CONSENSUS STATEMENT

American Diabetes Association

Role of Cardiovascular Risk Factors in Prevention and Treatment of Macrovascular Disease in Diabetes

Diabetes mellitus is a major risk factor for morbidity and mortality due to coronary heart disease, cerebrovascular disease, and peripheral vascular disease in the United States. The prevalence of these macrovascular complications is increased about two- to fourfold in diabetic populations. In 1987, these macrovascular complications accounted for most of the hospitalizations for diabetes and contributed substantially to the 20.4 billion dollars spent for diabetes care in the United States.

Multiple risk factors for macrovascular disease are frequently found in individuals with diabetes. There is an increased prevalence of hypertension and lipid abnormalities in many populations with diabetes. Many individuals with diabetes have not stopped smoking despite evidence that this is a major cardiovascular risk factor. There are other factors that may be associated with macrovascular disease in diabetes, including obesity, impaired glucose tolerance (IGT), hyperglycemia, hyperinsulinemia, microalbuminuria, elevated fibrinogen levels, altered platelet function, and qualitative lipoprotein abnormalities.

Primary and secondary intervention trials directed at cardiovascular risk factors in nondiabetic individuals have been performed and data are now available. Advances have also occurred in nutritional management, exercise programs, behavioral approaches, and pharmacological therapy for diabetes and its major risk factors, and advances have been made in our understanding of atherogenesis. These developments led the American Diabetes Association (ADA) to convene a consensus development conference, on 10–12 May 1989, on the role of cardiovascular risk factors in the prevention and treatment of macrovascular disease in diabetes.

The conference consisted of 19 invited presentations and considerable discussion from a large audience of health-care professionals. A consensus panel with expertise in clinical diabetes, clinical investigation, epidemiology, nutrition, cardiovascular diseases (CVD), and lipid and lipoprotein disorders considered a broad spectrum of issues concerned with macrovascular disease in diabetes. The panel reached a consensus on answers to the following questions:

1. The commonly identified risk factors for macrovascular disease include hypertension, smoking, and lipid abnormalities. To what extent do these risk factors operate in people with diabetes?
2. Are cardiovascular risk factors and cardiovascular risk the same in all types of diabetes, and are there other risk factors of importance to people with diabetes?
3. What is the evidence for the value of modifying these risk factors in the general population and in people with diabetes?
4. What is the treatment of choice for each risk factor, and are there unique issues that should be considered in people with diabetes?
5. What additional research is needed in this area?

QUESTION 1: THE COMMONLY IDENTIFIED RISK FACTORS FOR MACROVASCULAR DISEASE INCLUDE HYPERTENSION, SMOKING, AND LIPID ABNORMALITIES. TO WHAT EXTENT DO THESE RISK FACTORS OPERATE IN PEOPLE WITH DIABETES?

The prevalence of coronary artery disease, stroke, peripheral vascular disease, and total mortality are sub-

stantially increased in diabetic subjects, even in the absence of hypertension, smoking, and lipid abnormalities. Diabetes adversely affects both men and women. The risk in female diabetic subjects is similar to the risk in nondiabetic males, and the risk in diabetic males is even greater. In most epidemiological studies the major risk factors total serum cholesterol and number of cigarettes smoked per day are similar, whereas mean systolic and diastolic blood pressures are only slightly higher in the diabetic population than nondiabetic population. Available data from the Framingham study and Multiple Risk Factor Intervention Trial (MRFIT) suggest that these risk factors retain the same adverse impact on the development of macrovascular disease in non-insulin-dependent diabetes mellitus (NIDDM) subjects as in nondiabetic subjects. Currently, there are no comparable data in insulin-dependent diabetes mellitus (IDDM) subjects.

Although the relationship between hypertension, smoking, or lipid abnormalities and cardiovascular risk are not exaggerated by diabetes, the imposition of these factors on the increased risk inherent in diabetes results in a markedly increased incidence of coronary heart disease, CVD, and overall mortality in diabetic patients. This relationship is shown for cardiovascular mortality in Fig. 1. These risk factors maintain predictive value in patients who have already had a cardiovascular event.

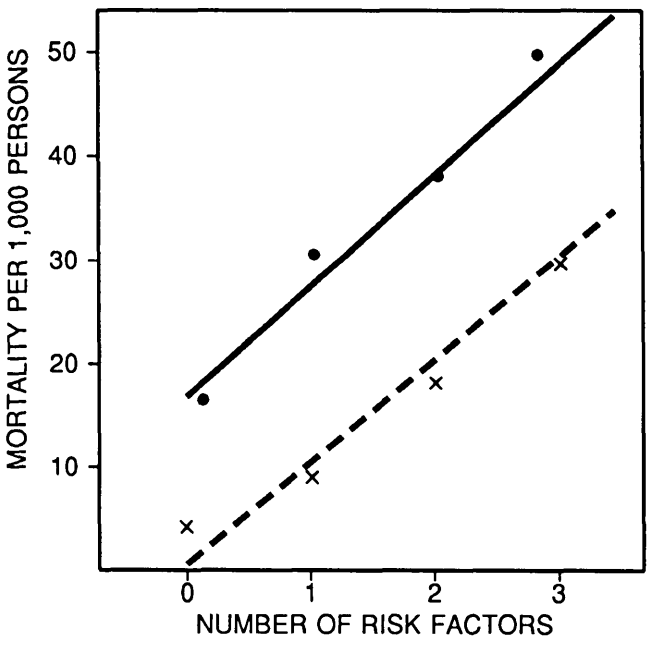

FIG. 1. Effects of three major risk factors (hypercholesterolemia, smoking, and diastolic hypertension) on age-standardized cardiovascular disease mortality in 5245 diabetic subjects (*solid line*) and 350,977 nondiabetic subjects (*broken line*) between ages 35 and 57 yr and free of myocardial infarction at baseline. Follow-up was in 6 yr. On the abcissa are the number of risk factors present. Number 1 refers to any one of the three, number 2 refers to any two of the three, and number 3 refers to all three. (Data adapted from the Multiple Risk Factor Intervention Trial. J. Stamler, personal communication; and Stamler J: Epidemiology, established major risk factors, and the primary prevention of coronary heart disease. In *Cardiology*. Parmley W, Chatterjee K, Eds. Philadelphia, PA, Lipincott, 1987, p. 1–41.)

Cross-population studies suggest that not all diabetic subjects are subject to the same increase in cardiovascular risk. Pima Indian and Japanese diabetic people have lower CVD than White diabetic subjects. These differences may be due to genetic or environmental factors.

Few data are available to differentiate the effects of various lipoprotein fractions on CVD risk in diabetic subjects. In diabetic as in nondiabetic subjects, CVD risk is directly proportional to low-density lipoprotein cholesterol (LDL-chol) and inversely proportional to high-density lipoprotein cholesterol (HDL-chol). Whereas hypertriglyceridemia is common in NIDDM, it is uncertain at present whether triglycerides have independent predictive value for macrovascular disease.

Increases in both systolic and diastolic blood pressure have the same adverse effect on macrovascular disease risk in diabetic and nondiabetic subjects; the risk increases linearly with elevations in blood pressure in both groups. Cigarette smoking exerts a detrimental effect on macrovascular disease as well. Although the relative risk of smoking may be slightly greater in nondiabetic subjects, the CVD mortality in diabetic subjects is significantly increased by smoking even less than a pack a day. The three major risk factors appear to be additive in their adverse impact on cardiovascular events in diabetic subjects.

QUESTION 2: ARE CARDIOVASCULAR RISK FACTORS AND CARDIOVASCULAR RISK THE SAME IN ALL TYPES OF DIABETES, AND ARE THERE OTHER RISK FACTORS OF IMPORTANCE TO PEOPLE WITH DIABETES?

Whereas hypertension, smoking, and lipid abnormalities are undoubtedly contributors to the risk of macrovascular disease among people with and without diabetes, there are numerous other factors that need to be considered. Among nondiabetic individuals, uncomplicated obesity has been established as a risk factor for CVD. This risk factor is of special importance in NIDDM subjects because 60–85% are obese and cardiovascular events account for most of the fatalities. It is now recognized that the distribution of adiposity has a significant impact on cardiac risks. Hypertension, hyperinsulinemia, diabetes, elevated very-low-density lipoprotein cholesterol (VLDL-chol), and low HDL-chol are highly associated with upper-body segment (abdominal) obesity, measured as an increased waist-to-hip ratio. In contrast, lower-body segment (femoral and gluteal) obesity appears to have less impact on these risks. Furthermore, it appears that men are less tolerant to the impact of obesity than women in the general population, but there are no data on people with diabetes.

Whether or not recurring or former obesity is a greater or lesser risk remains to be established.

The role of obesity in predisposing to macrovascular disease is complicated by the tendency for a sedentary life-style in obese subjects. Inactivity appears to be a risk factor for macrovascular events. This raises the possibility that increasing activity may be beneficial in its own right as well as an adjunct to weight reduction.

IGT has been shown to be a risk factor for macrovascular disease in several epidemiological studies. Because people with IGT are hyperinsulinemic, this raises the question of the role of hyperinsulinemia as a risk factor for macrovascular disease. Prospective studies have examined insulin levels, fasting and 1 or 2 h after glucose ingestion, as predictors of cardiovascular events. Whereas all of the studies show some positive relationship between insulin levels and a vascular event, none was completely controlled for confounding variables, such as smoking and HDL-chol. In contrast to these findings in Whites, obese hyperinsulinemic Pima Indians have a low cardiovascular mortality. There is no evidence that exogenous insulin administration has any adverse effect on cardiovascular risk.

In contrast to microvascular disease, the known duration of NIDDM does not appear to exert a major effect on macrovascular disease. In IDDM, however, there appear to be correlations between both attained age and duration of diabetes and macrovascular disease. The reason(s) for these discrepancies remain unknown.

Increased fibrinogen levels are an independent risk factor for CVD in nondiabetic subjects. In addition, fibrinogen levels have been found to correlate positively with blood glucose concentration in both men and women. However, the relationship between fibrinogen and CVD in diabetes remains to be determined. Platelets in patients with IDDM and NIDDM have been shown to hyperaggregate in response to various agonists in vitro, and platelet thromboxane production is increased. The exact relationship of these abnormalities to macrovascular disease is unclear.

Proteinuria has been found to predict the subsequent development of macrovascular disease. The significance of this observation remains to be determined.

Finally, qualitative abnormalities in lipoproteins occur in both IDDM and NIDDM. These include LDL-chol and HDL-chol apoprotein glycation, triglyceride enrichment of VLDL-chol, LDL-chol, and HDL-chol, and possibly enhanced oxidative modifications. Based on the current understanding of atherogenesis, these abnormalities could contribute to enhanced coronary heart disease in diabetes.

The risk of macrovascular disease is not confined to NIDDM. Epidemiological studies indicate that people with IDDM and free of renal disease have a fourfold increased risk of CVD. This increased risk does not appear to be explained by an atherogenic lipid profile. This alarming increased risk appears to occur in the absence of hypertension, obesity, and the major risk factors of macrovascular disease found in NIDDM. The advent of renal disease increases this risk to 12 times that of age-matched nondiabetic control subjects. The reason for this inordinate risk is enigmatic.

QUESTION 3: WHAT IS THE EVIDENCE FOR THE VALUE OF MODIFYING THESE RISK FACTORS IN THE GENERAL POPULATION AND IN PEOPLE WITH DIABETES?

LIPID ABNORMALITIES

General population. The evidence that the risk for CVD can be reduced in the general population by reducing plasma lipid and lipoprotein levels derives from several large randomized intervention trials with diet alone or in combination with drugs. Reductions of total cholesterol and LDL-chol in the Oslo Heart Study, Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), and Helsinki Heart Study, were associated with statistically significant reductions of definite fatal and nonfatal coronary artery disease events. Several other endpoints, such as incidence of angina, abnormal exercise electrocardiograms, and need for coronary artery bypass surgery were also reduced in these studies.

In the Helsinki Heart Study, the reduction in definite coronary endpoints was greater than that anticipated from the reduction in total cholesterol and LDL-chol. It has been suggested that the increase in HDL-chol in this study was responsible for this favorable effect. Increases of HDL-chol in the LRC-CPPT were also related to the reduction in CVD. Reduction of plasma triglyceride levels were marked in the Helsinki Heart Study, raising the possibility that these changes also contributed to the beneficial outcome. There have been no trials aimed at lowering plasma triglyceride or VLDL-chol levels as a primary goal.

In contrast to the reduction in cardiovascular events, the above-mentioned trials did not demonstrate reductions in total mortality in the treatment groups. Posttrial follow-up of the niacin-treated group in the coronary drug project did, however, demonstrate a beneficial effect on total mortality. Total mortality was also reduced by hypolipidemic therapy in the recently reported Stockholm study. Finally, two studies have now demonstrated that correction of lipid abnormalities can halt progression and possibly even cause regression of atheromatous lesions in native and bypass-graft coronary arteries. The small number of strokes and peripheral vascular disease events in the studies mentioned above precludes evaluation of the effects of lipid-lowering on these endpoints.

Diabetic subjects. No randomized clinical trial has tested the hypothesis that lowering lipid levels will reduce the risk of CVD in people with diabetes. However, in view of the lack of any evidence demonstrating differences between nondiabetic and diabetic subjects in the role of plasma lipids (total cholesterol, LDL-chol and HDL-chol) as risk factors, it seems reasonable to assume that beneficial effects on cardiovascular events would result from lowering lipids.

HYPERTENSION

General population. Several large randomized clinical trials, including the Veterans Administration Cooperative Studies, Hypertension Detection and Follow- Up Program, Australian Trial of Therapy of Mild Hypertension, and Medical Research Council Study, have demonstrated that lowering blood pressure reduces total and cardiovascular mortality.

Whereas the incidence of stroke, renal failure, and congestive heart failure have been reduced by antihypertensive therapy, the incidence of myocardial infarction has not been affected. In addition, a beneficial effect of treatment of individuals with mild hypertension has not been clearly demonstrated.

Diabetic subjects. No randomized clinical trial has tested the hypothesis that lowering blood pressure will reduce the risk of CVD in diabetic subjects. As in the case of hyperlipidemia, however, the effect of blood pressure on CVD appears to be the same in diabetic and nondiabetic subjects. Therefore, it would seem prudent to treat hypertension with the goal of reducing risk.

SMOKING

General population. In the Oslo Heart Study, reduced cigarette smoking in association with dietary modification led to a 47% lowering of fatal and nonfatal myocardial infarctions and sudden death. Statistical analysis suggested that cessation of smoking accounted for a significant portion of the overall benefit. In addition, a subgroup analysis of MRFIT, in which all individuals who quit smoking were pooled regardless of their group assignment, showed a significant reduction in risk for cardiovascular events in this group.

Diabetic subjects. There are no randomized clinical trials addressing the effect of smoking cessation on the risk for CVD. However, the great impact that smoking has on both diabetic and nondiabetic populations (in terms of ischemic heart disease, stroke, and peripheral vascular disease) supports agressive attempts to achieve smoking cessation in diabetic subjects.

OTHER RISK FACTORS

Various factors may contribute to macrovascular disease in patients with diabetes. Unfortunately, no randomized trials have been conducted to determine the effects of weight reduction, increasing physical activity, or lowering of insulin or fibrinogen levels on the incidence of macrovascular disease.

The effects of antiplatelet therapy, with aspirin and dipyridamole, on CVD death and opposite-extremity amputation in diabetic men with one amputation has been examined. A modest reduction in strokes and transient ischemic attacks was found, but no beneficial effect was seen on opposite-leg amputation and cardiovascular death. After a cardiovascular event, antiplatelet treatment appears to have a protective effect on subsequent cardiovascular mortality and morbidity in nondiabetic subjects. Therefore, there is reason to believe that in light of increased platelet aggregability in diabetes antiplatelet therapy may have a significant role to play.

Increased urinary protein excretion is a predictor of subsequent macrovascular events. Restricting protein intake or treatment with an angiotensin-converting enzyme inhibitor may reduce proteinuria and retard progression of renal failure. The effect of reducing proteinuria on macrovascular events is unknown.

QUESTION 4: WHAT IS THE TREATMENT OF CHOICE FOR EACH RISK FACTOR, AND ARE THERE UNIQUE ISSUES THAT SHOULD BE CONSIDERED IN PEOPLE WITH DIABETES?

Historically, the treatment of diabetes has been dominated by efforts to lower blood glucose. Whereas such efforts are obviously indicated, they are by themselves rarely sufficient to constitute a comprehensive program for preventing the macrovascular complications which are the leading cause of morbidity, functional disability, and mortality in diabetic patients. In most patients with diabetes, additional therapeutic interventions will be needed to reduce cardiovascular risk factors.

PRIMARY INTERVENTION

Lipid abnormalities. Total cholesterol, HDL-chol, and triglycerides should be measured in the fasting state and LDL-chol calculated on diagnosis of diabetes and annually therafter in adults and every 2 yr in children. If hyperlipidemia is found, secondary causes should be excluded. In the absence of definitive data, but in light of the great increase in coronary heart disease in diabetic subjects, the panel recommends a modification of the guidelines suggested by the National Cholesterol Education Program (NCEP). For both men and women, the panel recommends that the cutpoint for diet therapy be set at an LDL-chol of $\geq$130 mg/dl with a goal of reducing LDL-chol to <130 mg/dl. If after dietary intervention LDL-chol remains $\geq$160 mg/dl, drug therapy should be initiated. Hypertriglyceridemia is common in poorly controlled diabetes but may represent a primary lipid abnormality. Whether hypertriglyceridemia is a risk factor for macrovascular disease in diabetes is unknown. Initial therapy for hypertriglyceridemia is improved blood glucose control. Persistent hypertriglyceridemia (>250 mg/dl) will require additional therapy.

Nutritional strategies are fundamental in the overall management and prevention of lipid abnormalities in people with diabetes. Of prime importance is the need to individualize nutritional recommendations and education. Individuals with diabetes who have lipid abnormalities should be referred for nutrition education to a registered dietitian knowledgeable in diabetes and lipids. Strategies should include:

1. Weight reduction if obesity is present.

2. Restriction of saturated fatty acids. The ADA nutrition recommendations and the NCEP Step One diet recommend ≤10% of the total calories from saturated fats and <7% for the NCEP Step Two diet.
3. Limiting dietary cholesterol consumption. The ADA and NCEP Step One diet recommend <300 mg dietary cholesterol/day and <200 mg/day on the NCEP Step Two diet.
4. Restriction of total fat. ADA and NCEP recommend ≤30% of the total calories from all types of fat.
5. Up to 50–60% of calories from carbohydrate. Complex carbohydrates can be substituted for the usual intake of saturated fats. Increased use of foods high in fiber, especially soluble fiber, may have a beneficial effect on lipids.

Preliminary studies suggest that in some diabetic subjects with poorly controlled glycemia or hypertriglyceridemia, restricting carbohydrate intake to 40–45% of total calories may be beneficial. In those patients, monounsaturates may be useful to maintain calorie balance.

Regular aerobic exercise of prolonged duration has also been shown to have beneficial effects on lipids. The major effect of exercise is to decrease triglyceride levels. Exercise has also been shown in individuals without diabetes to increase HDL-chol, to have minimal effect on total cholesterol levels, and to cause a relatively modest drop in LDL-chol. However, there are certain caveats. Patients with diabetes should be screened for diabetic complications before beginning an exercise program. There are increased risks associated with exercise if the patient has proliferative retinopathy, CVD, nephropathy, or neuropathy. These patients should exercise only after taking appropriate precautions, be under close supervision, and avoid vigorous exercise.

Five different classes of hypolipidemic drugs are currently available. These include bile acid–binding resins, nicotinic acid, fibric acid derivatives, HMG CoA reductase inhibitors, and probucol. Use of these drugs in the diabetic subject presents special concerns, and an optimal drug regimen has not yet been defined. Bile acid–binding resins, in part because they are not absorbed, are free of serious toxicity. They are, however, associated with increased abdominal discomfort and constipation. In the diabetic subject, the mild hypertriglyceridemic effect may be of greater concern than in nondiabetic subjects. Nicotinic acid not only lowers LDL-chol but also lowers triglycerides and raises HDL-chol and thus may be particularly useful in diabetic subjects; however, it worsens glucose tolerance. Whereas gemfibrozil may improve the overall lipid profile, its propensity to increase LDL-chol in hypertriglyceridemia may limit its use in diabetic subjects. HMG CoA reductase inhibitors have been shown in a small group of diabetic patients to lower both triglycerides and LDL-chol but their long-term safety is unknown. Probucol, whereas relatively ineffective in lowering LDL-chol, is a potent antioxidant and may have antiatherogenic actions which must be further explored in diabetic subjects.

Unfortunately, there are insufficient clinical observations in diabetic subjects to formulate specific recommendations. Therefore, based on the above concerns and guided by safety first, the panel recommends use of bile acid–binding resins as initial treatment for patients with isolated elevations in LDL-chol. In patients with combined total cholesterol and triglyceride elevations, nicotinic acid may be preferable if tolerated and adequate safety monitoring indicates no toxicity. Alternatively, either HMG CoA reductase inhibitors or gemfibrozil, in combination with bile acid–binding resins, may be tried. HMG CoA reductase inhibitors (in combination with nicotinic acid or gemfibrozil) increase the risk of severe myositis and should be used with extreme caution. In all cases, pharmacological hypolipidemic therapy should be individualized and both response and toxicity monitored closely.

Hypertension. By inference from studies on people without diabetes, and in light of the known adverse effects of elevated blood pressure on macrovascular disease in diabetes, aggresive treatment of hypertension is recommended.

Although increased cardiovascular risk has been demonstrated in adult diabetic subjects with pressures >125/80 mmHg, in the absence of specific data demonstrating clinical efficacy in diabetic subjects with mild hypertension, the indications for initiating antihypertensive treatment should be the same as those in nondiabetic hypertensives. The decision to treat mild hypertension must be made on clinical grounds in individual cases, depending on age of the patient and the presence or absence of other risk factors, such as impaired renal function and congestive heart failure. Isolated systolic hypertension is more common in diabetic than nondiabetic subjects, and is a risk factor for the development of macrovascular disease. Benefits of routine treatment have not been established.

Because obesity is frequently associated with hypertension in NIDDM, and because calorie restriction, weight loss, and exercise frequently have a beneficial effect on blood pressure, these nonpharmacological modalities should be fully pursued in all cases. Nutritional strategies include *1*) weight reduction, *2*) limiting sodium intake to ~3,000 mg/day, and *3*) restriction of alcohol. Regular exercise has also been shown to have a beneficial effect on blood pressure.

The selection of an appropriate drug regimen for the treatment of hypertension in diabetic subjects entails special consideration. Thiazide diuretics may have adverse effects on glucose levels and lipid profiles; β-blockers may also adversely affect lipid profiles and may present special problems with counterregulation in patients treated with insulin. Therefore, drugs of these classes cannot be considered first-line agents in the treatment of hypertensive diabetic subjects. Although long-term studies are lacking, preliminary evidence indicating a beneficial effect of angiotensin-converting enzyme inhibitors on proteinuria and renal function in

diabetic subjects, in conjunction with demonstrated antihypertensive efficacy, suggest a primary role for this class of agents in the treatment of hypertension. Renal function and serum potassium levels must be monitored carefully during treatment with angiotensin-converting enzyme inhibitors. Calcium channel blocking agents may be beneficial as well, but more data on the long-term effects of these agents is required. The addition of other agents in refractory cases should follow the guidelines used in the treatment of nondiabetic hypertension.

Smoking. The treatment of cigarette smoking is to stop and every attempt should be made to prevent young people from smoking. However, because of the addictive nature of cigarette smoking, cessation is difficult and associated with significant relapse rates. Treatment aimed at achieving smoking cessation needs to address the physiological, psychological, and social dependency components. Nicorette gum may be used for physiological dependency, and behavioral treatment is recommended for psychological and social dependency components.

Obesity. Weight control treatment objectives include *1*) long-term weight loss, *2*) preservation of lean body mass, and *3*) reduced waist-to-hip ratios. Individualized and reasonable weight goals need to be negotiated.

For weight control programs to be successful they need to incorporate behavior modification techniques and extend for long periods of time. Without attention to these two issues, regaining of the weight lost is likely. Other strategies include *1*) decrease in calorie intake, *2*) restriction of dietary fat, *3*) hypocalorie diet eaten as frequent small meals, and *4*) regular exercise.

Glycemia. Hyperglycemia is the primary metabolic abnormality of diabetes. Therefore, it is logical to consider elevated blood glucose as a possible risk factor in the development of macrovascular disease. Although associations between hyperglycemia and diabetic complications have been repeatedly shown for microvascular disease, such an association is less strong for macrovascular disease. The only clinical trial (University Group Diabetes Program) to examine the effect of blood glucose control on macrovascular disease failed to show any benefits.

Treatment of hyperglycemia is mandated by the need to eliminate symptoms and to correct associated lipid abnormalities. Should glycemic control be demonstrated to prevent, retard, or ameliorate microangiopathy or macrovascular disease, then euglycemia should be the goal of therapy in diabetic subjects at risk for these complications. Until such data is available, a prudent course of action is to achieve the best glucose control possible keeping in mind the risk/benefit ratio of therapy, which is impacted by age, presence of complications (micro and/or macrovascular), hypoglycemic unawareness, motivation of the patient, and life expectancy from concurrent disease.

Hyperinsulinemia. Treatment of hyperinsulinemia is directed at amelioration of the underlying cause of insulin resistance, usually excess calorie consumption, obesity, and sedentary life-style.

Prediabetes. There is evidence that the pathogenic mechanisms leading to macrovascular disease among NIDDM patients begin long before the onset of diabetes, during the prediabetic period. Macrovascular risk factors in prediabetic subjects may include increased body mass index, upper-body fat distribution, hyperinsulinemia, hypertension, and lipid abnormalities. Therefore, a comprehensive program to prevent the macrovascular complications of diabetes would ideally begin during the prediabetic period. Unfortunately, there is no definitive way to identify prediabetic individuals. However, by taking into account the known risk factors for NIDDM, it is possible to identify individuals who are likely to be prediabetic. These risk factors include obesity, family history of diabetes, history of gestational diabetes and/or large babies (>9 lb), and belonging to a high-risk ethnic group such as American Indians, Hispanics, or Blacks. These individuals should be screened for diabetes and macrovascular risk factors. If they are found to have such risk factors, appropriate preventive interventions should be vigorously instituted.

Educational programs directed at physicians and the general public should be developed to increase awareness of the characteristics of the prediabetic state.

SECONDARY INTERVENTIONS

There are limited data regarding secondary intervention in diabetic subjects, and therefore therapeutic strategies should follow the lead set by studies in nondiabetic subjects. Unless contraindicated, aspirin should be given after acute myocardial infarction. Because of their ability to prevent reinfarction in nondiabetic subjects, β-blockers should be used in diabetes after myocardial infraction despite possible adverse effects on lipids and counterregulation. The following interventions should also be instituted when appropriate: diet and drug treatment of lipid abnormalities and exercise. Smoking after myocardial infarction should be strongly discouraged.

QUESTION 5: WHAT ADDITIONAL RESEARCH IS NEEDED IN THIS AREA

Little is known about the mechanisms responsible for accelerated macrovascular disease in diabetes and the reasons why other risk factors are frequently present. Furthermore, there is scant data on diabetic subjects that evaluates the impact of single or multiple risk-factor reduction. In fact, patients with diabetes have generally been excluded from the large multicenter primary and secondary drug intervention trials related to CVD. The following unexplored areas are the focus of the consensus panel's recommendations for future research:

1. Basic and clinical investigations designed to elucidate the unique alteration(s) in IDDM, IGT, and NIDDM responsible for accelerated macrovascular disease. Target areas should include arterial

wall injury and repair, lipid and lipoprotein metabolism, hyperinsulinemia, insulin resistance, hyperglycemia, nonenzymatic glycosylation, and platelet and clotting functions.
2. Primary and secondary intervention trials limited to patients with the various classifications of diabetes to evaluate the impact of risk-factor reduction on prevention and reversal of macrovascular disease. The specific new trials should evaluate antihypertensive drugs, lipid-lowering drugs, smoking cessation programs, antiobesity strategies, and antiplatelet drugs.
3. Studies to identify the optimum pharmacological approach to lipid and blood pressure lowering in diabetes.
4. Nutritional studies designed to determine diets for patients with diabetes to maximize the reduction or prevention of relevant cardiac risk factors including carbohydrate intolerance, obesity, hypertension, and lipid abnormalities. Specific issues that should be addressed include weight loss maintenance and the effect of macronutrient composition on insulin sensitivity and on glucose and lipid profiles. Furthermore, studies are needed to identify which patients will benefit most from exercise programs.
5. Investigations to identify individuals at high risk for development of overt diabetes. Because IGT is associated with enhanced macrovascular disease, assessment of reduction of cardiovascular risk factors in this presumed pre-NIDDM state is warranted.

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