

Diabetes Prevalence, Development, and Progression

... OVERVIEW ...

Many Type 2 diabetics remain undiagnosed and undertreated, making the effective management of complications a daunting task. The panelists, who included diabetologists and other clinicians as well as representatives from managed care organizations, discussed the extent of diabetes underdiagnosis and the feasibility of more widespread screening efforts. They concluded that a more diligent approach to public education and greater primary care physician awareness are needed.

Preventing diabetes from developing and progressing is difficult when the precise roles of impaired glucose tolerance (IGT) and hyperinsulinemia are still unclear. Although it is clear that IGT often progresses to overt diabetes, the question of when to start drug treatment in an IGT patient is still unresolved. Diet, exercise, and lifestyle modification programs should be advocated, panelists agreed, even though there is still debate as to what extent these interventions can actually prevent disease. Likewise, the mechanism of hyperinsulinemia and the role it may play in the process of accelerated atherosclerosis are not yet clearly defined. Some answers may be forthcoming from the Diabetes Prevention Program (DPP), a multicenter trial now underway. An important goal of this trial—which was launched in June, 1996—is to determine if the onset of diabetes and macrovascular complications (eg, coronary artery disease) can be prevented or delayed in people with

IGT. Patients in the following four treatment cohorts will be followed for 3 to 6 years: (1) a control group; (2) those receiving intensive diet and exercise intervention; (3) those receiving intensive diet and exercise intervention along with troglitazone; and (4) those receiving intensive diet and exercise intervention along with metformin. The DPP study is scheduled to end in 2003.

Until such information is available, it may be best to improve awareness of IGT and hyperinsulinemia and to recommend modifications in lifestyle. Prediabetic and diabetic patients, panelists emphasized, represent a group with very heterogeneous characteristics and should accordingly be approached on an individual basis.

... DISCUSSION HIGHLIGHTS ...

Prevalence and Underdiagnosis

Dr. Kelley: One of the most telling statistics is that half of Type 2 diabetics are undiagnosed (Figure 1).¹ I do not believe that the majority are undiagnosed because they have no access to medical care or because physicians aren't testing often enough. Instead, I think that a common metabolic characteristic of most undiagnosed patients is that they do not have a fasting glucose above 140 mg/dL. Many may have a fasting blood sugar above the normal range but they don't quite make that 140 mg/dL threshold. In the minds of many internists and family physicians, these patients have an "intermediate" or "borderline" status and are only being followed when in fact,

they should be considered to have out-right diabetes. The condition remains undetected, which is unfortunate because many treatments can lower diabetes risks when given at this point. This opportunity to intervene is being missed.

Mr. Vodoor: Would another reason for the 50% undiagnosed rate be that we, as managed care providers, are not given the tools or the opportunities we need to educate primary care doctors?

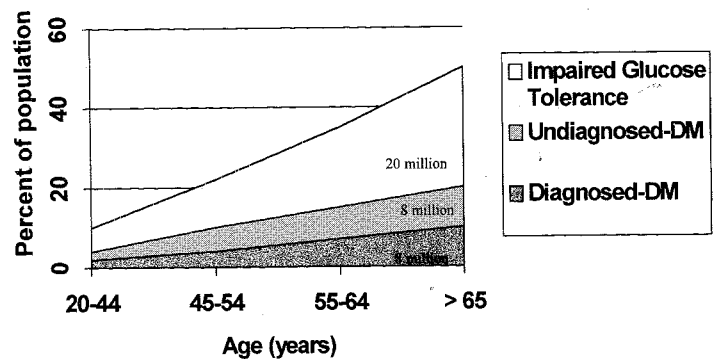
Dr. Zonszein: Educating healthcare professionals is always important, but in this case many other factors are involved. Late diagnosis is often associated with the presence of complications; this is an important reason why the criteria for diagnosis might be changed.* Preliminary, unpublished results from the DPP indicated that when using the old criteria for screening study volunteers (fasting blood sugars of ≥ 140 mg/dL), about one third of the otherwise eligible subjects were found to have diabetes.^{2†}

Dr. Henry: Yes, we were struck by that finding. The initial impression at our center was that this might reflect a discordant population in the initial patients studied. It subsequently became clear that up to one-third of the patients were consistently found to have diabetes by glucose tolerance testing throughout this multicenter study. In some centers it was higher than one-third, but when the data were reviewed, it was clear that *underdiagnosis* was the cause of the problem. Type 2 diabetes is probably even more common than we currently estimate. The proposed change in fasting glucose criteria from ≥ 140 mg/dL to ≥ 126

mg/dL will significantly increase the prevalence of Type 2 diabetes.³

Dr. Garber: We analyzed our database for the prevalence of diabetes among our health plan members by using a criterion that is relatively insensitive in that it requires a diabetes diagnosis in a hospital or outpatient setting and a prescription for a diabetic agent. Not included are patients who are new to the health plan, get their prescriptions through some other source, or are treated with medications in the hospital. If anything, this system underestimates the number

Figure 1. Estimated Prevalence of Diagnosed and Undiagnosed Type 2 Diabetes and Impaired Glucose Tolerance



Source: Joel Zonszein, MD. Adapted from *Diabetes in America*, 2nd Edition.¹

of people who are diabetic, but the good thing about it is that it is very clear that the people who are detected are in fact diabetic. Still, the analyses varied from setting to setting. For instance, in our 65-and-older patients, we have a documented diabetes incidence of 9%. However, among our younger patients, we document a 1.5% to 1.8% incidence, which is obviously low for an urban-based, mostly nonwhite population. There has been a big movement in our area to capture Medicare patients and it

*Editor's Note. Several weeks after this symposium, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus recommended changing the diagnostic criteria. See *Update*, S6-S8 for details

†Editor's Note. Drs. Zonszein and Henry are investigators for the DPP trial for the Bronx and San Diego sites, respectively

may be that Medicare patients with pre-existing conditions such as diabetes flock to managed care types of arrangements. That may account for why our system picks up so many diabetics within the Medicare enrollees.

Dr. Guthrie: Screening standards, even when they are available, are not often followed very closely. One study suggested that surveyed physicians did not feel that Type 2 was as serious as Type 1.⁴ I think that's probably largely true in primary care. A recent report showed that only 56% of diabetic patients had undergone a glycosylated hemoglobin within the previous year.⁵ These assays are available in the managed care setting so it's not an access or resource issue but is clearly a lack of understanding by both patients and physicians as to how important this disease is.

Dr. Gleeson: Absolutely. When we surveyed all physicians in New Mexico we found that Type 2 diabetes was seen by a large number as a very benign disease that doesn't require much attention—especially if the fasting blood sugar is less than 200 mg/dL.

Dr. Zonszein: What can we do to capture these undiagnosed patients? Should we push for more professional education?

Dr. Guthrie: I think there are three approaches. One is education, the second is to set standards into algorithms that physicians can have easy access to and the third is to increase the use of midlevel providers who tend to follow guidelines very well. This last component has been particularly neglected, which is unfortunate, because midlevel providers can be much more efficient than physicians in assuring that patients have eye exams and so on. Since we now have many more therapeutic options, physicians will find diabetes treatment is more complicated, and they may need algorithms to help guide treatment decisions. Unfortunately, physicians don't

generally respond well to the idea of using algorithms.

At the Ochsner Clinic we are conducting a 1-year, randomized, controlled study with more than 200 patients focusing on using a staged diabetes management (SDM) algorithm versus usual diabetes care. These algorithms, developed by the International Diabetes Center to help primary care physicians care for their patients with diabetes, were modified for use by diabetes nurse educators as an aid to physicians. Development of the SDM algorithm and the study were supported by an educational grant from Becton-Dickinson. After the first 6 months, the group using the SDM algorithm had outperformed the usual care group in terms of both preventive screening procedures and achieving a 1% larger reduction in glycohemoglobin. These data will be published when the final analysis is complete.

Glucose Intolerance Issues

Dr. Koda-Kimble: The DPP used the ≥ 140 mg/dL criteria when it started. If a fasting plasma glucose criteria of ≥ 126 mg/dL had been used when that trial started, how many of the patients who were found to have IGT might have been diagnosed with diabetes?

Dr. Henry: I believe we diagnosed 7% to 8% more cases of diabetes when the ≥ 126 mg/dL measure was used. Even at this lower criteria, some subjects have glucose levels above 200 mg/dL at 2 hours following a 75-gram oral glucose load. This is also diagnostic of diabetes.

Dr. Zonszein: I want to clarify that hemoglobin A_{1c} (HbA_{1c}) is not accepted as a diagnostic standard but is mainly an indicator of treatment response. Patients with mildly elevated glucose, even if the HbA_{1c} is only 7% with a normal of 6.1%, tend to have other cardiovascular risk factors such as hypertension and dyslipidemia, and therefore continue to exhibit a high morbidity and

mortality rate.⁶ It appears that when we start treatment early, the benefits are tremendous. However, once there is organ damage as a result of chronic diabetic complications, we have less impact on slowing the progression of the disease.

Dr. Henry: That underscores the fact that hyperglycemia isn't the only metabolic abnormality of diabetes. We need to be looking at the other associated metabolic abnormalities such as hypertension and hyperlipidemia. The new criteria for the diagnosis of diabetes will permit earlier detection and treatment before complications occur.

Dr. Gleeson: The current treatment of diabetes is directed toward treating hyperglycemia and microvascular complications. This approach frequently overlooks macrovascular complications and the necessity for modification of these complications.

Dr. Garber: Even if there is controversy about treating hyperglycemia, these patients still need aggressive blood pressure control, a serum lipid check annually instead of every 5 years, and a more aggressive approach to smoking cessation. We need to implement these higher levels of care regardless of whether a physician or midlevel professional provides them.

Dr. Koda-Kimble: It seems that a key player in early diagnosis would be the patient. I think many more people would be diagnosed by simply putting out the word that those at high risk for diabetes should come in for a prevention program. I think the patient has to be an integral part of early detection.

Mr. Vodoor: Before trying to put patients into a smoking cessation program, exercise program, or other preventive program, I think we need to increase their awareness of the disease. Once they are more aware they'll be more proactive about recognizing and seeking

treatment for symptoms. Patients have to start taking a bigger role in their own care.

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— Joel Zonszein, MD, FACP

Dr. Guthrie: I would emphasize that the focus for IGT patients should be to look at their risk factors and recognize they are at increased risk of macrovascular disease. Right now, any attempt to pharmacologically treat patients with IGT is considered "experimental" because the final data on whether pharmacologic therapy is beneficial for these patients are not yet available.

Dr. Zonszein: Unfortunately, IGT is a nonentity to insurance companies. They haven't caught up with the concept that it is a disorder unto itself, not just a "borderline" level of diabetes. Since there are no billing codes for an IGT diagnosis, we should use the codes for hypertension, obesity, or dyslipidemia, instead.

Dr. DiPette: I'd like to make the point that it is extremely difficult for primary care physicians to have to worry about things like that. They are asked to do quite a bit in terms of education, treatment implementation, and hospital administration. We have to educate physicians in ways that do not make treatment implementation more complicated, but more convenient. Disease management of diabetes will have a place in the primary physician's world, but it must be done succinctly. A team

approach with nurse providers and midlevel educators is clearly going to be more effective than using a physician alone. Perhaps this is where managed care can step in and help practitioners. Managed care can give us the resources to carry out these interventions.

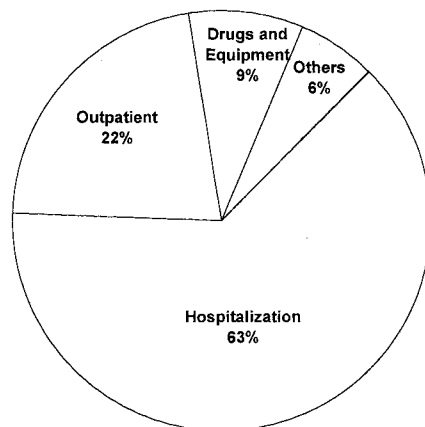
Dr. Gleeson: I agree. We are using this approach. Our primary care physicians are extremely receptive to interventions that make providing needed care easier to achieve. However, a disease management approach that significantly increases physician workload will probably fail. Many physicians already know what they should do but their practice environment makes it difficult to accomplish. Managed care can make it easier to take care of diabetes patients by providing information and feedback without burdening doctors with additional work, record-keeping, and the like.

Dr. Zonszein: Fortunately, I have hope that increased awareness will improve our ability to diagnose and care for diabetes patients. Many clinical studies now show an important difference in disease outcomes.

For example, the Diabetes Control and Complications Trial [DCCT] showed we can impact disease progression and decrease the incidence and progression of retinopathy, nephropathy, and neuropathy by improving glycemic control.⁷ The Diabetic Retinopathy Study showed that early detection of retinopathy and treatment with photocoagulation can prevent blindness.⁸ Treating hypertension and using ACE [angiotensin converting enzyme] inhibitors have been shown to slow progression of renal failure and decrease the need for renal replacement (dialysis or kidney transplantation) by more than 50%.⁹ We have seen that aggressive lowering of LDL-C [low-density lipoprotein cholesterol] levels has an impressive effect on cardiac morbidity and mortality, particularly among diabetics.¹⁰

In addition, proper education and intervention by "diabetes teams" is associated with decreased hospital admissions and length of stay for foot complications and other acute diabetic complications.¹¹ It is clear that we can now intervene with effective treatments that enable patients to live longer and better. However, we still need an effective method for primary care physicians to implement these strategies, since they see the majority of diabetic patients.

Figure 2. Annual Healthcare Expenditures for People with Diabetes, 1992.



Annual healthcare expenditures for people with diabetes in the United States based on data from 1987, adjusted for 1992 prices. Overall, \$105 billion (approximately 15% of US healthcare dollars) were consumed for the care of patients with diabetes. Note that 63% were used for inpatient services.
Source: Joel Zonszein, MD. Adapted from: Rubin RJ, et al. *J Clin Endocrinol Metab* 1994;78:809A-809F.

Early Treatment and Cost Effectiveness

Dr. Garber: Although the DCCT demonstrated that early treatment is clinically effective, it did not demonstrate cost effectiveness.⁷ Money was not saved in any demonstrable model—this is a problem with implementing the DCCT interventions. "Will we have the resources?" is going to remain a pressing question.

Dr. Zonszein: In the DCCT the cost was more than \$10,000 for each patient but a large component of that was for research—not clinical costs. I think we can do a very good job of managing Type 1 with intensive therapy for about \$3,000 a year with approximately 40% of the cost being allocated for medical supplies. The expense involved in treating patients with diabetes is very high—typically three to four times higher than treating other diseases. Most of the expense goes for managing diabetic complications, with inpatient care representing more than half of the cost (Figure 2). The message should be clear: Shifting costs from managing diabetic complications to preventing is long-term cost effective. Unfortunately, managed healthcare organizations are often reluctant to fund or support prevention strategies.

Dr. Guthrie: As a Board of Governors member of the Ochsner Clinic, one of my responsibilities is to think about business strategies as managed care becomes more common. Currently, the theory of population medicine seems to be viewed as an important mechanism to control the costs of chronic disease states such as diabetes. One of the problems in the past has been that job switching resulted in insurance switching. However, now, a larger portion of our revenue is coming from Medicare risk contracting and those patients can choose to stay in our health plan as long as they desire because they won't be switching jobs. Also, there is likely to be legislation allowing people to retain their insurance when they do change jobs. Therefore, we're starting to view managed care as having a more long-term relationship with the patient. I think population medicine will eventually have to be considered for all disease states.

Diabetes Development

Dr. Henry: Probably the pivotal underlying abnormality in Type 2 diabetics—

certainly the earliest documentable abnormality—is insulin resistance, which leads to hyperinsulinemia. Insulin resistance can eventually lead to impaired glucose tolerance; in the United States, it is estimated that approximately 5% of IGT patients will develop Type 2 diabetes each year.¹² The percentage may change somewhat when the new diagnostic criteria for diabetes are adopted. This disease progression model affords us the opportunity to intervene in a very high risk population in an attempt to prevent the next step, which is greater beta-cell failure and the development of overt Type 2 diabetes.

Dr. Koda-Kimble: When does beta-cell failure really come in? Is it after IGT develops or before?

Dr. Henry: It probably occurs very early, along with the start of insulin resistance. In fact, some studies have shown abnormalities in insulin secretory patterns at the very early stage of diabetes and in individuals with IGT; but in terms of quantity and severity, insulin resistance is much more dominant at this stage.

Dr. Kelley: The early defects in secretory capacity seen in IGT revolve around how quickly insulin is released postprandially—how well it responds to glucose levels. This defect requires a sophisticated look because if one simply measures insulin concentrations after a meal, insulin secretions will be quite robust. This fact makes a difference as we consider therapy based on disease mechanisms. The recognition that there are some early secretory defects doesn't necessarily mean the initial treatment should be directed at boosting insulin secretion because the absolute amount of insulin secreted is robust. However, with very precise physiological studies, some loss of coupling between insulin secretion and glucose may be seen. There are some suggestions that the liver may start to be abnormal, even at this stage, with an inability to be sup-

pressed.^{13,14} But in terms of quantitative difference, muscle defect is far more severe.

Dr. Guthrie: There is some debate about which medications should be used to treat early Type 2 diabetes if the diagnostic criteria change. This is a very controversial area because in terms of effects on insulin levels, sulfonylureas may not show much of a difference in long-term outcomes compared with treatments that lower insulin levels. The 1995 American Diabetes Association (ADA) consensus statement said that the difference may not be important, but now we have newer data.¹⁵ What is not as controversial is the idea that if we're ever going to prevent the development of Type 2 diabetes, we should naturally begin at the level of hyperinsulinemia, since that is the accepted pathogenetic basis of diabetes. The NIH [National Institutes of Health] decision to include metformin and troglitazone as the two drug arms of the DPP trial makes a lot of sense because the agents that prevent hyperinsulinemia are theoretically agents that will prevent Type 2 diabetes.²

Dr. Henry: I would go one step farther and include not only agents that directly prevent hyperinsulinemia but those that treat the underlying insulin resistance as well. This treatment may be at the genetic level. The DPP will tell us whether or not treating insulin resistance or hyperinsulinemia, or both, will slow or halt the progression of IGT to Type 2 diabetes.

High-Risk Patients and Screening

Dr. Henry: Populations vary in diabetes risk, based upon genetic origin.¹⁶ The risk of progressing from IGT to outright diabetes ranges from being relatively low for Caucasians in England to being very high in Mexican-Americans from Colorado, and even higher in the Pima Indians, who have the highest incidence of diabetes in North America and one of

the highest in the world.^{17,18} It is also important to emphasize that environment has a decisive impact in individuals who have a genetic likelihood of developing Type 2 diabetes. We see that individuals who move from a low to a relatively high economic status develop diabetes much more frequently. Similarly, many other populations, in migrating to more affluent societies, have a marked increase in the development of diabetes. Type 2 diabetes is a genetic disorder that can be influenced very dramatically by the environment, which largely includes lifestyle changes—meaning more activity and a healthier diet.

Dr. Zonszein: The environmental impact on genetic predisposition can be illustrated by the higher incidence of microvascular diabetes complications in Mexican-Americans compared to Mexicans living in Mexico, and by Mexican-Americans who live in the "barrios" of Texas compared to those living in Colorado. One theory is that this may be because Mexican-Americans have a relatively higher socioeconomic status than their counterparts in Mexico. This often translates into more food consumption, less physical activity, and higher rates of obesity. The Mexicans studied in Colorado tend to be migratory workers who are in the US only temporarily and who, by the nature of their work, are obviously physically active.¹⁹⁻²¹ Conversion of IGT to diabetes mellitus is also higher in Japanese-Americans than among IGT Japanese patients who live in Japan.²²⁻²⁴

Dr. Henry: Hispanic-Americans are a very diverse group in themselves, and their development of Type 2 diabetes is variable, depending on their genetic ancestry. Those who are more genetically native North American tend to have a higher incidence of diabetes. African-Americans and Pacific Islanders also have a higher diabetes risk, although there are more Type 2 diabetics among Caucasians due to their sheer numbers in this country. We certainly need to look

at high-risk individuals over the age of 45 because the prevalence of diabetes increases dramatically with age. Besides ethnicity, another high-risk group is patients with a family history of Type 2 diabetes. The more individuals with diabetes in a family, the greater the likelihood that unaffected family members will also develop diabetes. The presence or development of intra-abdominal obesity—particularly visceral obesity—is a contributing factor and a sedentary lifestyle can also contribute.^{25,26} We should also remember that women who deliver large babies (≥ 9 lbs) and those who experienced gestational diabetes while pregnant are also at risk for developing Type 2 diabetes. Women with gestational diabetes have a high risk of developing diabetes after pregnancy. We should target all of these populations, including, of course, anyone with IGT.

Dr. Peters: At what age would you recommend starting to screen high-risk patients?

Dr. Henry: We are grappling with this issue now in San Diego because there is a fairly substantial pediatric population of Type 2 diabetics that unfortunately seems to be growing in number. I suspect we are missing the diagnosis of Type 2 diabetes in some high-risk children. We usually see them only when they present with frank hyperglycemia, although occasionally diabetes is detected with routine screening.

Dr. Zonszein: We have a similar problem in New York, where a high rate of teenage pregnancy has resulted in a tremendous increase of gestational diabetes. Many of these individuals—particularly Latina women—probably already had diabetes but were screened only after they became pregnant. This is one reason why it is important to screen more often, and at earlier ages, in high-risk populations.

Dr. Henry: I don't have a fixed recommendation for when screening should

start in children, but since the early onset of Type 2 diabetes is often related to lifestyle, I think young children who are obese and have a family history of Type 2 diabetes should be screened, at least with a fasting plasma glucose measurement. Based on available data, if the fasting serum glucose in children is over 100 mg/dL, then an oral glucose tolerance test is probably warranted. There

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— Robert Henry, MD, FRCP

are some data that indicate the likelihood of preadult individuals developing diabetes.^{27,28} Logically, we should try to make the diagnosis earlier and then institute intervention. Lifestyle changes are likely to make a difference in this high-risk population,²⁹ if they can be effectively instituted—but the long-term failure rates are high. An important issue is whether it is warranted to put children with IGT on the same kind of program as the DPP program for adults. If so, the question then becomes whether it is safe to use metformin, troglitazone, or some other pharmacologic agent to treat young people who don't have overt diabetes. Unfortunately, the DPP study excludes subjects who are younger than 25.

Mr. Vodoor: There are many challenges to instituting interventional diet, exercise, smoking cessation, and stress management programs in the managed care environment. For one thing, such programs are very expensive to develop and implement. Another challenge is to encourage patients to participate on an ongoing basis. Every year on January 1, people all across the country enroll in

exercise and weight loss programs that they don't continue. By about the middle of February most have lost motivation. It's important to try to convince patients to stay in these programs so at least some of them can be effectively treated without pharmacology.

Dr. Henry: I think it can be difficult to get people involved in their care—particularly with a disease like diabetes, because as long as there are no complications, it usually doesn't cause any pain or discomfort—at least not in the early stages. We need to continue to improve our lifestyle management techniques, but admittedly, it isn't an easy therapeutic option.

Insulin Resistance Syndrome

Dr. Koda-Kimble: What is the prevalence of insulin resistance syndrome, or "syndrome X," and what portion of these patients have IGT?

Dr. Henry: There are probably at least 50 million people who have syndrome X, also called metabolic syndrome X, metabolic cardiovascular syndrome, or more precisely, *insulin resistance syndrome*. I suspect these numbers are growing steadily. Of the 50 or so million, perhaps 20 to 30 million have IGT.¹⁵ The most easily identified abnormality of insulin resistance is the development of hyperglycemia. However, our goal should be to prevent or treat the whole syndrome. There is evidence both for and against the role of hyperinsulinemia, but insulin resistance certainly seems to be the key metabolic abnormality in insulin resistance syndrome. Improving insulin resistance is an important step toward treating this syndrome.

Dr. Zonszein: Controversy surrounds the role of hyperglycemia in macrovascular disease, and the beneficial effect that treating it may have in ameliorating the progression of macrovascular complications. For instance, individuals with

insulin resistance syndrome have minimal hyperglycemia, yet experience a high incidence of coronary events. These have been attributed to hyperinsulinemia. While hyperinsulinemia is an independent risk factor for coronary heart disease, a cause-and-effect relationship has not been well documented. Insulin resistance syndrome is a very complex entity and many other factors—such as hypercoagulability—interplay with hyperinsulinemia, hypertension, obesity, and dyslipidemia to form an adverse milieu that is conducive to accelerated atherosclerosis.

Dr. DiPette: I completely agree that it's important to remember that insulin resistance syndrome is a constellation of known cardiovascular risk factors including, as you said, Dr. Zonszein, hyperinsulinemia, hyperlipidemia, and hypertension. When these risk factors are present together, the cardiovascular risk profile is not just additive but exponential! This may be one explanation why coronary artery disease, morbidity, and mortality is seen even when hyperglycemia is apparently "minimal."

Dr. Henry: We have to consider *why* we treat diabetes and insulin resistance syndrome. A major reason is to prevent acute complications, but we want to prevent chronic complications as well. We know that microvascular disease is affected by glycemic control—at least in Type 1 diabetes—and there is also some evidence that glycemic control has a positive effect on microvascular disease in Type 2 diabetes (Table 1).³⁰ The jury is still out on whether there is a similar relationship between glycemic control and macrovascular disease. There are some indications that good glycemic control may minimize macrovascular complications, but more long-term data are needed.^{31,32} I believe good glycemic control will prevent or delay the development of cardiovascular disease and that reducing insulin resistance and hyperinsulinemia may further at least reduce the risk of macrovascular disease

over time. Unfortunately, at the current time we do not have solid data to confirm this suspicion.

Hyperinsulinemia and IGT

Dr. Kelley: It appears that some of the risk of macrovascular disease begins early in IGT. If intervention is aggressively focused on glycemic control once Type 2 diabetes has established itself, much of the macrovascular disease cycle may have already taken place. For example, data from Finland show that good glycemic control can reduce heart disease mortality in elderly Type 2 patients, but the degree of glycemic control required can be difficult to attain.³³ Glycohemoglobin needs to be restored almost to normal in order to achieve results, indicating that the risk factors for heart disease surface very early on.

Dr. Henry: The relationship between glycemia and complications is best illustrated by the association between diabetic retinopathy and poor glycemic control. Also, once diabetes develops, the risk of premature death increases considerably and disproportionately with age.^{34,35} Cardiovascular disease is the major cause of death among Type 2 diabetics, and the prevalence of angina, myocardial infarction, and abnormal cardiac findings in diabetics ages 40 to 69 are substantially higher than in the otherwise comparable nondiabetic population.¹ Also, the worse the glycemic control, the higher the incidence of amputations.³⁶ I want to emphasize the apparent role of hyperinsulinemia in all of this. To me, it seems likely that high insulin levels are involved in the development of macrovascular complications, and perhaps other complications as well. A little insulin is good and necessary, but high circulating levels may have adverse effects.

Dr. Kelley: Although information is available on the three fundamental de-

fects—the start of insulin resistance, a sudden excessive amount of glucose production, and beta-cell dysfunction—I think primary care physicians don't often keep in mind the rapidly progressive nature of Type 2 diabetes. The one metabolic characteristic that consistently emerges is the degeneration of beta-cell function; that is what is driving the deterioration of diabetes control over time. This was clearly brought out by the UK Prospective Diabetes Study.³⁷ Practitioners treating Type 2 diabetes need to understand how important it is to adjust treatment to compensate for beta-cell dysfunction and they should realize it might be a factor in why patients with the same diagnosis have different responses to the same medical approach.

Dr. Garber: Are there data to suggest that pancreatic decompensation isn't inevitable? In other words, if one intervenes and manages to reverse frank diabetes, are there instances where diabetes seems to be held off indefinitely?

Table 1. Reductions in Microvascular Complications with Improved Glycemic Control According to Two Studies

| Complication | Reduction, Study 1 | Reduction, Study 2 |
|------------------|--------------------|--------------------|
| Retinopathy | 76% | 65% |
| Nephropathy | 54% | 70% |
| Neuropathy | 60% | -- |
| Microalbuminuria | -- | 57% |

Sources: Study 1: The Diabetes Control and Complications Trial⁷; Study 2: The Ohkubo Y, et al study³⁰

Dr. Kelley: There are bits of data emerging that address that issue. A number of studies have characterized insulin secretory capacity in patients with IGT. They demonstrate that some of the very early defects in insulin secretion may best be

appreciated in terms of glucose entrainment. If the glucose level varies or fluctuates subtly, there is a synchronized capture of insulin secretion that doesn't occur in IGT. Intervention with troglitazone can substantially recapture the capacity to entrain. This indicates that although the pancreas may be programmed to fail, the programming may be malleable with intervention.³⁸

Hyperinsulinemia as a Risk Factor

Dr. Guthrie: My opinion is that endogenous hyperinsulinemia may play an independent role in the pathogenesis of complications. The difficulty we have is that this has not been conclusively proven. The 1995 ADA consensus statement pointed out that hyperinsulinemia appears to be more of a marker for risk factors than a risk factor itself. But since then, a contradictory study has been published indicating that hyperinsulinemia is an independent risk factor.³⁹ This was a retrospective cohort study of more than 2000 male patients that related the incidence of cardiac events to insulin levels. Even after diabetic patients were excluded, high fasting insulin concentrations were an independent predictor of ischemic heart disease. However, IGT patients were not excluded. I don't believe one can definitively conclude from this study that hyperinsulinemia is an independent risk factor for ischemic heart disease when IGT patients were not excluded since IGT itself is considered a risk factor for atherosclerotic disease. There hasn't been a study to tell us what happens when hyperinsulinemia is present without IGT.

Dr. Zonszein: It is very difficult to determine if hyperinsulinemia is directly responsible for some of these complications, or if it is only a marker. People with Type 2 diabetes constitute a very heterogeneous population, and the same applies to those with IGT. For instance, some IGT patients never develop diabetes.

Dr. Guthrie: The next question is even more complicated: Is insulin resistance alone a risk factor, even *before* hyperinsulinemia develops?

Dr. Gleeson: There are absolutely no data on whether reducing insulin resistance has an effect on outcomes. It is even less clear whether or not hyperinsulinemia itself is the key target for reduction.

Dr. Henry: There is also the issue of exogenous hyperinsulinemia—high circulating insulin levels induced by the administration of exogenous insulin. While there is probably some involvement of insulin and/or insulin resistance in the genesis of macrovascular complications, the data are only inferential. The question I have about diabetes treatment is whether or not we should actively try to reduce both hyperinsulinemia and hyperglycemia, using the concept of achieving the best glycemic control at the lowest circulating insulin level, instead of the concept that glycemic control is all-important regardless of the amount of circulating insulin. I prefer the approach of the best glycemic control possible at the lowest circulating insulin level.

Dr. Garber: If we are going to determine who to target as a future hyperinsulinemic patient, we will need to define the clinical characteristics independent from the measurement. Hyperinsulinemia will have to be termed a phenotypic syndrome because the measurement itself will not only be costly, but it may be inaccurate because it's not sensitive enough. I think we need to fall back on clinical features when deciding who to target.

Dr. Henry: If we knew for sure that hyperinsulinemia contributes to the complications and/or the progression of diabetes, I think we would aim for the best glycemic control at the lowest circulating insulin level. These issues must be addressed because they have immense therapeutic implications.

Treatments for Hyperinsulinemia

Dr. Kelley: Treatments should not only target glucose control but should also have neutral effects, or ideally, positive effects on lipids. How then, will therapy to control glucose interplay with other pharmacologic demands such as treating hypertension, and how will such treatment affect obesity, which is a marker for insulin resistance? With the growing obesity rate in this country, many patients can be targeted as being at high metabolic risk.⁴⁰ Obesity is a challenge for primary care physicians because they cannot focus on glucose alone. They also have to deal with an awful lipid situation, the difficult behavioral features that drive obesity, and all the psychological problems attendant to obesity.

Dr. Zonszein: I think the message is out among primary care physicians. Eighty percent of the insulin that is used in this country is used for Type 2 diabetes, because of the size of the Type 2 population and because many of them are resistant and need high doses. When I talk to primary care physicians, they seem perfectly aware of the risks associated with both endogenous and exogenous hyperinsulinemia. I think the concern is global but we don't have good evidence that exogenous hyperinsulinemia is deleterious. A great number of patients are being treated incorrectly with insulin—they are frequently treated with high doses and multiple injections as if they had Type 1. However this iatrogenic hyperinsulinemia is often accompanied by weight gain and persistently elevated HbA_{1c}. When primary care physicians continue to notice high blood sugar levels, they tend to give more insulin. Primary care physicians need to know that very often insulin can be adjusted with dietary restrictions or by the way the insulin is administered.

Dr. Peters: Some study populations show an association between hyperinsulinemia and risk but in other popula-

tions, for example, in women, there may be no association. One concern is that some community physicians use exogenous hyperinsulinemia as a reason not to treat diabetes aggressively enough to achieve good glycemic control. I advocate treating hyperglycemia and in my own practice I try to decrease exogenous hyperinsulinemia as well. I see better results with treatment combinations than with insulin alone; and by trying to lower exogenous hyperinsulinemia, I find that patients do not gain weight or become hypoglycemic. However, I am not sure we know enough to make a definitive statement about the role of exogenous hyperinsulinemia.

Dr. Zonszein: I want to point out that some primary care physicians resist putting patients on insulin not because they fear the possible atherogenic effect, but because of other drawbacks associated with insulin treatment. Many patients are reluctant to take insulin for many different reasons.⁴¹

Dr. Henry: Most studies show an association between high insulin levels and cardiovascular disease, but this association doesn't always hold up. Hyperinsulinemia may be a risk factor only for certain populations—including those with diabetes—and we shouldn't lose sight of the fact that some populations may be uniquely susceptible to the effects of hyperinsulinemia. Patients with endogenous hyperinsulinemia tend to have upper-body obesity and more commonly have impaired glucose tolerance, or overt diabetes. Such individuals frequently develop the classic lipid abnormality of small, dense LDL particles, which appear to be more oxidizable and may enter vessels more easily, possibly contributing to an accelerated atherosclerotic process.⁴²⁻⁴⁴

Triglyceride abnormalities, small, dense LDL-C particles, decreased HDL-C [high-density lipoprotein cholesterol] levels, hypertension, elevated levels of plasminogen-activating inhibitor-1, along with many other metabolic

abnormalities, are all often present in the insulin-resistant hyperinsulinemic. These abnormalities may contribute to cardiovascular disease. Many of us believe this entire collection of abnormalities evolves from the insulin resistance syndrome and this belief is partially fueling the concern about hyperinsulinemia and its potential adverse effects.

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