American College of Endocrinology Pre-Diabetes Consensus Conference: Part One

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The American College of Endocrinology held a Consensus Conference in Washington, DC, on 21–22 July 2008 on the topic of pre-diabetes, organized around a series of interrelated questions. This is the first of a three-part series summarizing presentations at the conference.

What should be the criteria for diagnosis of nondiabetes, pre-diabetes, and diabetes?

Michael Stern (San Antonio, TX) opened the conference by discussing approaches to identifying pre-diabetes, noting that, of course, there is always pre-diabetes before diabetes and that, of course, diabetes is associated with a number of complications such that pre-diabetes cannot be considered a benign condition (as it is clearly associated, for example, with increased cardiovascular risk). Pre-diabetes is, however, an asymptomatic condition not associated with functional impairment, Stern argued, suggesting that if a state is associated with future morbidity and mortality, one should not use the paradigm of treating illness in devising approaches to manage the condition. Citing the adage "prediction is very difficult, especially about the future," variously attributed to Niels Bohr and Yogi Bera, he pointed out that predictions applying to a group differ somewhat from those applying to individuals. He reviewed a well-recognized approach to assessing the performance of continuous risk factors, the receiver operating characteristic (ROC) curve of sensitivity vs. false-positive rate, with the area under the curve (AUC) a measure of the reliability of the test, ranging from 0.5 for a test no better than a flip of a coin to 1.0 for a completely reliable test (1). Relative risk ratios that are considered important are associated with a very modest AUC_{ROC}, with an odds ratio of 1.5 only associated with an AUC_{ROC} of 0.56 and relative risk ratios of 9–10 required for AUC_{ROC} >0.8. It should be noted, however, that the analysis to which Stern referred simply noted the complexity of relative risk in establishing disease likelihood in an individual of a population with modest a priori disease risk, such that the population-attributable risk for a threefold increase in relative risk may be quite substantial.

Stern emphasized what he considered to be the greater usefulness of continuous rather than dichotomous risk scores. With the latter, sensitivity, specificity, and target population are fixed, while with the former all are flexible if one "tweaks the cut point," allowing one to optimize test behavior. He suggested that a continuous risk score such as the Framingham equation predicting 10-year likelihood of cardiovascular disease is more useful than a dichotomous measure, such as, in a sense, the concept of pre-diabetes. Using data from a San Antonio epidemiologic study, his group calculated a diabetes risk score, showing it to be a better predictive approach than either impaired fasting glucose (IFG) (fasting glucose 100–125 mg/dl) or impaired glucose tolerance (IGT) (glucose 2-h postload 75-g oral glucose 140–199 mg/dl). The model includes as factors age, sex, Hispanic vs. non-Hispanic white ethnicity, fasting glucose, systolic blood pressure, HDL cholesterol, BMI, and family history, although Stern noted that ethnicity limits the degree to which the model can be generalized (2). The model has somewhat better ability to predict diabetes than either fasting or postload blood glucose alone. Furthermore, Stern noted, the use of variables such as LDL cholesterol allows considerably greater cardiovascular disease prediction than available with IFG and IGT, similar to the performance of the Framingham model (3).

To establish that risk factors are valid for predictive models, a prospective cohort study must be performed with the new risk factor along with conventional risk factors measured at baseline, with outcomes of interest measured at follow-up, and with independent validation datasets showing the same characteristics. "A considerable effort is required to improve upon the models that we already have," Stern said. An important barrier to adoption of predictive models is that health professionals tend to consider that they lack naturally occurring cut points, he noted. In fact, however, cut points for established risk factors such as glucose, blood pressure, and lipids also tend to be arbitrary, as are the various criteria used for metabolic syndrome. He concluded that the notion of pre-diabetes as a condition necessitating treatment requires careful examination. It is an asymptomatic state, the significance of which lies in its ability to predict adverse health outcomes for individuals diagnosed. As there is no evidence that early intervention (prior to diagnosis of diabetes) is better than late intervention (after diabetes is present), he suggested that "it is a very profound question" as to whether the concept of pre-diabetes should be applied to individuals. Rather, he suggested, it needs to be demonstrated, both in terms of cost versus benefit and in terms of outcome, at what point glycemic intervention should begin; strong clinical trial data for glucose interventions, just as we now have for lipid and blood pressure interventions, must be developed.

Jacqueline Dekker (Amsterdam, the Netherlands) discussed the Hoorn Study, emphasizing the need for evidence-based prevention of diabetes and vascular complications. She discussed the complex history of criteria for diabetes and pre-diabetes. The World Health Organization (WHO) and the American Diabetes Association (ADA) definitions of diabetes accept fasting plasma glucose ≥126 mg/dl

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(7.0 mmol/l/l) and 2-h post–75-g glucose load levels ≥200 mg/dl (≥11.1 mmol/l). In 2003, the ADA suggested that the lower limit of IFG be reduced from 110 to 100 mg/dl, putting it in conflict with the WHO guidelines. Genuth and Kahn have recently argued that neither IGT nor IGT is useful (4). Recently, there have been proposals that A1C should be used in the diagnosis of diabetes (5). There are, then, a number of approaches to assessing diabetes risk: those based on direct measures (IFG and IGT) and those based on markers like A1C and the presence of metabolic syndrome. Dekker proposed that we endeavor to understand the performance of the differing definitions and the prevalence of the (pre-) disease states so defined, their agreement, and their associations with cardiovascular disease (CVD) and with diabetes from the dual perspectives of clinical care and public health interests.

The Hoorn study began in 1989–1990, involving 2,484 men and women ages 50–75 years, with follow-up evaluations performed in 1996, 2000, 2005, and 2007 including oral glucose tolerance testing (GTT), A1C, lipids, blood pressure, and anthropometric measures. Using the WHO criterion with a cut point of 110 mg/dl, 12% had IFG, while 35% had IFG by the ADA criterion of 100 mg/dl; 5 and 4% had newly diagnosed and previously known diabetes, respectively. Others have reported a similar increase in IFG with the lower ADA criterion (6). Consequently, individuals with IGT satisfying the ADA criterion have considerably lower risk of diabetes than those satisfying the WHO criterion (7). In the Hoorn dataset, individuals with either IFG (based on fasting glucose ≥110 mg/dl) or IGT alone had 33–34% 6-year cumulative incidence of diabetes, while 65% of those having both elevated fasting and 2-h glucose developed diabetes during the same period (8). Hoorn study data comparing glucose tolerance in 1998 and 2005 similarly suggested that the 110 mg/dl cut point more strongly predicts CVD mortality than the 100 mg/dl cut point (9). Dekker showed data from the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study favoring the use of 2-h glucose without a threshold for mortality, as the 2-h glucose increased from ≤3 to ≥11.1 mmol/l/l, while there is a definite difference in outcome for fasting glucose between ≥7 and <7 mmol/l/l (10). Similar evidence of greater association with mortality of 2-h than of fasting glucose was found in analysis of the Atherosclerosis Risk in Communities study (11).

Addressing the use of A1C in pre-diabetes, Dekker noted that 10% of the nondiabetic population in the Hoorn study had A1C ≥6%, with the percentage only increasing to 16% of the IFG/IGT population. There was a weak correlation of A1C with fasting glucose and an even weaker correlation of A1C with 2-h glucose among nondiabetic individuals. Dekker reviewed the concept that there is heterogeneity in the degree to which different people glycate hemoglobin for a given blood glucose concentration. In the Islington Diabetes Survey, only 19–41% of the variance in glycated hemoglobin was explained by the 2-h glucose (12). Although a proposal is currently being advanced that A1C should be expressed as an estimated average glucose (13), only a small number of nondiabetic people have been studied in this fashion. There appear to be genetic determinants of A1C (14), with differing degrees of hemoglobin glycation potentially related to differences in erythrocyte survival, different intracellular oxygen tension, 2,3-diphosphoglycerate levels, pH, or different degrees of erythrocyte permeability to glucose. (More information on this point is present in a recent analysis of the topic of variability in the relationship between glucose and A1C [15]). Dekker did, however, review intriguing information from the Hoorn study suggesting a relationship of A1C with CVD risk, both in male and female subjects, with much but not all of the increase in risk explained by other CVD risk factors; she noted that similar reports have been made from analysis of other epidemiological studies and that A1C is also associated with future risk of microalbuminuria and retinopathy.

Dekker concluded by discussing metabolic syndrome as a marker of pre-diabetes, noting that its many definitions give rise to high variability in reported prevalence. Metabolic syndrome is associated with increase in the risks of diabetes (most but not all of which are due to glucose as a factor) and CVD, with heterogeneity between studies (16), presumably due largely to the use of different definitions. The rationale for the paradigm that insulin resistance underlies both diabetes and CVD has recently been questioned. Hyperinsulinemic-euglycemic clamp studies of 1,308 nondiabetic individuals show remarkably little overlap between the upper quartiles of large waist, insulin resistance, and hyperinsulinemia (17). In the analysis, insulin resistance was much more strongly associated with 2-h than with fasting glucose but also showed associations with free fatty acid and triglyceride levels, suggesting that many of the physiologic assumptions of metabolic syndrome need reevaluation. Dekker concluded that proposed definitions of pre-diabetes vary greatly with respect to a number of factors as a result of heterogeneity between individuals with hyperglycemia within the normal range. As with any condition, the bulk of people who will develop diabetes have only modest increase in risk, such that approaches appropriate for overall populations may be rather different from individual treatment recommendations. Pharmacologic intervention with glucose-lowering agents or other drugs directed at CVD will only be appropriate with high-risk patient programs individually focused on intensive lifestyle behavior modification, but this does not preclude more general population–focused lifestyle campaigns.

Barbara Viventi Howard (Washington, DC) discussed CVD-hyperglycemia associations from the Strong Heart Study, discussing impaired glucose and pre-diabetes versus diabetes relationships to CVD risk factors and the prediction of CVD. A caveat is the degree of interindividual and interlaboratory variability in glucose values, which may change markedly on retesting. She cited a study performed by William Knowler showing that, for IFG, 6% of repeat tests shows diabetes but 16% show normal glucose tolerance (NGT), with corresponding frequencies of 13 and 38%, respectively, for IGT. Insulin resistance is a major determinant of type 2 diabetes and is almost always present both in people with IFG and in people with IGT. Given its association with CVD risk, she suggested that effects of insulin resistance must be considered when examining relationships between pre-diabetes and CVD. She suggested that metabolic syndrome be used as a proxy for insulin resistance and analyzed relationships between IGT, IFG, and metabolic syndrome with Strong Heart Study data beginning in 1988, comprising 4,549 American Indians ages 45–74 years undergoing three examinations measuring risk factors and preclinical disease during a 20-year follow-up.

At baseline, 816 had NGT, 1,243 IFG (using ADA criteria), 619 IGT, 1,420 pre-diabetes, and 2,222 diabetes—almost

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.

The FDA has indicated ongoing concern about the use of ezetimibe, announcing that it intended to investigate the report from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial of a possible association between the use of Vytorin and increased incidence of cancer. Cardiovascular risk was not reduced with the agent in the study of individuals with aortic stenosis.

Expanding on its October 2007 report of 30 individuals receiving Byetta and developing pancreatitis, the FDA announced that it had learned of six cases of hemmorrhagic or necrotizing pancreatitis in patients receiving this agent, with all requiring hospitalization and two dying. There are well-documented associations of pacreatitis with obesity, with dyslipidemia, and with diabetes itself, and pancreatitis may be associated with use of many medicines given to diabetic patients, including sulfonylureas, ACE inhibitors/angiotensin receptor blockers, and diuretics, such that the expected incidence among the more than 700,000 patients treated with Byetta might be double or more the expected pancreatitis rate of somewhere >0.01% in the general population—perhaps 150 cases. The reported 36 cases, then, represents an unknown fraction of those expected. One might, then, question the FDA's implication that Byetta increases the risk of pancreatitis, recognizing that while underreporting of adverse events to the agency might make any apparent grouping of events potentially serious, there may now be an opposite effect of the earlier announcement increasing such reporting.

Finally, the FDA announced that it has approved six manufacturers' influenza vaccines for the 2008-2009 season. Every year, 5-20% of the U.S. population gets influenza, more than 200,000 people are hospitalized from its complications, and there are ~36,000 flu-related deaths; vaccination of people with chronic medical conditions such as diabetes and of health care personnel is thus critical. The FDA newsletter pointed out that just 40% of health care workers in the United States receive an influenza vaccination (http://www.fda.gov/bbs/topics/NEWS/2008/NEW01872.html).

half of this very high-risk population. IFG, IGT, and pre-diabetes led to a threefold increase in diabetes risk in the population, leading Howard to conclude that, in this population, the GTT offered relatively little additional information to that available from fasting glucose. Triglyceride levels were ~105 in NGT, 140 in pre-diabetic, and 180 in diabetic men, with a similar stepwise increase in women. Intermediate glycemia was associated with an intermediate decrease in HDL, and there was lower LDL with diabetes and intermediate lowering with pre-diabetes, although Howard pointed out that LDL is altered in composition in states of dysmetabolism, becoming more atherogenic. Macroalbuminuria was somewhat increased with pre-diabetes, the prevalence of carotid plaque was increased in diabetes but not in pre-diabetes, and echocardiographic left ventricular hypertrophy showed an intermediate elevation with pre-diabetes. The 7- and 15-year coronary artery disease and stroke risks were, however, only increased among individuals who had diabetes. Metabolic syndrome was present in 10.6 and 21% of men and women, respectively, with NGT, in 57 and 69%, respectively, of those with pre-diabetes, and in 69 and 86%, respectively, of those with diabetes. Metabolic syndrome was also associated with greater age, BMI, and cigarette use, all of which increase the likelihood of adverse outcome. There was a 25% 6-year incidence of diabetes among those with metabolic syndrome, compared with a 13% incidence for those without. Metabolic syndrome doubled the risk of left ventricular hypertrophy, and there was increased risk of CVD events with metabolic syndrome among both diabetic and nondiabetic individuals.

Certainly, one needs to consider CVD risk factor modification in diabetic patients, considering the great deal of data showing benefits of LDL cholesterol and blood pressure reduction, and there should similarly be benefit among pre-diabetic individuals in preventing diabetes and in treating risk factors. An important question is whether, with a more accurate measure of risk of diabetes, those who subsequently develop diabetes would show increased CVD risk before diabetes development, as has been shown in analysis of the Nurses' Health Study (18). Corollary questions include *1*) whether it would be better to (pharmacologically) treat blood glucose elevations before development of diabetes or to wait for diabetes to develop before initiation of pharmacologic diabetes treatment and *2*) what should be the CVD risk factor goals for pre-diabetic individuals. The clinical outcome data required to answer these questions are not available, although surrogate outcomes may give relevant information. Recognizing that the very high diabetes risk of Native Americans may lead to specific characteristics of those populations differing from those of other groups at lower risk, Howard suggested that a distinguishing feature may simply be that this group "got fatter earlier . . . [and that] some of the other populations aren't as far along this continuum." Pharmacologic glucose-lowering interventions might be appropriate for pre-diabetic individuals with both IFG and IGT or for those with particularly high-risk ethnicity, those with IFG plus metabolic syndrome, or, along the lines described by Stern, those satisfying a risk score based on multiple markers.

Silva Arslanian (Pittsburgh, PA) discussed glucose intolerance in youth. In the National Health and Nutrition Examination Survey (NHANES) in 1999–2000, 7% of non-Hispanic white adolescents in the U.S. between ages 12 and 19 years had IFG (19). She showed a study of overweight adolescents in which the correlation of two fasting blood glucose levels was 0.72 while that of two 2-h postload glucose levels was 0.34, with mean absolute differences of 4 and 17 mg/dl, respectively. Fasting glucose, however, missed 70–90% of youth with abnormal 2-h glucose, suggesting that in this population the GTT would be useful and, perhaps, that it might be reasonable to follow this serially for adequate diagnosis of pre-diabetes.

In studies of the role of abdominal obesity in children, both abdominal magnetic resonance imaging (20) and waist circumference (21) predict insulin resistance and increased triglycerides, and waist circumference at age 13 years predicts metabolic syndrome in adulthood

(22). An interesting consideration is "metabolic fitness," with a subset of overweight youth having greater maximal oxygen consumption with lower visceral fat than BMI- and percent body fat–matched control subjects (23). Arslanian reviewed evidence that the metabolic defect in pre-diabetes in youth involved reduced insulin secretion (24,25), with IGT to a greater extent than IFG associated with insulin resistance. Both factors are represented in the disposition index, which is particularly decreased in youth with both IFG and IGT (26). This becomes even more apparent in type 2 diabetes in youth, involving both insulin resistance and loss of the first and second phases of insulin secretion, leading to a 90% reduction in the glucose disposition index (27). She described a recent study from her group showing that a subset of clinically diagnosed type 2 diabetic children have positive GAD, islet-associated, or islet cell antibodies and tend to have greater loss of insulin secretion and lesser insulin resistance, leading to the same reduction in disposition index as in those who have negative antibody levels, with greater insulin resistance and lesser insulin secretory deficiency. Data on complications are, she noted, somewhat scanty, but there is evidence that atherosclerotic complications begin in childhood (28). Arslanian showed evidence of increased pulse wave velocity (a measure of arterial stiffness) in type 2 diabetic children, with lesser but still significant increase in obese nondiabetic children (29), indicating premature aging of the cardiovascular system. Both black and white children with insulin resistance have increased systolic blood pressure and triglyceride and decreased HDL cholesterol and adiponectin levels, with evidence of endothelial dysfunction in whites (30) and with IFG associated with increased blood pressure and triglyceride levels among adolescents in NHANES (19). "The big question," Arslanian concluded, "is what is the tempo of progression. . . . In pediatrics it is going to be highly difficult to answer this question." To stop the progression to diabetes in youth, we need to learn how to intervene, what the timeline of obesity-related diabetes development will be, and what the magnitude of risk is for a given degree of obesity.

What is the potential negative effect of not treating pre-diabetes?

Jaakko Tuomilehto (Helsinki, Finland) discussed the CVD risk of pre-diabetes (31). Diabetes and CAD occur together more commonly than usually recognized, with the negative impact of dysglycemia apparent before diabetes. In the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE), a group of studies of ~25,000 individuals were analyzed together, showing that 2-h glucose levels increased with age, with less evidence for such an increase in fasting glucose and with 2-h glucose rather than fasting glucose predicting all-cause mortality and CVD risk (32). There was a continuous increase in CVD risk with increasing 2-h glucose, a phenomenon not clearly found for fasting glucose. Adjusting for fasting glucose, 2-h glucose continued to significantly predict increased CVD, coronary heart disease (CHD), and total mortality. Furthermore, although the absolute risk was greater for diabetic individuals, in DECODE there were more excess deaths related to hyperglycemia among men with IGT than among those with diabetes because of the greater prevalence of the former group, implying that this group could benefit from treatment. All-cause mortality was increased to a greater extent than CVD among individuals with IGT, presumably because of the increase in cancer mortality, a less well-recognized adverse association. Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Asia (DECODA), a similar study, showed similar data, with the effect of fasting glucose on risk eliminated by adjusting for 2-h glucose, whereas adjustment for fasting glucose failed to eliminate the association of 2-h glucose with CVD, CHD, stroke, and total mortality (33).

Tuomilehto showed data from an unpublished ADA work group on outcomes of hyperglycemia similarly suggesting that high 2-h glucose levels carry greater risk than high fasting glucose, leading him to suggest that the current recommendation that GTT be performed with abnormal fasting glucose "doesn't make any sense," as those with normal fasting glucose may particularly benefit from identification of IGT. Furthermore, he showed a 10-year follow-up of Finns in which CVD was similarly increased among individuals with elevated 2-h glucose who did and who did not subsequently develop diabetes, even after correction for obesity, blood pressure, lipids, and cigarette use. The increase in CVD and total mortality associated with newly diagnosed diabetes is not as well seen at 0–5 years as at 5–10 and 10–15 years (34), suggesting that diabetes may differ from other risk factors in requiring a very long follow-up for demonstration of adverse effect. Studies in Europe (35) and Asia (36) show that the minority of individuals with heart disease have NGT, with measurement of fasting glucose alone insufficient to ascertain glycemic abnormality in this group (37), and that there is reduced survival in individuals with heart disease found to have diabetes (38), further suggesting the importance of assessing glucose tolerance. In this study, the minority of newly identified diabetic patients received glucose-lowering drugs, but those so treated showed a significant threefold reduction in cardiovascular events (39). Interestingly, a study of individuals with myocardial infarction showed that among those having diabetes, the use of β-blockade, renin-angiotensin inhibition, antiplatelet treatment, and statins reduced mortality, whereas this was not demonstrated for those without diabetes. Similarly, in this study, revascularization was highly beneficial for the diabetic but not for the nondiabetic subgroup (40). Although these studies cannot distinguish benefits of treatment from underlying differences in characteristics of patients and/or providers, there is a body of evidence favoring diabetes identification and treatment for individuals with heart disease.

Similar studies suggest association of glycemia with cerebrovascular disease. Carotid intima-media thickness (IMT) is increased in people with diabetes and, to a lesser extent, in those with pre-diabetes (41). The majority of people with stroke have evidence of glycemic abnormality when glucose tolerance testing is performed (42). Finally, the risk of recurrent stroke is increased with glycemic abnormality (43).

Tuomilehto reviewed the FINnish Diabetes RIsk Score (FINDRISC) for predicting 10-year risk of type 2 diabetes in adults (available at www.diabetes.fi/english), with age, BMI, waist circumference, daily physical activity, dietary vegetables and fruits, diagnosis of hypertension and abnormal glucose levels, and family history of diabetes used to calculate a score that he showed to strongly correlate with 10-year diabetes risk (44), with each 1-point increase in the score associated with a 16–23% increase in likelihood of CVD and mortality (45).

Diabetes prevention with lifestyle intervention has been shown in the U.S. Di-

abetes Prevention Program (DPP) (46); the Finnish Diabetes Prevention Study (47), in which the intervention was most effective in the highest-risk group, with ongoing benefit for 4 years after the conclusion of the formal lifestyle intervention (48); and in the Chinese Da Qing Diabetes Prevention Study, with separation between the control and intervention groups maintained for a 20-year period (49). Based on the differences reported in the DECODE analysis, Tuomilehto suggested that treatment to reduce 2-h glucose by 2 mmol/l/l would reduce adverse outcomes by 20%. These interventions could then be of great benefit, although it will be important that adequately powered studies with sufficiently long follow-up are carried out.

Robert Ratner (Washington, DC) discussed the potential impact of diabetes prevention on micro- and macrovascular disease based on data from the DPP. Does diabetes prevention, he asked, reduce microvascular disease, decrease CVD risk factors, reduce intermediate end points, or decrease events?

Diabetes prevention might reduce microvascular disease, although this is based on limited data. In the DPP, diabetic retinopathy occurred in 7.9% of those not developing diabetes but in 12.6% of those who did develop diabetes, with mild-to-moderate nonproliferative diabetic retinopathy developing in 1.0 vs. 1.8% and microaneurisms in only 6.9 vs. 10.8% of subjects, respectively (50). Similarly, regardless of treatment with placebo, metformin, or lifestyle modification, those who progressed to diabetes had greater likelihood of worsening microalbuminuria, with a net 1% increase in prevalence of microalbuminuria in the placebo group, no change among those assigned to metformin, and a 1.3% decrease with the lifestyle intervention. In the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial, 9.2% of those receiving rosiglitazone, but 10.8% of the placebo group, progressed from normo- to microalbuminuria, similarly suggesting benefit of treatment (51).

Participants in the DPP had decreased blood pressure, in association to a lesser extent with metformin than with lifestyle modification, with lifestyle modification patients having a reduction in need for antihypertensive treatment (52). In the STOP type 2 diabetes study with acarbose (53) and in the DREAM study with rosiglitazone, blood pressure similarly benefited. In the DPP, LDL decreased similarly with metformin and lifestyle, and for HDL cholesterol and triglyceride levels the lifestyle group showed greater benefit. Among the 1,079 DPP participants in the placebo group, blood pressure, triglyceride, HDL cholesterol, and LDL size improved in the 154 subjects developing NGT while worsening in the 191 progressing to type 2 diabetes. Of those not having metabolic syndrome at entry, two-thirds of the placebo group developed the syndrome during the study period; development of metabolic syndrome was reduced 17% with metformin and 41% with the lifestyle intervention (54). Levels of tissue plasminogen activator, plasminogen activator inhibitor-1, and C-reactive protein similarly showed greatest improvement with lifestyle intervention, intermediate improvement with metformin, and little change or worsening in the placebo group (55). Diabetes prevention does, then, appear to reduce CVD risk.

There are limited data on surrogate end points, with evidence of benefit in carotid intima-media thickness in the Troglitazone in Prevention of Diabetes (TRIPOD) study with troglitazone (56) and in the STOP-type 2 diabetes study with acarbose (57). Ratner reviewed a model based on data from the DPP suggesting that, with metformin and lifestyle treatment delaying mean time to development of diabetes by 3.4 and 11.1 years, respectively, the development of blindness and renal failure would be reduced 20 and 40% and there would be 25 and 45% reductions in amputation, respectively, with lesser relative but greater absolute decreases in stroke and CHD (58). Lifetime costs of the interventions are minimal or even cost-saving, he pointed out, and "in essence the costs of prediabetes will be paid later if we don't do anything today." Is it possible to carry out a trial demonstrating such benefit? To prove, say, that diabetes prevention reduces CVD events—with an annual CVD event rate of 1.5 and a 25% risk reduction—for the statistical certainty to be 0.05 and the trial power to be 90%, 3-, 5-, and 10-year studies would require 28,000, 14,700, and 6,800 people. Actual annual CVD rates might be 0.5–1%, and the degree of reduction might only be 5–15%, further increasing the number of participants required to successfully carry out such a study. Also, there may well be a lag period, as suggested by Tuomilehto, of over 5 years, beginning at the time of development of diabetes, such that the trial would require at least a decade. Would it, however, be ethical to have a placebo control group if we know that a safe intervention such as lifestyle reduces diabetes development by more than half? Ratner concluded that although diabetes prevention may well reduce CVD events, "it is going to be very difficult to prove."

George Bakris (Chicago, IL) discussed issues of the impact of pre-diabetes on nephropathy and hypertension. He pointed out that microalbuminuria is a marker, not a risk factor, as it has not fully been shown to affect the course of renal disease or CVD when taking all other factors into account. Furthermore, in addition to having 20–25% biologic variability, the assays themselves have 5–10% variability, such that a 30% change is required for meaningful benefit. Bakris pointed out that many inflammatory conditions are associated with microalbuminuria, with albuminuria improving when they resolve. The Diabetes Control and Complications Trial appears to be the only study showing a relationship between glycemia and albuminuria, although a number of preclinical studies support this effect. Bakris noted that the usual upper limit of normal for urine microalbumin, 30 mg/g creatinine, is unlikely to be correct, suggesting that 20 or even 15 may be the better cutoff. Albuminuria is strongly associated with CVD, in a fashion additive to the association with blood pressure (59). Bakris pointed out that the relationship between microalbuminuria and CVD is considerably stronger than that of CRP with CVD, such that he did feel this to be a useful measure (60). Macroalbuminuria is an even stronger CVD risk factor (61).

Bakris considered glomerular filtration rate (GFR) a sturdier measure of renal disease than urinary albumin. Based on creatinine clearance, 15.5% of the adult U.S. population has stage 3 chronic kidney disease (CKD) with GFR 30–59 ml/min, whereas only ~1% of the population has GFR <30 ml/min (62). More than renal failure, the great risk of CKD is its associated increase in CVD, with a Medicare database showing that CKD and diabetes are additive in causing cerebrovascular disease, coronary artery disease, congestive heart failure, and amputation or peripheral arterial insufficiency.

The greatest challenge in preventing progression of CKD and its complications is the treatment of hypertension. Most groups suggest goal blood pressure levels <130/80 mmHg, recommending renin-angiotensin system (RAS)-based treat-

ments as first line, although Bakris commented that reduction of blood pressure should be the overriding consideration, with multiple drugs usually required (63). Taken together, Bakris stated, it appears that with systolic blood pressure <135 mmHg, the rate of fall in GFR stabilizes at ~2 ml · min^{-1} · year^{-1}. There appears to have been modest improvement in blood pressure awareness, treatment, and control from 1999 to 2004 (63a). High-risk populations, particularly black and Hispanic, have the poorest blood pressure control (64). Dietary salt is important for limiting the benefit of RAS-based treatments. Sodium intake >4 g/day may decrease the antiproteinuric effect of RAS blockade by half (65), and this is only partially restored with thiazide diuretics (66). The DASH study showed that changes in albuminuria with lifestyle modification focused on sodium intake leads to reduction in albuminuria (67).

Bakris described a study comparing losartan plus hydrochlorothiazide with trandolapril plus verapamil in 240 individuals with IGT, showing the former to be associated with a 20–25 mg/dl increase in 2-h postload glucose and elevations in insulin levels and with a 9 vs. 2% likelihood of diabetes development, respectively (68). A similar study of benazapril-treated patients is in progress comparing the addition of hydrochlorothiazide vs. amlodipine (69) and addressing the question of whether the thiazide diuretic hydrochlorothiazide, even in doses not exceeding 25 mg, has adverse effects on glycemia.

Aaron Vinik (Norfolk, VA) discussed neurovascular dysfunction in pre-diabetes, reporting his findings that 11 and 13% of individuals with IFG and IGT had polyneuropathy, with 4 and 9% having neuropathic pain, respectively. This phenomenon of IGT neuropathy has been reported by a number of groups (70,71), with one-third to one-half of individuals with idiopathic sensory neuropathy having IGT (72) and IGT occurring in two-thirds of individuals with idiopathic painful neuropathy (73). Abnormal autonomic function is also associated with pre-diabetes—as demonstrated by spectral analysis of heart rate variability, which is a measure of sympathetic and parasympathetic function useful in demonstrating this association—and is perhaps associated with IGT but not IFG (74). Lifestyle intervention was associated with a 25% reduction in development of autonomic neuropathy in the DPP (75). Autonomic neuropathy also may have peripheral effects causing abnormality of vasomotion and thermoregulation with edema (76) in association with abnormality of small C-fiber nerves (77). The consequent impairment in gravitational blood flow correlates with systolic blood pressure, C-peptide, LDL cholesterol, triglycerides, and low HDL cholesterol (78). Vinik presented a study with photomicrographs of skin biopsy specimens showing reduction in intraepidermal nerve fibers in the proximal leg in association with metabolic syndrome as well as diabetes, with evidence that such abnormalities improve with lifestyle intervention (79). Cardiac autonomic neuropathy may also be associated with silent myocardial infarction (76), perhaps explaining the association of sudden death with pre-diabetes (80).

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