Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 59, No. 7, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.08.080

STATE-OF-THE-ART PAPER

Pre-Diabetes, Metabolic Syndrome, and Cardiovascular Risk

Scott M. Grundy, MD, PHD

Dallas, Texas

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. (J Am Coll Cardiol 2012;59:635–43) © 2012 by the American College of Cardiology Foundation

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 A_{1c}, or glycosylated hemoglobin (HbA_{1c}), 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 pertain. 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, HbA_{1c} 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

From the Center for Human Nutrition and Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas. Dr. Grundy has reported that he has no relationships relevant to the contents of this paper to disclose.

Manuscript received June 14, 2011; revised manuscript received August 17, 2011, accepted August 23, 2011.

JACC Vol. 59, No. 7, 2012
February 14, 2012:635–43

Abbreviations and Acronyms

ADA = American Diabetes Association

CI = confidence interval

CKD = chronic kidney disease

CVD = cardiovascular disease(s)

HbA_{1c} = glycosylated hemoglobin

HDL = high-density lipoprotein

IFG = impaired fasting glucose

IGT = impaired glucose tolerance

LDL = low-density lipoprotein

OGTT = oral glucose tolerance test

RR = relative risk

WHO = World Health Organization

progress to type 2 diabetes. For this reason, another name might be preferable. The WHO task force's "intermediate hyperglycemia" so far has not been widely adopted (5). Another possible name is "borderline diabetes," but this term is not currently recommended and has no formal definition. In this review, the term *pre-diabetes* will be used throughout, but with the recognition that it is not universally accepted nor does it always foretell conversion to diabetes.

Pre-Diabetes as Intermediate Hyperglycemia

The ADA previously equated pre-diabetes with the WHO's intermediate hyperglycemia, but recently added borderline levels of hemoglobin A_{1c} as another indicator. The WHO so far has not done so. The ADA's 3 indicators can be considered along with their pathogenesis and clinical significance.

Pathogenesis of intermediate hyperglycemia. Two metabolic defects occur in most patients with type 2 diabetes: insulin resistance and deficient insulin secretion. Elevated glucose levels in the intermediate range are caused primarily by a deficiency in insulin secreted by pancreatic beta cells. Deficient insulin secretion can result either from a loss of beta cells or impairment of beta cell function. Both occur in type 2 diabetes (7,8). Similar but less severe defects, especially in insulin secretion, characterize pre-diabetes (9). Most persons with pre-diabetes also are insulin-resistant (9).

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).

Impaired fasting glucose. IFG was introduced by the ADA in 1997 to classify fasting plasma glucose levels of 110 to 125 mg/dl (6.1 to 7.0 mmol/l) (16). By these criteria, the estimated U.S. prevalence of IFG in adults >20 years of age was approximately 6.9% (17). In 2003, the ADA changed its definition of IFG from a fasting level of 110 to 125 mg/dl to 100 to 125 mg/dl (18). The rationale for the ADA's change was several-fold. First, glucose levels of 100 to 110 mg/dl carry higher risk for diabetes compared with normoglycemia. 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).

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 fasting glucose. This latter percentage raises the question whether there is any utility in doing OGTT at all. Two proposed reasons for OGTT are to identify persons

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 A_{1c}

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 HbA_{1c} become an alternative to plasma glucose for diagnosing type 2 diabetes. Advances in the measurement of HbA_{1c} and growing evidence of its association with plasma glucose underlie this recommendation. The expert committee listed several advantages of HbA_{1c} testing compared with glucose measurements for the diagnosis of diabetes. HbA_{1c} is now better standardized. There is less biologic variability and pre-analytic instability. HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} threshold of 6.5%.

Whether HbA_{1c} 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 HbA_{1c} might obviate the need for OGTT to identify pre-diabetes. Still another report (23) showed that there is considerable discordance between HbA_{1c} and fasting glucose levels; it implied that many individuals would be misclassified by HbA_{1c}. However, because HbA_{1c} is a better indicator of integrated glucose levels, one can ask whether fasting glucose levels are more likely to misclassify a person than HbA_{1c} levels. If pre-diabetes is going to emerge as an important clinical category and if HbA_{1c} 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).

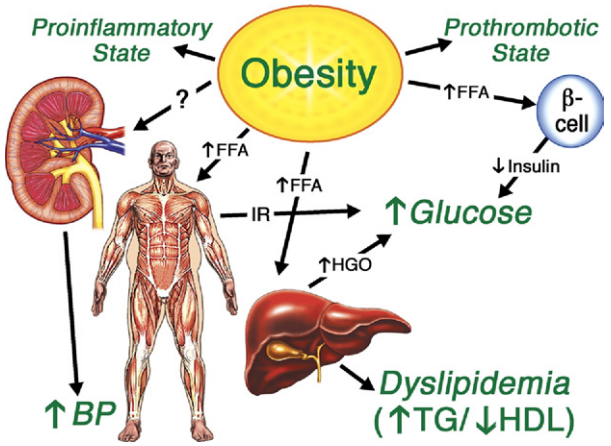

Figure 1 **Metabolic Pathways Underlying Pre-Diabetes and Metabolic Syndrome**

Most persons with both conditions are obese. An increase in adipose tissue results in elevations of circulating free fatty acids (FFA) and other "adipokines." The latter appear to underlie both a proinflammatory state and a prothrombotic state. An increase in FFA induces insulin resistance (IR) in muscle, which contributes to an elevation of plasma glucose. In the long run, a high FFA may impair beta-cell function through "lipotoxicity"; this too will promote a higher glucose concentration. Elevated FFA probably contributes to an increase in hepatic glucose output (HGO) and worsening hyperglycemia, but in addition, a high FFA underlies an increase in plasma triglycerides (TG), which in turn lowers high-density lipoprotein (HDL) cholesterol levels. Obesity is associated with an increase in blood pressure (BP), although the mechanisms for this effect are not well understood. A proinflammatory state likely predisposes to pre-diabetes by enhancing IR. Many investigators also believe that a proinflammatory state predisposes to cardiovascular disease, as does a prothrombotic state. Although obesity predisposes to both pre-diabetes and metabolic syndrome, various localized defects in specific organs or tissue likely contribute as well. Figure illustration by Craig Skaggs.

JACC Vol. 59, No. 7, 2012
February 14, 2012:635–43

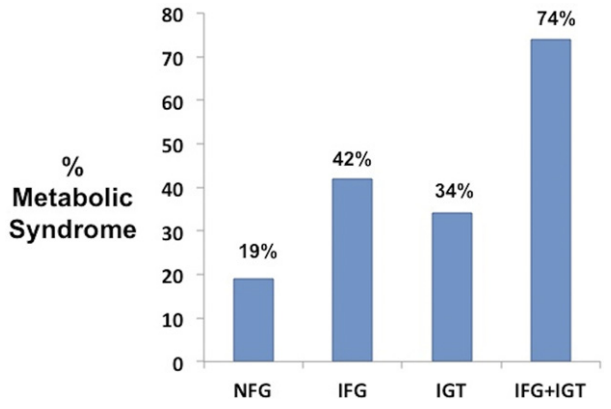

Figure 2 **Prevalence of Metabolic Syndrome in Different Categories of Pre-Diabetes in an European Population**

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.

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 (32). However, when pre-diabetes combines with metabolic syndrome, the risk is increased even more. We might ask why metabolic syndrome alone is a strong predictor of diabetes. For one reason, similar percentages of the population with metabolic syndrome and pre-diabetes are obese (29); thus, a metabolic syndrome like pre-diabetes is an insulin-resistant state, which imparts diabetes risk. The metabolic syndrome may further predispose to beta cell dysfunction through lipotoxicity (33). Thus, it should not be surprising that the metabolic syndrome associates with a high risk for diabetes.

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 dominate 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 HbA_{1c} 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.

Reprint requests and correspondence: Dr. Scott M. Grundy, Center for Human Nutrition and Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Suite Y3.206, Dallas, Texas 75390-9052. E-mail: scott.grundy@utsouthwestern.edu.

REFERENCES

1. Garber AJ, Handelsman Y, Einhorn D, et al. Diagnosis and management of prediabetes in the continuum of hyperglycemia: when do the risks of diabetes begin? A consensus statement from the American College of Endocrinology and the American Association of Clinical Endocrinologists. Endocr Pract 2008;14:933–46.
2. Alberti KG. Screening and diagnosis of prediabetes: where are we headed? Diabetes Obes Metab 2007;9 Suppl 1:12–6.
3. World Health Organization. WHO Expert Committee on Diabetes Mellitus: second report. World Health Organ Tech Reo Ser 1980; 646:1–80.
4. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2005;28 Suppl 1:s37–42.
5. World Health Organization. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia: Report of a WHO/IDF Consultation. Geneva: World Health Organization, 2006.
6. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;3 Suppl 1:S62–9.
7. Rhodes CJ. Type 2 diabetes—a matter of beta-cell life and death? Science 2005;307:380–4.
8. Kahn SE. Clinical review 135: The importance of beta-cell failure in the development and progression of type 2 diabetes. J Clin Endocrinol Metab 2001;86:4047–58.
9. Ferrannini E, Gastaldelli A, Iozzo P. Pathophysiology of prediabetes. Med Clin North Am 2011;95:327–39.
10. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28:1039–57.
11. Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988–1994 and 2005–2006. Diabetes Care 2009;32:287–94.
12. DECODE Study Group. Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. Diabetes Care 2003;26:61–9.
13. Knowler WC, Barrett-Connor E, Fowler SE, et al., for the Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.
14. Gerstein HC, Santaguida P, Raina P, et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. Diabetes Res Clin Pract 2007;78:305–12.
15. Nathan DM, Davidson MB, DeFronzo RA, et al., for the American Diabetes Association. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care 2007;30:753–9.
16. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20:1183–97.
17. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988–1994. Diabetes Care 1998;21:518–24.
18. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160–7.
19. Centers for Disease Control and Prevention. National diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2007. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2008.
20. International Expert Committee. International Expert Committee report on the role of the A_{1c} assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–34.
21. Ackermann RT, Cheng YJ, Williamson DF, Gregg EW. Identifying adults at high risk for diabetes and cardiovascular disease using hemoglobin A_{1c} national health and nutrition examination survey 2005–2006. Am J Prev Med 2011;40:11–7.
22. Saydah SH, Byrd-Holt D, Harris MI. Projected impact of implementing the results of the diabetes prevention program in the U.S. population. Diabetes Care 2002;25:1940–5.
23. Lipska KJ, De Rekeneire N, Van Ness PH, et al. Identifying dysglycemic states in older adults: implications of the emerging use of hemoglobin A_{1c}. J Clin Endocrinol Metab 2010;95:5289–95.
24. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement (erratum in: Circulation 2005;112:e297–8). Circulation 2005;112:2735–52.
25. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120:1640–5.
26. Deng Y, Scherer PE. Adipokines as novel biomarkers and regulators of the metabolic syndrome. Ann N Y Acad Sci 2010;1212:E1–19.
27. Reaven GM. Insulin resistance, the insulin resistance syndrome, and cardiovascular disease. Panminerva Med 2005;47:201–10.
28. Hanley AJ, Wagenknecht LE, D'Agostino RB Jr., Zinman B, Haffner SM. Identification of subjects with insulin resistance and beta-cell

dysfunction using alternative definitions of the metabolic syndrome. Diabetes 2003;52:2740–7.
29. Alexander CM, Landsman PB, Grundy SM. Metabolic syndrome and hyperglycemia: congruence and divergence. Am J Cardiol 2006;98: 982–5.
30. Bianchi C, Miccoli R, Bonadonna RC, et al., for the GENFIEV Investigators. Metabolic syndrome in subjects at high risk for type 2 diabetes: the genetic, physiopathology and evolution of type 2 diabetes (GENFIEV) study. Nutr Metab Cardiovasc Dis 2011;21:699–705.
31. Stern MP, Williams K, Gonzalez-Villalpando C, Hunt KJ, Haffner SM. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? Diabetes Care 2004;27:2676–81.
32. Lorenzo C, Williams K, Hunt KJ, Haffner SM. The National Cholesterol Education Program–Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. Diabetes Care 2007;30:8–13.
33. Cusi K. The role of adipose tissue and lipotoxicity in the pathogenesis of type 2 diabetes. Curr Diab Rep 2010;10:306–15.
34. He Z, King GL. Microvascular complications of diabetes. Endocrinol Metab Clin North Am 2004;33:215–38, xi–xii.
35. Bakker W, Eringa EC, Sipkema P, van Hinsbergh VW. Endothelial dysfunction and diabetes: roles of hyperglycemia, impaired insulin signaling and obesity. Cell Tissue Res 2009;335:165–89.
36. Tikellis G, Wang JJ, Tapp R, et al. The relationship of retinal vascular calibre to diabetes and retinopathy: the Australian Diabetes, Obesity and Lifestyle (AusDiab) study. Diabetologia 2007;50:2263–71.
37. Tapp RJ, Tikellis G, Wong TY, Harper CA, Zimmet PZ, Shaw JE; Australian Diabetes Obesity and Lifestyle Study Group. Longitudinal association of glucose metabolism with retinopathy: results from the Australian Diabetes Obesity and Lifestyle (AusDiab) study. Diabetes Care 2008;31:1349–54.
38. Sprague RS, Ellsworth ML. Vascular disease in pre-diabetes: new insights derived from systems biology. Mo Med 2010;107:265–9.
39. Singleton JR, Smith AG, Russell JW, Feldman EL. Microvascular complications of impaired glucose tolerance. Diabetes 2003;52: 2867–73.
40. Gabir MM, Hanson RL, Dabelea D, et al. Plasma glucose and prediction of microvascular disease and mortality: evaluation of 1997 American Diabetes Association and 1999 World Health Organization criteria for diagnosis of diabetes. Diabetes Care 2000;23:1113–8.
41. Satchell SC, Tooke JE. What is the mechanism of microalbuminuria in diabetes: a role for the glomerular endothelium? Diabetologia 2008;51:714–25.
42. Singh DK, Winocour P, Farrington K. Oxidative stress in early diabetic nephropathy: fueling the fire. Nat Rev Endocrinol 2011;7: 176–84.
43. Tapp RJ, Shaw JE, Zimmet PZ, et al. Albuminuria is evident in the early stages of diabetes onset: results from the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). Am J Kidney Dis 2004;44: 792–8.
44. Perkovic V, Verdon C, Ninomiya T, et al. The relationship between proteinuria and coronary risk: a systematic review and meta-analysis. PLoS Med 2008;5:e207.
45. Plantinga LC, Crews DC, Coresh J, et al., for the CDC CKD Surveillance Team. Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. Clin J Am Soc Nephrol 2010;5:673–82.
46. Fox CS, Larson MG, Leip EP, Meigs JB, Wilson PW, Levy D. Glycemic status and development of kidney disease: the Framingham Heart Study. Diabetes Care 2005;28:2436–40.
47. Singleton JR, Smith AG. Neuropathy associated with prediabetes: what is new in 2007? Curr Diab Rep 2007;7:420–4.
48. Smith AG, Singleton JR. Impaired glucose tolerance and neuropathy. Neurologist 2008;14:23–9.
49. Rajabally YA. Neuropathy and impaired glucose tolerance: an updated review of the evidence. Acta Neurol Scand 2011;124:1–8.
50. Horowitz SH. Recent clinical advances in diabetic polyneuropathy. Curr Opin Anaesthesiol 2006;19:573–8.
51. Pittenger GL, Mehrabyan A, Simmons K, et al. Small fiber neuropathy is associated with the metabolic syndrome. Metab Syndr Relat Disord 2005;3:113–21.
52. Kuroda N, Taniguchi H, Baba S, Yamamoto M. The pupillary light reflex in borderline diabetics. J Int Med Res 1989;17:205–11.
53. Kuroda N, Taniguchi H, Baba S, Yamamoto M. Cardiovascular and pupillary light reflexes in subjects with abnormal glucose tolerance. Diabetes Res Clin Pract 1989;7:213–8.
54. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A, for the KORA Study Group. Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg Surveys S2 and S3. Diabetes Care 2008;31:464–9.
55. Keenan JD, Fan AZ, Klein R. Retinopathy in nondiabetic persons with the metabolic syndrome: findings from the Third National Health and Nutrition Examination Survey. Am J Ophthalmol 2009; 147:934–44.
56. McVeigh GE, Cohn JN. Endothelial dysfunction and the metabolic syndrome. Curr Diab Rep 2003;3:87–92.
57. Czernichow S, Greenfield JR, Galan P, et al. Macrovascular and microvascular dysfunction in the metabolic syndrome. Hypertens Res 2010;33:293–7.
58. de Jongh RT, Serné EH, Ijzerman RG, de Vries G, Stehouwer CD. Impaired microvascular function in obesity: implications for obesity-associated microangiopathy, hypertension, and insulin resistance. Circulation 2004;109:2529–35.
59. Jadhav ST, Ferrell WR, Petrie JR, et al. Microvascular function, metabolic syndrome, and novel risk factor status in women with cardiac syndrome X. Am J Cardiol 2006;97:1727–31.
60. Bairey Merz CN, Shaw LJ. Stable angina in women: lessons from the National Heart, Lung and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation. J Cardiovasc Med (Hagerstown) 2011;12: 85–7.
61. Dean JD, Jones CJH, Hutchison SJ, Peters JR, Henderson AH. Hyperinsulinemia and microvascular angina (Syndrome X). Lancet 1991;337:456–7.
62. Li FYL, Cheng KKY, Lam KSL, Vanhoutte PM, Xu A. Cross-talk between adipose tissue and vasculature: role of adiponectin. Acta Physiol (Oxf) 2011;203:167–80.
63. Vanhoutte PM, Shimokawa H, Tang EH, Feletou M. Endothelial dysfunction and vascular disease. Acta Physiol (Oxf) 2009;196:193–222.
64. Liese AD, Hense HW, Döring A, Stieber J, Keil U. Microalbuminuria, central adiposity and hypertension in the non-diabetic urban population of the MONICA Augsburg survey 1994/95. J Hum Hypertens 2001;15:799–804.
65. Kim YI, Kim CH, Choi CS, et al. Microalbuminuria is associated with the insulin resistance syndrome independent of hypertension and type 2 diabetes in the Korean population. Diabetes Res Clin Pract 2001; 52:145–52.
66. Palaniappan L, Carnethon M, Fortmann SP. Association between microalbuminuria and the metabolic syndrome: NHANES III. Am J Hypertens 2003;16:952–8.
67. Chait A, Bornfeldt KE. Diabetes and atherosclerosis: is there a role for hyperglycemia? J Lipid Res 2009;50 Suppl:S335–9.
68. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 1999;22:233–40.
69. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006;332:73–8.
70. Alexander CM, Landsman PB, Teutsch SM, Haffner SM, for the NHANES III and NCEP Investigators. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 2003;52: 1210–4.
71. Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. J Am Coll Cardiol 2010;55:1310–7.
72. Knowler WC, Hamman RF, Edelstein SL, et al., for the DPP Research Group. Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program. Diabetes 2005;54:1150–6.
73. Dormandy JA, Charbonnel B, Eckland DJ, et al., for the PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. Lancet 2005;366:1279–89.

74. Gerstein HC, Yusuf S, Bosch J, et al., for the DREAM Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006;368:1096–105.
75. Lonn EM, Gerstein HC, Sheridan P, et al., for the DREAM (and STARR Investigators. Effect of ramipril and of rosiglitazone on carotid intima-media thickness in people with impaired glucose tolerance or impaired fasting glucose: STARR (STudy of atherosclerosis with Ramipril and Rosiglitazone). J Am Coll Cardiol 2009;53:2028–35.
76. Kaul S, Diamond GA. Diabetes: breaking news! Rosiglitazone and cardiovascular risk. Nat Rev Cardiol 2010;7:670–2.
77. Bierman EL. George Lyman Duff Memorial Lecture. Atherogenesis in diabetes. Arterioscler Thromb 1992;12:647–56.
78. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007;49:403–14.
79. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol 2010;56:1113–32.
80. Zidek W, Schrader J, Lüders S, et al. First-line antihypertensive treatment in patients with pre-diabetes: rationale, design and baseline results of the ADaPT investigation. Cardiovasc Diabetol 2008;7:22.
81. Okada S, Morimoto T, Ogawa H, et al., for the JPAD Trial Investigators. Differential effect of low-dose aspirin for primary prevention of atherosclerotic events in diabetic management: a subanalysis of the JPAD Trial. Diabetes Care 2011;34:1277–83.

Key Words: cardiovascular prevention ■ diabetes prevention ■ metabolic syndrome ■ pre-diabetes.