of *KCNJ11* (controlling the β-cell ATP-sensitive K^+ channel) (1), *PPARγ* (2), and *TFC7L2* (3), although he noted that candidate gene approaches are less efficient than genome-scanning approaches in finding gene associations, with nearly 20 validated genetic risk factors having been discovered, for example, in the Data from an Epidemiological Study on the Insulin Resistance syndrome (DESIR) study (4). In contrast, familial risk is the disease risk shared between biological relatives, but family members share behaviors as well and exposure to diabetes in utero is another potential factor. Using receiver-operating curve (ROC) analysis, family history gives a fairly modest ROC area of 0.57 and genetic markers are somewhat better with ROC area 0.63, but the combination of family history and clinical predictors from the Framingham score gives an ROC area of 0.88 (a powerful predictor), whereas adding genetic information in a Swedish

Zachary T. Bloomgarden, MD, is a practicing endocrinologist in New York, New York, and is affiliated with the Division of Endocrinology, Mount Sinai School of Medicine, New York, New York.
DOI: 10.2337/dc09-zb02

study of 17,000 individuals gave little additional information. Thus, such an approach may not yet be useful.

An alternative is the use of context-dependent genetic risk markers dependent on the level of environmental exposure: the use of genetic information in the context of specific environmental factors. In the DPP, 3,548 participants were genotyped. Metformin and intensive lifestyle decreased risk by 32 and 58%, respectively, with 90% reduction in diabetes among those adhering most strongly to lifestyle recommendations. The transcription factor 7–like 2 gene (*TCF7L2*) is the strongest single genetic risk factor for type 2 diabetes (5). In the DPP, the TCF7L2 genotype predicted progression to diabetes in the control group, with those having the TT genotype at rs7903146 at greater risk of decreasing insulin secretion while those in the lifestyle intervention group had no increased diabetes risk with the variant genotype, which can be considered an example of context-specific risk. Peroxisome proliferator–activated receptor γ (the target of thiazolidniediones, whose natural ligands are polyunsaturated fatty acids) displays *PPARG2* polymorphisms, with the ala-ala genotype associated with lower and the pro-pro with higher BMI and the environmental interaction being with dietary fat. Both *PPARG2* and *KCNJ11* E23K polymorphisms affected response to various DPP interventions. In assessing genomic analysis one needs to consider analytic and clinical validity, the ability of such testing to detect or predict diseases, and clinical utility when compared with existing screening approaches (6). There is a potential for both benefit and adverse consequence of such information, but Franks predicted that ultimately genetic screening will allow understanding of the risk of not only diabetes but a great variety of additional clinical conditions.

A number of studies presented at the ADA meeting addressed aspects of the genetics of type 2 diabetes. Frayling et al. (abstract 936) noted that sex hormone–binding globulin (SHBG) levels are reduced in individuals with insulin resistance and individuals with type 2 diabetes, finding among 1,200 individuals a variant allele of SHBG with frequency 0.31 associated with higher SHBG levels and 9% reduction in likelihood of diabetes, which suggests that the direction of causality may be from SHBG to diabetes rather than (as is usually assumed) an effect of reduced insulin sensitivity in lowering SHBG levels. Foo et al. (abstract 985) reported analysis of 135 nondiabetic men who requested evaluation for sexual dysfunction; fasting glucose showed negative correlation with testosterone and SHBG, the latter a significant predictor in multivariate analysis. (Abstract numbers refer to the ADA Scientific Sessions, *Diabetes* 57 [Suppl. 2], 2008).

Many other polymorphisms were reported to be associated with diabetes, including those of SLC24A3, an Na/K/Ca exchanger (NCKX3) highly expressed in skeletal muscle and brain (Powers et al., abstract 314); kalirin, also associated with atherosclerosis and metabolic syndrome (Rudock et al., abstract 140); BQ231042, of unknown function, expressed in brain, islet, liver, kidney, adrenal, thyroid and skeletal muscle (Zhang et al., abstract 138); a cluster spanning genes for glucose-6-phosphatase catalytic unit two and ATP-binding cassette, sub-family B (MDR/TAP), member 11 and a neuronal cell surface protein, neuroligin one (Watanabe et al., abstract 137); the vesicle transport soluble NSF attachment protein receptor vps10p tail interacting 1a gene, located on chromosome 10q, which also contains the *TCF7L2* gene (Lehman et al., abstract 136); the mannan-binding lectin-2 gene, encoding an important component of the innate immune system (Muller et al., abstract 135); the *JAZF1*, *CDC123/CAMK1D*, *ADAMTS9*, and *THADA* gene regions (Saxena et al., abstract 134); the *CDKAL1* and *HHEX-IDE* genes, in part mediating the association between low birth weight and diabetes (Freahy et al., abstract 133); the PPARγ coactivator 1 gene (Arya et al., abstract 1815); *TCF7L2* and *HHEX* genes (Horikoshi et al., abstract 1181; Shang et al., abstract 274; and Chang et al., abstracts 1168); the Lim domain homeobox gene, encoding a transcription factor involved in pancreatic development (Muller et al., abstract 1180); the perilipin gene, involved in regulation of adipocyte lipid storage (Li et al., abstract 1178); the adiponectin gene (Hivert et al., abstract 1178); the nuclear factor κB inhibitor-α gene (Miller et al., abstract 1176); the interleukin-18 gene (Presta et al., abstract 1170); the *Lass6* gene encoding a member of the longevity-assurance homologue family (Good et al., abstract 1167); a scavenger receptor class B type 1 gene (An et al., abstract 1166); the *TRIB3* gene inhibiting insulin-stimulated Akt phosphorylation (Prudente et al., abstract 1165); and some 27 further studies of genes covering the entire gamut of factors related to glycemia. Clearly, this is an important area of investigation likely to lead to new understanding of the pathogenesis of diabetes and the development of new therapeutic approaches.

William Knowler (Phoenix, AZ) discussed the importance of detecting impaired fasting glucose (IFG) and IGT. At fasting and 2-h glucose levels above 125 and 228 mg/dl, respectively, and at A1C above 6.6%, the prevalence of diabetic retinopathy in a study of 5,007 Pima Indians increased from negligible levels to ~12% (7,8). Analysis of 1,133 incident cases of diabetes in 31,563 person-years of follow-up of initially nondiabetic Pima Indians ≥20 years ago showed that as fasting glucose increased from <95 to 95–104, 105–109, and 110–125 mg/dl, the rate of subsequent development of diabetes increased from <20 to ~40, 80, and 120 cases/1,000 person-years, respectively. Analysis of the population based on A1C showed that levels <5.5, 5.5–5.9, 6–6.4 and ≥6.5% were associated with diabetes rates of <20, ~50, 120, and 340 cases/1,000 person-years, respectively. IFG and IGT can exist either separately or in combination and have been termed pre-diabetes, but Knowler pointed out that the glucose tolerance test is not highly reproducible, with fewer than half of individuals having IGT in the Hoorn study showing IGT on a second test 2–6 weeks later (9). Nevertheless, among Pima Indians, those with either IFG or IGT alone had a threefold increase and those with both had a seven- to eightfold increase in diabetes development. Knowler recommended that similar classifications be based on A1C given its predictive power and clinical utility.

There is good evidence that diabetes can be prevented by treatment of IFG/IGT. A 12-month period of 750 mg metformin daily versus placebo in 70 individuals having IGT on two consecutive tests led to reductions in both fasting and 2-h glucose levels (10), and the Da Qing Clinical Trial of lifestyle intervention with diet, exercise, both, or neither in 530 IGT patients reduced diabetes development over 6 years from ~68 to 40% (11). In the DPP, carried out from 1996–2001, diabetes incidence rates among high-risk individuals with IGT were 11, 7.8, and 4.8% per year with placebo, metformin, and an intensive lifestyle intervention, respectively (12). There is evidence of increased cardiovascular risk

with IGT, and some (13), though not all (14), studies show increased risk with IFG. Taking into account CVD risk factors may reduce the excess risk associated with pre-diabetes (15,16). Part of the difficulty in associating pre-diabetes with risk may be that only a subset of these individuals progress to diabetes, with evidence that adverse effects are restricted to those individuals who progress to development of diabetes shown in studies in the Netherlands (17) and among Pimas (18). Interestingly, A1C may be a more powerful risk factor than glucose, with analysis of the European Prospective Investigation of Cancer (EPIC)-Norfolk study showing a doubling of CVD mortality among individuals with A1C 5–5.4% or 5.5–6.9% compared with that among individuals with A1C <5% (19).

Stephen Colagiuri (Sydney, Australia) discussed the question of whether there is value in early detection of diabetes and of pre-diabetes in terms of individual outcomes and from a health system perspective. There is a hierarchy: from nondiabetic patients at lower versus higher risk to undiagnosed diabetes and then to diagnosed diabetes. Although microvascular risk has been thought to begin with the onset of diabetes, this is now being reconsidered, and macrovascular risk does precede diabetes onset. Improvement in both micro- and macrovascular outcomes is certainly achievable. Colagiuri reviewed the as yet indirect data suggesting benefit of preventing or delaying diabetes, beginning by mentioning the many studies showing benefit of lifestyle and of a variety of pharmacologic approaches in reducing diabetes development. Analysis of the small Malmöhus Prevention trial of 147 pre-diabetic individuals showed a trend to lower cardiovascular mortality with tolbutamide treatment (20). The Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) study showed reduction in a composite renal outcome with rosiglitazone (21). In the STOP-NIDDM study, acarbose treatment was associated with a reduction in myocardial infarction (22). The 20-year follow-up of the Da Qing lifestyle intervention showed a significant 40% reduction in incident diabetes and, although underpowered with fewer than 600 participants, did show a trend of lower CVD mortality (23).

Undiagnosed diabetes is certainly common, comprising 30–80% of diabetic individuals, depending on the population studied, and may be lengthy in duration and associated with risk of developing complications and premature mortality. There is no evidence that diabetes detection improves outcome. The Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION) assessed the risk of 400,000 individuals, of whom 76,000 had been recommended for an examination, and recruited 3,000 previously undiagnosed diabetic individuals to participate in a multifactorial intensive treatment versus standard treatment (24). Of this group, 72% have blood pressure ≥140/90 mmHg, 58% are not receiving antihypertensive treatment, mean A1C is 7%, and 70% have hypercholesterolemia, for which >90% are not receiving treatment. Results will be presented in 2009, although the study is underpowered to ascertain cardiovascular benefit. Colagiuri described several case-control studies based on a glycosuria screening of 300–500 individuals with a suggestion of benefit of treatment, though again with an inadequate sample size. Interestingly, analysis of UK Prospective Diabetes Study participants by fasting glucose at presentation indicates that those with levels 7.8–10 and >10 mmol/l had diabetes for 2–3 and 5 years longer, respectively, than those with fasting glucose <7.8 mmol/l. All end points occurred more often in the group with higher fasting glucose, and diabetes-related death and myocardial infarction were more common in the intermediate than in the low fasting glucose group; thus, given the appropriate patient population, early treatment might well be effective (25).

Health system value depends on both cost and cost-effectiveness. Diabetes screening is not particularly expensive. Colagiuri reviewed an Australian study finding a cost of approximately 746 USD per case. Information on outcome is needed, however, to calculate cost-effectiveness. Modeling, relying on assumptions as to long-term benefit, does suggest that an intervention such as that of the Diabetes Prevetnion Program would be cost-effective (26). An interesting cost-effectiveness modeling study of diabetes screening and prevention programs suggested that screening for diabetes alone is not as cost-effective as screening for pre-diabetes as well with either lifestyle or pharmacological interventions (27). We need to appropriately prioritize such efforts and to develop capacity and resources to care for undiagnosed diabetes and, perhaps, for pre-diabetes as well. "Events are overtaking us," Colagiuri concluded, with programs being developed in Finland and Australia and the Diabetes in Europe–Prevention using Lifestyle, physical Activity and Nutritional intervention (DE-PLAN) project in progress.

A number of studies presented at the ADA meeting further addressed aspects of pre-diabetes. Oza-Frank and Narayan (abstract 316) studied diabetes development in the U.S. foreign-born population. There are currently more than 35 million such individuals, with immigrants from the Indian subcontinent having the highest diabetes risk: 3.3-fold greater than that of those born in the U.S., adjusted for BMI, age, sex, poverty income ratio, and duration of residence. Imperatore et al. (abstract 26) analyzed cardiometabolic risk factors in adults age 20–44 years in the U.S. from 1988–1991, 1991–194, 1999–2002, and 2003–2004, showing that the prevalence of obesity increased from 19 to 31%, mean waist circumference increased from 89 to 94 cm, and diabetes prevalence increased from 0.5 to 1.5% between ages 20 and 34 years, without change from ages 35–44 years (decreasing from 2.5 to 2.4%). Fasting glucose ≥100 but <126 mg/dl increased from 20 to 24% in 20- to 34 year olds but declined from 22 to 15% in 35-to 44 year olds. Mean A1C levels increased 0.14% for 20- to 34 year olds and 0.08% for 35- to 44 year olds, and mean fasting insulin rose from 9 to 13 and from 11 to 13 μU/ml in the respective groups. Triglycerides increased 15 mg/dl in those aged 20–34 years. LDL cholesterol, blood pressure, and smoking failed to change during this period. Vella et al. (abstract 318) compared 329 individuals with cognitive impairment with 1,640 control subjects and found the former to have a lower prevalence of a cyclin-dependent kinase CKN2A/B polymorphism, also associated with diabetes and with vascular disease, which is of potential importance given evidence that dementia may be associated with insulin resistance. Scheen et al. (abstract 319) found metabolic syndrome by Adult Treatment Panel III criteria in 23% of 112 patients with bipolar disorder, 29% of 503 with schizophrenia, and 50% of 92 with schizoaffective disorder. Diabetes was present in 8%, and 22% had either impaired fasting glucose or impaired glucose tolerance. Differences between the condi-

tions remained after adjustment for medications and other factors.

Aspects of pre-diabetes in the pediatric population were also addressed in studies presented at the ADA. Sathasivam et al. (abstract 1774) analyzed characteristics of 88 obese youth, noting that those with fasting glucose 90–99 mg/dl had fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and triglycerides similar to those with fasting glucose 100–125 mg/dl, which suggests that the cutoff of 100 mg/dl may be appropriate for adults but not for children. Libman et al. (abstract 1779) performed two oral glucose tolerance tests in 60 overweight youth 5 days apart. Of 10 subjects with IGT, 7 normalized in the second test, and the correlation coefficient between fasting glucose levels was 0.73, exceeding that for 2-h glucose levels (0.37). One may speculate that in addition to inherent lack of reproducibility, there was a behavioral change between the two tests leading to improvement on retesting. Pettitt et al. (abstract 30) compared age of onset of type 2 and type 1 diabetic individuals exposed to maternal gestational diabetes mellitus in utero based on data from the SEARCH study. Of the diabetic patients aged <20 years, 111 with type 1 and 113 with type 2 diabetes also had mothers with diabetes—88 during gestation. Age at onset of type 1 diabetes was not significantly earlier with maternal diabetes before pregnancy, but type 2 diabetes occurred at an earlier age in association with maternal diabetes during the pregnancy, suggesting an adverse effect of the diabetic intrauterine environment. Lawrence et al. (abstract 25) described data from the SEARCH study pertaining to type 1 and type 2 diabetes incidence and prevalence among U.S. Hispanic Youth. Peak type 1 diabetes incidence was 20 per 100,000 for female subjects at age 5–9 years and 20 per 100,000 for male subjects at age 10–14 years, with type 1 rather than type 2 diabetes the most prevalent form. Vehik et al. (abstract 963) measured intramyocellular lipids using soleus muscle 1H-nuclear magnetic resonance spectroscopy in 67 children, age 8–12 years, and found levels to be similar in overweight/obese and nonobese children. Birth weight, however, was inversely proportional to muscle fat, with the highest levels among children in the lowest birth weight tertile who currently were overweight or obese, suggesting an in utero component to insulin resistance.

Nonalcoholic fatty liver disease

There is increasing interest in the interrelationships between pre-diabetes, insulin resistance, and liver fat. Cali et al. (abstract 33) found that 30, 25, and 67 of 122 obese adolescents had >15, 5–15, and <5% hepatic fat on magnetic resonance imaging (MRI), respectively, with higher liver fat associated with higher visceral fat, 2-h glucose, and fasting and postchallenge insulin levels. Saremi et al. (abstract 1009) measured liver fat on computerized tomography in 281 type 2 diabetic individuals, finding higher liver fat in younger patients with shorter diabetes duration in association with higher triglyceride and C-reactive protein and lower HDL cholesterol and adiponectin levels. Saluja et al. (abstract 657) found that 75% of 1,079 type 2 diabetic patients in their clinic in India had ultrasound evidence of hepatic steatosis, with 34% of this group vs. 19% of those without liver abnormality having coronary artery disease and 16 vs. 7%, respectively, having cerebrovascular disease. However, Hermans et al. (abstracts 640 and 649) failed to show a relationship between ultrasound hepatic abnormalities or upper γ-glutamyl transferase (GGT) quintile and cardiovascular disease among 488 patients having GGT measurement and 258 having sonography in Belgium, with 24 vs. 26% having CAD and 7% vs. 8% having cerebrovascular disease. Guo et al. (abstract 959) reported that four genes associated with insulin resistance (adiponectin structural gene; ectonucleotide pyrophosphatase/phosphodiesterase 1; growth factor receptor-bound protein 2; and protein tyrosine phosphatase, nonreceptor type 1) were also associated with liver enzyme abnormalities among nondiabetic individuals in a survey of ~1,800 participants in the Insulin Resistance Atherosclerosis Study. Rhee et al. (abstract 1015) followed 15,250 Korean men from 2002 to 2006, with those in the second, third, and fourth age-adjusted quartiles of serum GGT having 1.9 and 1.5-fold, 3.4 and 2.8-fold, and 5.5 and 7.2-fold increase in risk of developing metabolic syndrome by the International Diabetes Federation and Adult Treatment Panel III criteria, respectively. GGT was also associated with risk for metabolic syndrome components, and alanine aminotransferase was similarly associated with increased risk.

Several studies addressed therapeutic approaches. Tsuchiya (abstract 516) randomized 34 individuals with impaired glucose tolerance and 27 with diabetes and nonalcoholic fatty liver disease to 12 weeks of treatment with nateglinide, voglibose, or pioglitazone. Liver fat by computed tomography, inversely related to density in Housnfield units, increased from 51 to 58 with nateglinide and from 50 to 58 with pioglitazone while not changing with voglibose, suggesting that α-glucosidase inhibitors should be considered; adiponectin increased and visceral fat and liver enzyme levels decreased only with pioglitazone. Kantartzis et al. (abstract 34) studied 170 nonalcoholic individuals with increased diabetes and CVD risk having a 9-month lifestyle intervention, which was associated with reduction in total, subcutaneous abdominal, visceral, and, to the greatest extent, hepatic fat on MRI. High fitness at baseline strongly predicted the decrease in liver fat. Milner et al. (abstract 67) found reduced insulin sensitivity in 30 men with hepatitis C, appearing to reflect abnormal muscle glucose uptake. Hepatic fat content measured by MRI was increased in genotype 3, but not with the genotype 1 virus, and was not correlated with the reduction in insulin sensitivity.

Insulin resistance

Sumner et al. (abstract 1014) studied correlates of HOMA-IR among 3,692 nondiabetic adults from the National Health and Nutrition Examination Survey 1999–2004; for those in the highest tertile of HOMA-IR, the prevalence of low HDL cholesterol was greater than that of high triglycerides, particularly among non-Hispanic blacks. Homeostasis model assessment may not, however, be a reliable measure of insulin sensitivity. Munoz et al. (abstract 1013) compared HOMA-IR with glucose disposal rate measured by hyperinsulinemic-euglycemic clamp in 65 pairs of sex- and insulin sensitivity–matched blacks and whites, finding the square of the correlation coefficient (a measure of the fraction of variance explained by the relationship) to be only 0.14 among blacks and 0.25 among whites. In the middle and highest clamp insulin sensitivity tertiles, HOMA-IR was 53–54% higher in blacks than in whites, suggesting that it should not be used when individuals from different ethnic groups are studied (and may have limited

NEWS FROM THE FOOD AND DRUG ADMINISTRATION

From time to time, new announcements by the FDA pertaining to aspects of diabetes treatment will be highlighted in this section.

In December, 2008, the FDA issued a document entitled "Guidance for Industry Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" (http://www.fda.gov/cder/guidance/8576fnl.pdf), outlining "the Agency's current thinking" in an effort "to ensure that relevant issues related to minimizing cardiovascular risk are considered in ongoing drug development programs." The document begins by acknowledging that "reliance on HbA1C remains an acceptable primary efficacy endpoint for approval of drugs seeking an indication to treat hyperglycemia secondary to diabetes mellitus." This is an important statement. In the wake of questions regarding the cardiovascular safety of diabetes treatment, some authors suggested that simply demonstrating that an agent improves glycemia was not adequate, asking rather that there be "proof of health benefits" for every new agent (Psaty BM, Furberg CD: Rosiglitazone and cardiovascular risk. *N Engl J Med* 356:2522-2524, 2007).

The new document does, however, require that sponsors "demonstrate that [new antidiabetic] therapy will not result in an unacceptable increase in cardiovascular risk." The approach to be taken for such studies is given in some detail. For each new treatment, the document requires "an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints." Further, the document states that "to obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and phase 3 programs should include patients at higher risk of cardiovascular events, such as patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment." The approach to ascertainment requires that studies be carried out in such a fashion to allow meta-analysis of events occurring in multiple different studies of an agent, including placebo-controlled monotherapy, placebo-controlled add-on therapy, and active comparator trials. The document points out that "the controlled trials will need to last more than the typical 3 to 6 months duration to obtain enough events and to provide data on longer-term cardiovascular risk (e.g., minimum 2 years)."

Precise statistical criteria are given, and the document requires that, to earn approval, the meta-analysis must "show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio" is <1.3. It is instructive to consider the number of patients and the characteristics of the patients required for such trials. Individuals participating in clinical trials are, in general, somewhat healthier than the overall population with the given condition, with annual cardiovascular event rates of asymptomatic diabetic patients probably well below 1%. To obtain information regarding individuals at greater risk, the recent Veterans Affairs Diabetes Trial might be considered: 20,027 patients were screened to obtain information for 1,791 high-risk patients with mean age 60 years and diabetes duration 11.5 years and with an overall myocardial infarction, stroke, inoperable cardiovascular disease, cardiovascular death, and coronary, peripheral artery, and cerebrovascular intervention rate of 5.6% per year (Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD, the VADT Investigators: Glucose control and vascular complications in veterans with type 2 disbetes. *N Engl J Med*. 17 December 2008 [Epub ahead of print]). Calculation of the sample size required to distinguish a 25% greater event rate over a 2-year period (13.9% as opposed to 11.1% in the Veterans Affairs trial group) reveals that for a 0.05% type I error, with statistical power of 80%, approximately 2,200 individuals would be required in each group (http://department.obg.cuhk.edu.hk/researchsupport/Sample_size_Comp2Prop.asp)—approximately 2.5 times the number of participants in the Veterans Affairs trial, although observed for a shorter period of time. Individuals at lower risk could be more readily recruited. To fulfill the newly proposed requirements, however, studies of such patients would need to be considerably larger. To distinguish a 2.5 vs. 2% annual event rate, a 2-year study would require nearly 7,000 individuals in each group. One can speculate that such studies, although of great intrinsic interest, would be far more expensive to carry out than has been the case hitherto for registration trials of drug approval, with the potential undesirable consequence of reducing interest on the part of the pharmaceutical industry in developing new therapies for the treatment of diabetes.

utility in general, given the low correlation with true insulin sensitivity). Similarly, Shaibi et al. (abstract 234) compared changes in insulin sensitivity using HOMA-IR, frequently sampled intravenous glucose tolerance test, and clamp insulin sensitivity and found that neither with a 16-week exercise intervention nor with a 12-week dietary intervention in adolescents did HOMA-IR show significant improvement, despite improvements in the other measures of insulin sensitivity. Kim and Reaven (abstract 1298), however, noted that insulin sensitivity, based on steady-state plasma glucose during insulin and glucose infusion with suppression of endogenous insulin secretion in 446 nondiabetic individuals, had a correlation coefficient of 0.76 with the integrated insulin response to a 75-g oral glucose load and with 95% of those in the highest insulin resistance quartile having insulin response above the median while 92% of those in the lowest insulin resistance quartile had insulin response below the median, suggesting that "insulin resistance and hyperinsulinemia rarely exist in isolation." Of course, this simply means that HOMA-IR, which is roughly equivalent to the fasting insulin in nondiabetic individuals, is a good qualitative marker of insulin resistance, although it lacks sufficient precision to be used quantitatively

based on studies such as those of Munoz et al. and Shaibi et al.

DeFronzo et al. (abstract 151) measured insulin response and sensitivity in 174 individuals with isolated IGT, 50 with impaired fasting glucose IFG, 428 with both, and 115 with normal glucose tolerance (NGT) and found similar insulin sensitivity in those with normal glucose tolerance and and IFG. There was an 80% decrease in insulin secretion in individuals with fasting glucose between 115 and 125 mg/dl, whereas elevation in 2-h glucose was a combined result of insulin resistance and reduced insulin secretion. Xiang et al. (abstract 248) followed 60 women for up to 75 months after gestational diabetes mellitus and found a progressive fall in the acute insulin response to intravenous glucose, whereas insulin sensitivity was low at baseline and failed to decrease significantly during follow-up. Increasing weight, possibly mediated in part by falling adiponectin and increasing C-reactive protein, correlated with the worsening insulin secretion.

There is a relationship between inflammation and insulin resistance. Joshipura et al. (abstract 889) analyzed relationships between dental disease and diabetes in the 18-year Health Professionals' Follow-up Study of 39,964 men and the 12 year Nurses' Health Study of 67,394 women. Periodontitis was associated with 38 and 78% increase, and loss of ≥3 vs. 0 teeth during follow-up, with 57 and 29% increase in risk of diabetes in the respective studies. Xiao et al. (abstract 154) infused fat emulsion plus heparin for 48 h to six overweight and obese nondiabetic men, reducing insulin secretion without improvement in response to sodium salicylate, although salicylate increased insulin secretion during the lipid infusion. Jung et al. (abstract 565) studied effects of the short-chain fatty acid butyrate, found in dairy products and known to inhibit histone deacetylases such as that mediating the suppression of PPARγ function by tumor necrosis factor-α. In high-fat–fed mice with versus without butyrate supplementation, weight gain was reduced, with a 30% decrease in fat mass. Insulin sensitivity increased, with increased muscle and adipose tissue glucose utilization and increased insulin-mediated suppression of hepatic glucose production. Rumberger et al. (abstract 1384) found lipolysis to be stimulated by incubation of adipocytes with butyrate in a glucose-dependent fashion, suggesting this to be evidence of histone deacetylase inhibition. Dietary measures to increase butyrate intake might prove effective in diabetes and in treatment of other insulin resistant states.

Scully et al. (abstract 306) infused the erythropoietin receptor agonist CNTO530 in a dietary obesity and diabetes mouse model, reducing fasting glucose from 147 to 76 mg/dl with an 83% decrease in insulin level and increasing the glucose infusion required for euglycemia during an insulin infusion by 2.25-fold, with increased skeletal muscle glucose uptake; this suggests another potential approach. Xu et al. (abstract 305) administered fibroblast growth factor (FGF)-21, a peptide expressed in the liver under control of PPARα, to mice with high-fat diet–induced obesity mice and found a dose-dependent improvement in glucose, insulin, and triglyceride levels; reversal of fat-induced hepatosteatosis; and weight loss without change in food intake. Chavez et al. (abstract 110), however, measured levels of FGF-21 in 41 individuals with varying insulin sensitivity on a euglycemic-hyperinsulinemic clamp and found FGF-21 to correlate with worse glucose tolerance and lower insulin sensitivity, which is an association opposite that in rodent studies; thus, the role of FGF-21 in man remains to be fully elucidated. Araneta and Barrett-Connor (abstract 895), in a study of Filipino, black, and white women, and Ley et al. (abstract 894), in a Canadian aboriginal population, showed that differences in adiponectin explain much of the differences in development of metabolic syndrome and in type 2 diabetes, pointing out the potential importance of this insulin-sensitizing adipokine.

Diabetes and malignancy

Yeh et al. (abstract 265) determined the risks of incident cancer, cancer death, and all-cause death after cancer in adults with versus without diabetes in a cohort of 20,703 individuals without known cancer, 570 of whom had diabetes. Cancer incidence rates during 17-years of follow-up were 18 vs. 9/1,000 person-years among diabetic and nondiabetic trial participants, respectively. Overall cancer mortality was increased 30%, with a 2.5- to 3.0-fold increase in mortality related to colorectal, pancreatic cancer, and esophageal cancers. Mitri et al. (abstract 955) reported a meta-analysis of six prospective studies showing a 59% increase in non-Hodgkin's lymphoma in patients with diabetes, confirmed by a mean 14% increase in 11 case-control studies. Barone et al. (abstract 978) identified 16 studies allowing ascertainment of a 41% increase in risk of death among patients with cancer having preexisting diabetes. Bowker et al. (abstract 264) found a 22% lower cancer mortality in diabetic patients treated with metformin but 33–171% increases in mortality in the lowest, middle, and highest tertiles of insulin use. Whether this reflects benefit of metformin, adverse effect of insulin, or difference between type 2 diabetic patients requiring the two agents cannot be deduced from the reported associations.

Acknowledgments— Z.T.B. has served on speaker's bureaus of Merck, NovoNordisk, Lilly, Amylin, Daichi Sankyo, and GlaxoSmithKline; has served on advisory panels for Medtronics, Takeda, Merck, AtherGenics, CV Therapeutics, Daichi Sankyo, BMS, and Astra Zeneca; holds stock in Abbott, Bard, Medtronic, Merck, Millipore, Novartis, and Roche; and has served as a consultant for Novartis, Dainippon Sumitomo Pharma America, Forest Laboratories, and Nastech. No other potential conflicts of interest relevant to this article were reported.

References

1. Florez JC, Jablonski KA, Kahn SE, Franks PW, Dabelea D, Hamman RF, Knowler WC, Nathan DM, Altshuler D, the Diabetes Prevention Program Research Group: Type 2 diabetes–associated missense polymorphisms *KCNJ11* E23K and *ABCC8* A1369S influence progression to diabetes and response to interventions in the Diabetes Prevention Program. *Diabetes* 56:531–536, 2007
2. Franks PW, Jablonski KA, Delahanty L, Hanson RL, Kahn SE, Altshuler D, Knowler WC, Florez JC, the Diabetes Prevention Program Research Group: The Pro12Ala variant at the peroxisome proliferator-activated receptor gamma gene and change in obesity-related traits in the Diabetes Prevention Program. *Diabetologia* 50:2451–2460, 2007
3. Loos RJ, Franks PW, Francis RW, Barroso I, Gribble FM, Savage DB, Ong KK, O'Rahilly S, Wareham NJ: TCF7L2 polymorphisms modulate proinsulin levels and β-cell function in a British Europid population. *Diabetes* 56:1943–1747, 2007
4. Vaxillaire M, Veslot J, Dina C, Proença C, Cauchi S, Charpentier G, Tichet J, Fumeron F, Marre M, Meyre D, Balkau B, Froguel P, the DESIR Study Group: Impact of common type 2 diabetes risk polymorphisms in the DESIR prospective study. *Diabetes* 57:244–254, 2008

5. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadottir A, Styrkarsdottir U, Magnusson KP, Walters GB, Palsdottir E, Jonsdottir T, Gudmundsdottir T, Gylfason A, Saemundsdottir J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Gudnason V, Sigurdsson G, Thorsteinsdottir U, Gulcher JR, Kong A, Stefansson K: Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nat Genet* 38:320–323, 2006
6. Hunter DJ, Khoury MJ, Drazen JM: Letting the genome out of the bottle: will we get our wish? *N Engl J Med* 358:105–107, 2008
7. McCance DR, Hanson RL, Charles MA, Jacobsson LT, Pettitt DJ, Bennett PH, Knowler WC: Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. *BMJ* 308: 1323–1328, 1994
8. Gabir MM, Hanson RL, Dabelea D, Imperatore G, Roumain J, Bennett PH, Knowler WC: Plasma glucose and prediction of microvascular disease and mortality: evaluation of 1997 American Diabetes Association and 1999 World Health Organization criteria for diagnosis of diabetes. *Diabetes Care* 23:1113–1118, 2000
9. Mooy JM, Grootenhuis PA, De Vries H, Kostense PJ, Pop-Snijders C, Bouter LM, Heine RJ: Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance tests in a general Caucasian population: the Hoorn Study. *Diabetologia* 39:298–305, 1996
10. Li CL, Pan CY, Lu JM, Zhu Y, Wang JH, Deng XX, Xia FC, Wang HZ, Wang HY: Effect of metformin on patients with impaired glucose tolerance. *Diabet Med* 16: 477–481, 1999
11. 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
12. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, the Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
13. Sorkin JD, Muller DC, Fleg JL, Andres R: The relation of fasting and 2-h postchallenge plasma glucose concentrations to mortality: data from the Baltimore Longitudinal Study of Aging with a critical review of the literature. *Diabetes Care* 28: 2626–2632, 2005
14. DECODE Study Group, the European Diabetes Epidemiology Group: Glucose tolerance and cardiovascular mortality comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 161:397–405, 2001
15. Hunt KJ, Williams K, Resendez RG, Hazuda HP, Haffner SM, Stern MP: All-cause and cardiovascular mortality among diabetic participants in the San Antonio Heart Study: evidence against the "Hispanic Paradox". *Diabetes Care* 25:1557–1563, 2002
16. Pankow JS, Kwan DK, Duncan BB, Schmidt MI, Couper DJ, Golden S, Ballantyne CM: Cardiometabolic risk in impaired fasting glucose and impaired glucose tolerance: the Atherosclerosis Risk in Communities study. *Diabetes Care* 30:325–331, 2007
17. Rijkelijkhuizen JM, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD, Dekker JM: High risk of cardiovascular mortality in individuals with impaired fasting glucose is explained by conversion to diabetes: the Hoorn study. *Diabetes Care* 30:332–336, 2007
18. Kim NH, Pavkov ME, Looker HC, Nelson RG, Bennett PH, Hanson RL, Curtis JM, Sievers ML, Knowler WC: Plasma glucose regulation and mortality in Pima Indians. *Diabetes Care* 31:488–492, 2008
19. Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A, Day N: Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC-Norfolk). *Br Med J* 322:15–18, 2001
20. Knowler WC, Sartor G, Melander A, Scherstén B: Glucose tolerance and mortality, including a substudy of tolbutamide treatment. *Diabetologia* 40:680–686, 1997
21. DREAM Trial Investigators, Dagenais GR, Gerstein HC, Holman R, Budaj A, Escalante A, Hedner T, Keltai M, Lonn E, McFarlane S, McQueen M, Teo K, Sheridan P, Bosch J, Pogue J, Yusuf S: Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. *Diabetes Care* 31:1007–1014, 2008
22. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, the STOP-NIDDM Trial Research Group: Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 290:486–494, 2003
23. Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, Li H, Li H, Jiang Y, An Y, Shuai Y, Zhang B, Zhang J, Thompson TJ, Gerzoff RB, Roglic G, Hu Y, Bennett PH: The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* 371:1783–1789, 2008
24. Lauritzen T, Griffin S, Borch-Johnsen K, Wareham NJ, Wolffenbuttel BH, Rutten G, the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care: The ADDITION study: proposed trial of the cost-effectiveness of an intensive multifactorial intervention on morbidity and mortality among people with Type 2 diabetes detected by screening. *Int J Obes Relat Metab Disord* 24 (Suppl. 3):S6–S11, 2000
25. Colagiuri S, Cull CA, Holman RR, the UKPDS Group: Are lower fasting plasma glucose levels at diagnosis of type 2 diabetes associated with improved outcomes? U.K. prospective diabetes study 61. *Diabetes Care* 25:1410–1417, 2002
26. Eddy DM, Schlessinger L, Kahn R: Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes. *Ann Intern Med* 143:251–264, 2005
27. Gillies CL, Lambert PC, Abrams KR, Sutton AJ, Cooper NJ, Hsu RT, Davies MJ, Khunti K: Different strategies for screening and prevention of type 2 diabetes in adults: cost effectiveness analysis. *BMJ* 336:1180–1185, 2008