Pre-diabetes represents an elevation of plasma glucose above the normal range but below that of clinical diabetes. Pre-diabetes can be identified as either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). The latter is detected by oral glucose tolerance testing. Both IFG and IGT are risk factors for type 2 diabetes, and risk is even greater when IFG and IGT occur together. Pre-diabetes commonly associates with the metabolic syndrome. Both in turn are closely associated with obesity. The mechanisms whereby obesity predisposes to pre-diabetes and metabolic syndrome are incompletely understood but likely have a common metabolic soil. Insulin resistance is a common factor; systemic inflammation engendered by obesity may be another. Pre-diabetes has only a minor impact on microvascular disease; glucose-lowering drugs can delay conversion to diabetes, but whether in the long run the drug approach will delay development of microvascular disease is in dispute. To date, the drug approach to prevention of microvascular disease starting with pre-diabetes has not been evaluated. Pre-diabetes carries some predictive power for macrovascular disease, but most of this association appears to be mediated through the metabolic syndrome. The preferred clinical approach to cardiovascular prevention is to treat all the metabolic risk factors. For both pre-diabetes and metabolic syndrome, the desirable approach is lifestyle intervention, especially weight reduction and physical activity. When drug therapy is contemplated and when the metabolic syndrome is present, the primary consideration is prevention of cardiovascular disease. The major targets are elevations of cholesterol and blood pressure.

The prevalence of type 2 diabetes is increasing in the United States and worldwide. Because of many complications and the high costs of diabetes, its prevention and its complications demand more attention. The major complications of diabetes are cardiovascular diseases (CVD)—both microvascular disease and macrovascular disease. The leading risk factor for type 2 diabetes is a condition called pre-diabetes. The latter’s predisposition to type 2 diabetes makes it a potential risk factor for CVD as well. Pre-diabetes moreover aggregates commonly with other CVD risk factors that make up the metabolic syndrome.

An ongoing debate is whether pre-diabetes deserves targeted identification and clinical intervention (1). Pre-diabetes generally is defined by either an elevation of fasting or post-prandial plasma glucose levels. Elevated hemoglobin A1c, or glycosylated hemoglobin (HbA1c), which integrates plasma glucose over time, is promoted by some as another indicator of pre-diabetes. This paper will review the pathogenesis and diagnostic criteria for pre-diabetes, its relation to macrovascular and microvascular diseases, and potential intervention strategies.

**What Is Pre-Diabetes?**

The term pre-diabetes has had a checkered history. Alberti (2) states that it was first used to denote abnormalities of pregnancy (e.g., high–birth weight babies, hydramnios) or a strong family history of type 2 diabetes. However, in 1980, the World Health Organization (WHO) (3) discarded the term largely because many subjects with borderline glucose levels do not convert to diabetes and because many would be alarmed unnecessarily. These problems still persist. Yet in 2005, the American Diabetes Association (ADA) reintroduced pre-diabetes to cover impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) but not other risk factors for diabetes (4). In 2008, WHO’s diabetes task force again repudiated the term and discouraged its use (5). Instead, they suggested “intermediate hyperglycemia” to signify IGT and IFG. The ADA nonetheless continues to use pre-diabetes and defines it as IFT, IGT, and now, HbA1c of 5.7% to 6.4% (6).

Any definition of pre-diabetes that is restricted to IGT and/or IFG fails to include other risk factors for diabetes, such as, a family history of type 2 diabetes or the metabolic syndrome. Another telling criticism of the term pre-diabetes is that the many subjects with either IFG or IGT will not
Impaired glucose tolerance. Normal fasting plasma glucose is a level of <100 mg/dl (<5.6 mmol/l) or a 2-h plasma glucose in response to a 75-g oral glucose tolerance test (OGTT) of <140 mg/dl (<7.8 mmol/l). IGT is recognized as an intermediate level of post-prandial glucose that carries essentially no risk for microvascular complications (10). It is diagnosed exclusively by OGTT; the 2-h plasma glucose is 140 to 199 mg/dl (7.8 to 11.0 mmol/l). According to recent NHANES (National Health and Nutrition Examination Survey) data (11), overall IGT prevalence in U.S. adults >20 years of age is 13.8%. The prevalence rises progressively with age. In the European DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study, IGT rose from 2.9% in 30- to 39-year-old men to 15.1% in 70- to 79-year-old men (12). One disadvantage of testing for IGT is the necessity for OGTT; another is that the results are not highly reproducible. Nonetheless, it is a relatively strong, albeit variable, predictor of type 2 diabetes (13). A predominant metabolic characteristic is insulin resistance in muscle, which exists along with defective insulin secretion (9). In most Western countries, conversion rates for isolated IGT range from 4.35% to 6.35% per year (14). In the DPP (Diabetes Prevention Program) study, in which IFG also was common, conversion to diabetes was approximately 10% yearly (13,15).

Combined Impaired Glucose Tolerance and Impaired Fasting Glucose

One reason the ADA lowered the threshold for IFG was to avoid the need for OGTT to diagnose IGT. This aim did not entirely succeed. From 1988 to 1994, among U.S. adults aged 40 to 74 years, 33.8% had IFG by the revised definition, whereas only 15.4% had IGT (19). Only about 6% of the population had IGT but not IFG because of normal glycemia. Second, receiver-operator characteristic analysis of several studies found that 100 mg/dl is a threshold level of fasting glucose that maximizes sensitivity and specificity for predicting diabetes. Third, the expert committee postulated that reducing the threshold for IFG would make the prevalence of IFG and IGT concordant. However, the latter did not work out. Prevalence of IFG in the United States after lowering the threshold jumped from 6.9% to 25.7%, which was double the 12.9% for IGT (11).

Applying this percentage to the U.S. population >20 years of age gave IFG to an estimated 57 million adults (19). Ethnic breakdown for IFG prevalence showed 21.1% in non-Hispanic blacks, 25.1% in non-Hispanic whites, and 26.1% in Mexican Americans. Other populations had similar increases after this change in IFG definition, for example, from 11.8% to 37.6% in Denmark and from 10.6% to 37.6% in India (5).

There have been 2 major criticisms of the ADA’s change in definition of pre-diabetes based on fasting glucose levels. First, a high proportion of the population becomes “medicalized,” and second, persons with fasting glucose levels of 100 to 110 mg/dl convert to diabetes with a lower frequency than do those with levels of 110 to 125 mg/dl. Regarding the latter, compared with individuals with fasting levels of 100 to 110 mg/dl, those in the range of 110 to 125 mg/dl have a 2- to 6-fold higher risk for developing diabetes (5).
with undetected diabetes or to find those at very high risk for diabetes. Persons who have both IGT and IFG plus metabolic syndrome are at greater risk for conversion to diabetes than are those with only IGT or IFG (15). Such persons may be better candidates for aggressive therapy to delay onset of diabetes (14).

**Hemoglobin A1c**

In 2009, an expert committee organized by the ADA, the International Diabetes Federation, and the European Association for the Study of Diabetes (20) recommended that HbA1c become an alternative to plasma glucose for diagnosing type 2 diabetes. Advances in the measurement of HbA1c and growing evidence of its association with plasma glucose underlie this recommendation. The expert committee listed several advantages of HbA1c testing compared with glucose measurements for the diagnosis of diabetes. HbA1c is now better standardized. There is less biologic variability and pre-analytic instability. HbA1c gives a better measure of overall glycemic exposure and likely risk for long-term complications. There is no need for fasting or timed samples, and HbA1c is less affected by conditions to produce perturbations in glucose levels. Moreover, it is a better guide to clinical management of patients. For these reasons, it is likely that HbA1c will become a standard approach to the diagnosis and clinical management of type 2 diabetes. For the diagnosis of diabetes, the expert committee recommended an HbA1c threshold of 6.5%.

Whether HbA1c can also be used to identify pre-diabetes is an important question. The WHO expert committee advised against its use for this purpose, citing lack of sufficient evidence (5). The ADA/International Diabetes Federation/European Association for the Study of Diabetes expert committee was noncommittal; it speculated on a range of 6% to 6.5%, but did not recommend it. The ADA recently proposed a pre-diabetes range of 5.7% to 6.4% (6), which accords with updated NHANES data (21). Another study (22) suggested that HbA1c might obviate the need for OGTT to identify pre-diabetes. Still another report (23) showed that there is considerable discordance between HbA1c and fasting glucose levels; it implied that many individuals would be misclassified by HbA1c. However, because HbA1c is a better indicator of integrated glucose levels, one can ask whether fasting glucose levels are more likely to misclassify a person than HbA1c levels. If pre-diabetes is going to emerge as an important clinical category and if HbA1c becomes the primary screening method for dysglycemia, its use to identify subjects with pre-diabetes will have to be seriously considered.

**Pre-Diabetes and the Metabolic Syndrome**

An elevated glucose level is one component of the current consensus definition of the metabolic syndrome (24,25). Others are abdominal obesity, elevated blood pressure, elevated triglycerides, and reduced high-density lipoprotein (HDL) cholesterol. Any 3 of these 5 components confer a diagnosis of the syndrome. Most individuals with the metabolic syndrome have abdominal obesity. Excess adipose tissue releases excess fatty acids and a variety of adipokines that seemingly elicit metabolic risk factors that predispose to both diabetes and CVD (26) (Fig. 1). To manifest the syndrome in obese persons, one must also have metabolic susceptibility; the latter in turn can be conferred by other factors (e.g., genetics, physical activity, and drugs). Many investigators believe that insulin resistance mediates all the metabolic risk factors of the metabolic syndrome (27). The role of insulin resistance in causing hyperglycemia is well established, but whether insulin resistance per se elicits dyslipidemia and hypertension is uncertain. Regardless, most persons with the metabolic syndrome are insulin-resistant (28). Therefore, it is not surprising that prevalence of pre-diabetes and metabolic syndrome overlap—although not precisely. For example, in the nondiabetic population over 50 years of age, about twice as many individuals have IFG plus metabolic syndrome as have IFG alone (29). A sizable portion of this population also has metabolic syndrome without IFG and vice versa. The overlap of pre-diabetes and metabolic syndrome in other populations is similar to that of the United States, where it has been determined (30) (Fig. 2).
The metabolic syndrome in fact can be considered a pre-diabetic state. Compared with persons without metabolic syndrome, those with the syndrome have an approximate 5-fold increase in diabetes risk (31). Although it might be assumed that this greater risk is due to IFG or IGT in patients with metabolic syndrome, Lorenzo et al. (32) found that metabolic syndrome without pre-diabetes carries an approximate 5-fold increase in diabetes risk. For patients with IFG or IGT, the diabetes risk is 5- to 7-fold higher for than normoglycemia (30). But in those with both IFG and IGT, approximately three-fourths of the population had metabolic syndrome. NFG = normoglycemia.

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**Figure 2** Prevalence of Metabolic Syndrome in Different Categories of Pre-Diabetes in an European Population

The prevalence in persons with either isolated impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) was approximately twice that of persons with neither (30). But in those with both IFG and IGT, approximately three-fourths of the population had metabolic syndrome. NFG = normoglycemia.

**Metabolic Syndrome, Pre-Diabetes, and Cardiovascular Risk**

**Should pre-diabetes be called a disease?** There is general agreement among diabetologists that diabetes deserves to be called a disease and not just a risk factor for CVD. This agreement rests on the broad range of complications accompanying hyperglycemia: macrovascular diseases, microvascular diseases, and various forms of neuropathy, among others. Patients with diabetes are prone to coronary heart disease, stroke, and peripheral vascular disease along with retinopathy, chronic kidney disease, bladder dysfunction, erectile dysfunction, orthostatic hypotension, gastroparesis, and skin disorders. In a variety of ways, these conditions can be attributed to prolonged hyperglycemia. Although in the sense that diabetes is a “risk factor” for these disorders, their aggregation justifies calling diabetes a disease. To call pre-diabetes per se a disease is less clear-cut. All of the preceding complications are less common, although they have been reported in some patients. A review of available literature may shed light on the clinical significance of pre-diabetes.

**Pre-diabetes and microvascular disease.** A sine qua non for diabetes contrasted with pre-diabetes is occurrence of microvascular disease; these diseases include retinopathy, glomerular disease, and likely neuropathy. The primary target of hyperglycemia appears to be endothelial cells. Thickening of the membrane beneath endothelial cells is a fundamental structural change. This occurs in both capillaries and arterioles. Other changes are pericyte loss and capillary microaneurysms, and later, vascular proliferation. Although elevated glucose levels per se must be primarily responsible for microangiopathy, the molecular mechanisms are not fully understood. Several mechanisms may account for these changes: activation of protein kinase C, formation of advanced glycation end products, formation of reactive oxygen species, flux through the hexosamine pathway, induction of the polyol pathway, overexpression of growth factors and inflammatory cytokines, and defective insulin signaling (34,35). Presumably, these microvascular changes are widespread throughout the body, but mainly affect the eyes, kidneys, and peripheral nerves.

The issue of whether intermediate hyperglycemia (pre-diabetes) can induce diabetic microvascular disease is discussed in detail in the WHO report of 2006 (5). The conclusion was that there is no certain plasma glucose threshold for the development of microangiopathy. Several reports indicate that in patients with pre-diabetes, “diabetic retinopathy” can occur (36–39). In Pima Indians, pre-diabetes was associated with retinopathy in 2% to 4% of affected subjects (40).

**Microalbuminuria.** Another putative indicator of microvascular disease is microalbuminuria, which is believed to be secondary to glomerular endothelial thickening and capillary leakage (41). Hyperglycemia may be the dominant cause of glomerular damage, but other factors—advanced glycation products, oxidative stress, and inflammation—have been implicated (42). In subjects with pre-diabetes, the prevalence of microalbuminuria is approximately twice that of normal subjects, but less than that of long-standing diabetes (43). Whether intermediate glycemia per se accounts for an increase in microalbuminuria is uncertain. Microalbuminuria has received a great amount of attention because it is associated with both chronic kidney disease (CKD) and macrovascular disease complications (44). Investigators hypothesize that it is a reflection of widespread endothelial dysfunction.

**Chronic Kidney Disease.** Diabetes is a major cause of CKD, and pre-diabetes accompanies increased prevalence...
of CKD as well. For the NHANES study, Plantinga et al. (45) reported that 39.6% of people with diagnosed diabetes and 41.7% with undiagnosed diabetes had CKD; 17.7% with pre-diabetes and 10.6% without any kind of diabetes had CKD. The reason for more cases of CKD in pre-diabetes has not been determined. Microvascular disease may not be the cause. Fox et al. (46) from the Framingham Heart Study observed a stronger association between other cardiovascular risk factors and CKD than with hyperglycemia. This suggests that most of CKD observed in patients with pre-diabetes is due to macrovascular disease, especially hypertension, and not to microvascular disease.

**NEUROPATHY.** Subjects with pre-diabetes can show various forms of diabetic neuropathy: peripheral neuropathy (47–49), polyneuropathy (50), small-fiber neuropathy (51), and autonomic neuropathy (52,53). In the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) study, “diabetic” polyneuropathy was approximately twice that of normal subjects in those with IFG and IGT, whereas it was doubled again in patients with diabetes (54). The neuropathy observed in patients with diabetes consists of several changes: demyelination, axonal thickening, and loss of nerve fibers. In diabetes, hyperglycemia appears to be the dominant cause of these changes, and presumably, intermediate hyperglycemia can account for more cases of neuropathy seen in patients with pre-diabetes.

**Metabolic syndrome and microvascular disease.** Beyond elevated glucose levels, metabolic syndrome generally is thought not to be related to diabetes-like microvascular disease. Of note, it is not directly accompanied by “diabetic” retinopathy (55). If patients with the metabolic syndrome are found to have retinopathy, it is most likely due to intermediate hyperglycemia or hypertensive retinopathy. Other than these retinopathies, metabolic syndrome may mediate small vessel disorders through endothelial dysfunction (56–58). It seems important to distinguish between structural damage to small vessels, which occurs with diabetes and hypertension, and endothelial dysfunction. The latter can be considered a form of microvascular disease. For example, the metabolic syndrome has been related to microvascular angina (cardiac syndrome X) (59); this condition may be secondary to endothelial dysfunction in small coronary arteries (60). Some believe that insulin resistance is a cause of the endothelial dysfunction of cardiac syndrome X (61). Other factors, for example, inflammatory cytokines and low levels of adiponectin, also could promote endothelial dysfunction and microvascular dysfunction (62,63). Microalbuminuria is another reflection of endothelial dysfunction and occurs in some persons with the metabolic syndrome (64–66).

**Pre-diabetes and macrovascular disease.** Long unresolved questions relate to whether elevated glucose levels are a direct cause of atherosclerosis or clinical CVD (67–70). If so, then IFG or IGT could carry some risk for macrovascular disease. Recently Ford et al. (71) carried out a systematic review of the relationship between pre-diabetes and CVD risk. They searched the literature for IFG, IGT, or both for their relation with CVD. IFG was defined by fasting glucose levels of 100 (or 110) mg/dl to 125 mg/dl and IGT was defined by OGTT. The findings of this meta-analysis can be summarized as follows. Eighteen reports examined IFG (110 to 125 mg/dl) (designated IFG 110); relative risk (RR) estimates for CVD ranged from 0.65 to 2.50. The fixed-effects summary RR was estimated to be 1.20 (95% confidence interval [CI]: 1.12 to 1.28). Another 8 reports looked at IFG (100 to 125 mg/dl) (IFG 100). The RRs estimates for individual studies ranged from 0.87 to 1.40, whereas the fixed-effects summary RR estimate was 1.18 (95% CI: 1.09 to 1.28). In 8 reports on IGT, individual estimates of RR varied from 0.83 to 1.34, with a summary RR estimate of 1.20 (95% CI: 1.07 to 1.34). Five studies combined IFG and IGT; the summary RR was 1.10 (95% CI: 0.99 to 1.23). There was no significant difference between the summary estimates for men and women.

Even if we were to accept this analysis as indicating that pre-diabetes imparts a modest increase in risk for CVD, such as in the range of 20%, this does not prove that a pre-diabetic range of glucose levels directly causes atherosclerosis or its complications. The data are consistent with this action, but important questions remain. The problem lies in our ability to dissect away confounding variables such as concomitant obesity, dyslipidemia, hypertension, and proinflammatory and prothrombic states. All of the confounding variables listed, which are the components of metabolic syndrome, are commonly present in persons with pre-diabetes (9).

Of course, if intermediate hyperglycemia independently does raise CVD risk by 20%, this would be no trivial matter. It would justify efforts to lower plasma glucose levels to the normal range. Most arguments in the diabetes field have been whether it is beneficial to lower glucose levels in patients with pre-diabetes to delay conversion to diabetes. The argument against drug intervention in pre-diabetes is that it may not prevent the development of diabetic microvascular disease in the long run. However, if glucose concentrations in this range do in fact raise risk for CVD by 20%, a strong argument can be made to intervene for the purpose of reducing macrovascular-disease outcomes. The only way to resolve this issue would be through a clinical trial.

One important clinical trial, the DPP (13), tested whether lifestyle intervention, metformin, or a thiazolidinedione will delay conversion of pre-diabetes to diabetes. All three effectively lowered glucose levels and retarded the development of diabetes over the duration of the study (13,72). However, DPP was not sufficiently powered to determine whether any of these modalities would reduce CVD events in patients with pre-diabetes. In a subsequent clinical trial using a thiazolidinedione, pioglitazone, to determine whether it would reduce CVD events in diabetic patients with established CVD (73). In fact, atherosclerotic
events were marginally reduced, although the benefit was partially offset by an increase in “heart failure,” that is, fluid overload. In the DREAM (Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication) trial (74), which was carried out in patients with pre-diabetes, rosiglitazone was tested for retardation of conversion to diabetes. Although this study showed a reduced conversion rate to diabetes, it did not reduce CVD events. In an ancillary study to DREAM, however, rosiglitazone modestly reduced progression of carotid intimal medial thickness (75). This finding cannot be ignored. It keeps alive the possibility that glucose lowering in patients with pre-diabetes will retard atherogenesis. On the other hand, there is the ongoing controversy whether rosiglitazone will increase coronary events (76). This being the case, only a clinical trial with a glucose-lowering drug can answer the question whether treatment of intermediate hyperglycemia will retard atherogenesis.

Most individuals with pre-diabetes have both hyperinsulinemia and insulin resistance. It has been speculated for many years that 1 or another of these finding may promote atherogenesis (77). If so, it is possible that lowering glucose through lifestyle changes or drugs that target insulin resistance might reduce atherogenesis through this mechanism.

### Metabolic Syndrome and Macrovascular Disease

Two large meta-analysis have shown that metabolic syndrome raises the risk for macrovascular CVD by approximately 2-fold (78,79). Because a high proportion of patients with metabolic syndrome will have pre-diabetes, it can be expected that pre-diabetes will also be accompanied by increased risk for CVD when the metabolic syndrome is present.

### Dual Goals for Pre-Diabetes Intervention

The major detrimental outcomes in persons with pre-diabetes are macrovascular diseases and type 2 diabetes, the leading contributors to microvascular disease. Macrovascular disease occurs both before and after onset of diabetes, whereas microvascular disease occurs almost exclusively several years after conversion to diabetes. The following section provides an overview for prevention of both macrovascular and microvascular disease.

### Screening for Pre-Diabetes

Should an effort be made to detect pre-diabetes, and if so, when and how? As desirable as general health screening may be for prevention of chronic disease, there is little motivation for a universal national program because of costs. However, because most people visit physicians periodically, opportunities exist to test for pre-diabetes. Several clinical features increase the likelihood of a positive finding: advancing age, obesity, other features of the metabolic syndrome, family history of diabetes or CVD, signs of atherosclerotic disease. At the present time, we are left with clinical judgment to motivate testing. Measurement of fasting glucose is the least expensive way to detect pre-diabetes. OGTT and HbA1c are not currently recommended, but they can be added if suspicion is high. Their incremental value has not been adequately studied. However, the combination of IFG and IGT increases the likelihood of developing diabetes. In the big picture, prevention of macrovascular disease takes priority over microvascular disease. Therefore, the first step should be to carry out a thorough assessment of cardiovascular risk.

### Prevention of Macrovascular Disease

Whether pre-diabetes per se produces atherosclerosis and its complications is uncertain. Nonetheless, many persons with pre-diabetes have metabolic syndrome, which undoubtedly is a risk factor for macrovascular disease. Moreover, pre-diabetes increases with age, and aging itself is accompanied by increased risk. Therefore, it is reasonable to intensively intervene on all CVD risk factors in patients with pre-diabetes. First-line management is lifestyle intervention: weight reduction in obese subjects, reduced intakes of dietary saturated and trans-fatty acids, cholesterol, and sodium, and increased physical activity. The use of drugs to control CVD risk factors likewise deserves consideration.

Targets of therapy include dyslipidemia, hypertension, and prothrombotic factors. The prime lipid targets are atherogenic lipoproteins—low-density lipoprotein (LDL) and very LDL. In patients with CVD plus metabolic syndrome, LDL cholesterol levels should be reduced to <70 mg/dl, and LDL + very LDL cholesterol (non-HDL cholesterol) to <100 mg/dl. Statins are first-line drugs to achieve these reductions. If these goals are not attained with a statin, a second-line LDL-lowering drug can be used: nicotinic acid, bile acid sequestrant, or ezetimibe. If CVD is not present, goals are an LDL cholesterol <100 mg/dl and a non-HDL cholesterol <130 mg/dl. In most patients, a statin alone usually is sufficient to achieve this goal.

Blood pressure should be lowered to <130/85 mm Hg, and preferably to <120/80 mm Hg. Any of the standard blood pressure–lowering drugs (e.g., angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium blockers, diuretics, beta-blockers) can be employed. Evidence favoring 1 drug over another is limited. Nonetheless, physicians should keep in mind that beta-blockers and higher doses of thiazide diuretics raise glucose levels and predispose patients to conversion to diabetes. Opinion is divided whether these actions have clinical significance in patients with pre-diabetes (80).

A large clinical trial recently found that aspirin therapy does not overall reduce CVD events in patients with diabetes (81). However, this failure appeared to be limited to persons on hypoglycemic drugs; those on diet-therapy alone showed risk reduction. This suggests that patients with early diabetes and almost certainly those with pre-diabetes will benefit.
Prevention of Microvascular Disease

The only way to prevent (or delay) microvascular disease in patients with pre-diabetes is to prevent (or delay) the development of diabetes. Unfortunately, there is no proven way to prevent the decline in beta cell function in persons destined to have diabetes. Therefore, priority must be given to reducing insulin resistance. This is best achieved by lifestyle intervention—weight reduction and increased physical activity. The DPP (13) demonstrated the efficacy of this approach. Consequently, all persons with pre-diabetes should be encouraged to engage in a lifestyle intervention program. If need be, professional assistance is useful. The DPP found that metformin therapy also could delay conversion of pre-diabetes to diabetes in about 40% of subjects. This has led to a recommendation on the part of some diabetologists for the use of metformin in persons with IFG plus IGT and other metabolic syndrome risk factors (15). Whether this approach will materially retard the development of microvascular disease would require a major clinical trial that is unlikely in the near future.

Public Health Prevention

The public at large is increasingly concerned about the diabetes epidemic. Most people know relatives or friends who have diabetes so that they have first-hand knowledge of the suffering imposed by this chronic disease. Therefore, when a person is told that he or she has pre-diabetes, this person’s concern is usually increased substantially. This provides an incentive for effective intervention. It further offers the opportunity to detect the metabolic syndrome, which carries greater risk for macrovascular CVD. In a word, use of the concept of pre-diabetes can be a useful tool for intervention to prevent both macrovascular and microvascular disease. In the view of this author, the time is ripe to make use of this concept in clinical and public health spheres.

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