Diabetic Dyslipidemia and Atherosclerosis: Evidence from Clinical Trials

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Current Diabetes Reports 2008, **8:**71–77
Current Medicine Group LLC ISSN 1534-4827

Diabetes is a highly prevalent disease in the United States and is increasing in both incidence and prevalence. Atherosclerotic vascular disease is a major cause of morbidity and mortality in diabetic patients. Type 2 diabetes is characterized by insulin resistance and frequently co-exists with a variety of cardiovascular risk factors, including hypertension, obesity, dyslipidemia, and physical inactivity. Hygienic measures such as weight loss and exercise should form the basis of therapeutic interventions in the prevention and treatment of type 2 diabetes. The role of dyslipidemia as a causal factor in vascular disease associated with diabetes was previously downplayed because total cholesterol was frequently normal or minimally elevated. However, diabetic dyslipidemia is characterized by elevated triglycerides, low high-density lipoprotein, and small, dense low-density lipoprotein, the combination of which has been termed the "lipid triad." The role of lipid modification as a means to decrease cardiovascular risk in type 2 diabetes has recently been clarified by a number of clinical trials. Subgroup analysis in early studies implied the potential for benefit of lipid modification in diabetes. The results of these early studies prompted the design of large-scale intervention trials that employed statin and fibric acid derivatives in diabetes patients. The preponderance of data from the statin trials implicates significant clinical benefit in cardiovascular risk reduction. The fibric acid derivatives have theoretic advantages in diabetic dyslipidemia. However, the robust bulk of clinical data obtained from prospective statin studies is lacking for the fibric acid derivatives, and the results of the major trials are equivocal.

Introduction

Age-adjusted cardiovascular mortality has been decreasing in the United States for the past three decades due to improvements in medical therapy, diagnostic modalities, and revascularization techniques [1]; however, diabetes and obesity have been dramatically increasing in both incidence and prevalence [2]. The concern has been raised that if the present trends continue, the encouraging improvements in atherosclerosis-related complications may be blunted due to the high prevalence of peripheral, coronary, and cerebrovascular disease in diabetes. The probability of developing vascular complications in diabetes mellitus is increased by two- to fourfold [3]. The vascular complications associated with diabetes are predominantly related to coronary artery disease, which accounts for approximately 75% of all atherosclerosis-related events. The remaining 25% of vascular complications occur as manifestations of peripheral vascular or cerebrovascular disease. Diabetes has been termed a coronary risk equivalent as observational studies indicate that the 7-year risk of a subject with diabetes and no clinical evidence of vascular disease (primary prevention) is virtually identical to a nondiabetic person who has suffered an acute myocardial infarction (secondary prevention) [4]. Type 2 diabetes has long been considered to be a disorder of insulin resistance that is manifest by hyperglycemia in the face of elevated levels of insulin. However, reduction in cardiovascular morbidity and mortality associated with intensive management of hyperglycemia in type 2 diabetes mellitus is controversial. Increased clinical focus has been directed at the role of dyslipidemia in diabetes, and several recent trials have addressed the role of lipid management in the diabetic subject. This review focuses on the role of insulin resistance and dyslipidemia in type 2 diabetes mellitus and the pathogenesis of atherosclerosis. Additionally, evidence will be presented from recent clinical trials that tests the hypothesis that optimization of lipid abnormalities by pharmacologic therapy in diabetes will reduce cardiovascular events.

Insulin Resistance, Dyslipidemia, and Atherosclerosis

Atherosclerosis is best regarded as a syndrome composed of multiple disparate factors that influence the initiation and progression of vascular disease. Multiple genetic and environmental influences are associated with diabetes,

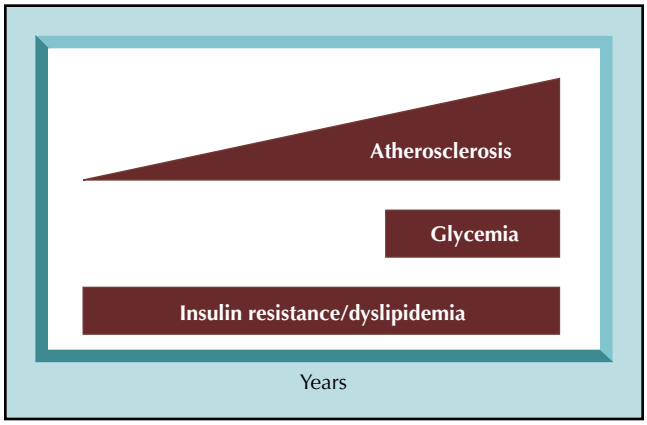

Figure 1. Time course of metabolic complications and diabetes.

such as frequently co-existent cardiovascular risk factors (eg, obesity, hypertension, and dyslipidemia). Diabetes has long been linked to an increased risk for the development of cardiovascular, cerebrovascular, and peripheral vascular disease. Diabetes was recognized as a potential modifiable risk factor in atherosclerosis, although early trials focused on optimization of the carbohydrate abnormality as a means to improve vascular outcomes. The United Kingdom Prospective Diabetes Study (UKPDS) [5] was designed to evaluate the potential benefits of aggressive risk factor modification in diabetic subjects due to the positive observational correlation between hyperglycemia and both macro- and microvascular complications. However, in the UKPDS trial, aggressive management of the carbohydrate abnormality in diabetes was associated with a statistically significant reduction only in microvascular event rates. The aggressive modulation of the glucose abnormality resulted in a small relative risk (16%) reduction in myocardial infarction that did not reach statistical significance. The improvements in macrovascular event rates were positively correlated with optimization of blood pressure and lipid control.

Diabetes has been classified as type 1 (which is characterized by the essential lack of insulin production) and type 2 (which is associated with variable levels of insulin due to impaired insulin action or insulin resistance). The presence of insulin resistance is frequently demonstrable in classical cardiac risk factors including obesity, hypertension, dyslipidemia, and physical inactivity. The frequently observed risk factor clustering has been termed the metabolic syndrome, although the term has recently become controversial [6•]. However, the frequently demonstrable insulin resistance in multiple risk factors implies the presence of shared metabolic pathways. The resistance to the action of insulin creates a vicious cycle that is associated with a progressive increase in circulating levels of insulin and potential impairment in the ability to regulate circulating lipoprotein and glucose levels due to β-cell exhaustion. In fact, dyslipidemia can be demonstrated to be present in insulin-resistance states well before the onset of abnormal glucose levels (Fig. 1). The presence of dyslipidemia in insulin resistance and diabetes has focused attention on the optimization of circulating lipoproteins as a potential means to reduce cardiovascular morbidity and mortality.

The lipid hypothesis for the development of atherosclerosis is based on the premise that dyslipidemia (elevated low-density lipoprotein [LDL], very low density lipoprotein [VLDL], remnant particles, lipoprotein (a), and/or decreased levels of high-density lipoprotein [HDL]) is central to the process of obstructive vascular disease. The lipid hypothesis has been substantiated by extensive genetic, pathologic, experimental, and clinical studies. However, the interpretation of the early (prior to the advent of statins) prospective clinical studies designed to test the lipid hypothesis generated considerable clinical controversy. The dispute over the benefits of lipid lowering arose following the realization that although cardiovascular outcomes were improved, the absolute benefits were minimal and no reduction in total mortality was achieved. The failure to reduce total mortality in the face of a decrease in cardiovascular events implicated a potential adverse effect of lipid lowering by increasing noncardiovascular morbidity. The advent of statin therapy provided adequate pharmacologic power to markedly reduce circulating levels of LDL and has been demonstrated to improve cardiovascular mortality across the risk spectrum of atherosclerosis (eg, primary and secondary prevention). Additionally, in adequately powered studies, statin therapy has been demonstrated to improve total mortality.

The mechanism underlying dyslipidemia in diabetes or insulin resistance has been clarified. Insulin resistance is associated with an overproduction and reduced catabolism of circulating lipoproteins [7]. The increased levels of circulating free fatty acids that are characteristic of insulin resistance are subsequently taken up by the liver and provide the metabolic substrate for the synthesis of the endogenously produced triglyceride-rich VLDL. Additionally, insulin is an agonist for lipoprotein lipase, which is the key enzyme in the degradation of circulating triglyceride-rich lipoproteins and remnant particles [8]. Insulin resistance is thus associated with reduced catabolism of VLDL and chylomicron remnants, with resultant hypertriglyceridemia. The impaired catabolism of VLDL also is associated with reduced cholesterol transfer into HDL with a subsequent reduction in the circulating level of this cardioprotective lipoprotein. The resultant hypertriglyceridemia and low HDL are also associated with an abnormal and highly atherogenic form of LDL (small, dense LDL). Small, dense LDL is felt to demonstrate increased atherogenicity due to increased susceptibility to oxidation, endothelial cytotoxicity, and increased ability to traverse the endothelial barrier [9]. The term "lipid triad" has been employed to describe the frequently demonstrated lipid phenotype in diabetes or insulin

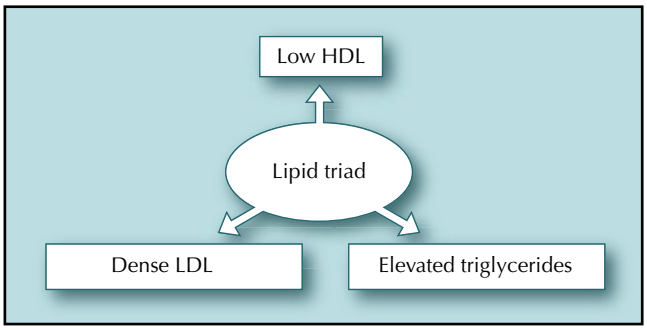

Figure 2. A diagram of diabetes and dyslipidemia. HDL—high-density lipoprotein; LDL—low-density lipoprotein.

resistance and is characterized by hypertriglyceridemia, low HDL, and small, dense LDL (Fig. 2) [10].

The initial selection of pharmacologic therapy for improvement of the lipid profile is frequently predicated on the lipid phenotype obtained from a basic fasting-screening panel. The initial selection may be based on the predominant phenotype (elevated LDL or a predominant aberration of triglycerides and HDL). Statin therapy results in a major reduction in LDL, which is associated with a quantitatively diminished impact on triglycerides and HDL. The mechanism of statin therapy in improving the lipid profile is complex [11]. Intrahepatic cholesterol is kept at a constant level by a balance between synthesis via 3-hydroxy-3-methylglutaryl coenzyme A reductase activity and upregulation of the LDL receptors. Lipophilic statins (eg, atorvastatin and simvastatin) may have an additional beneficial effect by decreasing the production and release of VLDL as a result of diminished incorporation of apolipoprotein (apo) B-100 during the synthetic process [12]. Statins also have complex nonlipid or pleiotropic effects and have beneficial effects on inflammation, endothelial function, and fibrinolysis [13••]. Fibric acid derivatives and nicotinic acid demonstrate a predominant effect on the lowering of triglycerides and the raising of HDL whereas the effect on LDL is less significant. The fibric acid derivatives are part of the peroxisome proliferator-activated receptor-α (PPAR-α) family, a system that is a member of the steroid hormone receptor superfamily, which modulates a variety of aspects of lipid metabolism [14]. The major effect of the fibric acid derivatives is to activate the ubiquitous endothelial-bound enzyme lipoprotein lipase, which results in enhanced degradation of the triglyceride-rich lipoproteins (Fig. 3) [15]. Fibric acid derivatives might also modify the atherogenicity of LDL by alteration of the structure to a larger, less dense particle (Fig. 4) [16]. Fibric acid derivatives may also enhance HDL production by increasing the synthesis of apoA-1 [17]. Nicotinic acid has not been extensively studied in diabetic subjects due to the frequently encountered impaired glucose tolerance that is especially pronounced in older subjects [18]. However, nicotinic acid is a versatile pharmacologic agent with beneficial effects on all circulating lipoproteins, including lipoprotein(a). Insulin

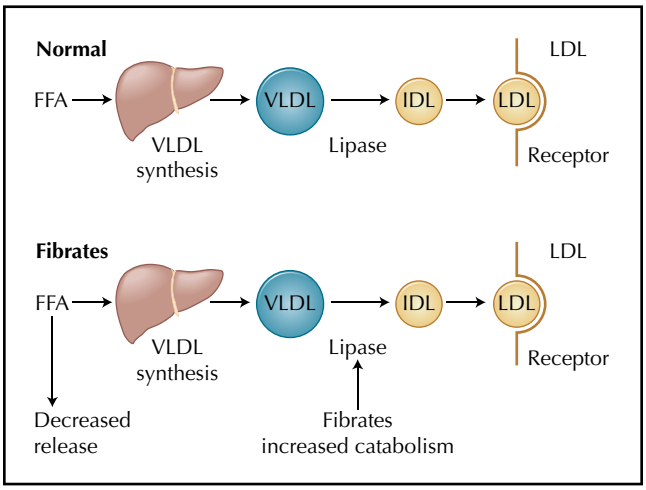

Figure 3. Mechanism of action of fibrates. FFA—free fatty acid; IDL—intermediate-density lipoprotein; LDL—low-density lipoprotein; VLDL—very low density lipoprotein.

resistance in and of itself is not a contraindication to the use of nicotinic acid.

Clinical Trials of Lipid Lowering in Type 2 Diabetes Mellitus

Statins

Collaborative Atorvastatin Diabetes Study (CARDS)

The CARDS study [19] evaluated the role of atorvastatin therapy in type 2 diabetes mellitus. The CARDS trial randomized a total of 2838 diabetic subjects between the ages of 40 and 75 years to receive either placebo or 10 mg/d of atorvastatin. Baseline entry lipids required that the LDL be less than 160 mg/dL and triglycerides could not exceed 600 mg/dL. In addition to the diagnosis of diabetes, subjects were required to have at least one additional risk factor, which could include hypertension, tobacco usage, retinopathy, or albuminuria. Atorvastatin therapy resulted in a significant improvement in the lipid profile with reductions in LDL, total cholesterol, and triglycerides of 40%, 26%, and 19%, respectively. Additionally, HDL cholesterol was increased by 1%. The primary end point of the CARDS trial was the time to first occurrence of acute coronary heart disease events, coronary revascularization procedures, or cerebrovascular accident. The CARDS trial was terminated early due to the earlier than expected demonstration of a statistically significant reduction in the primary end point of 37%. The results of the CARDS trial demonstrated the clinical benefit of atorvastatin in a cohort of diabetic subjects whose lipid values were not dramatically elevated and emphasized the role of lipid modification in diabetes.

Treatment to New Targets (TNT)

The TNT trial [20] was designed to test the hypothesis that aggressive hypolipidemic therapy would be potentially beneficial relative to more conservative measures

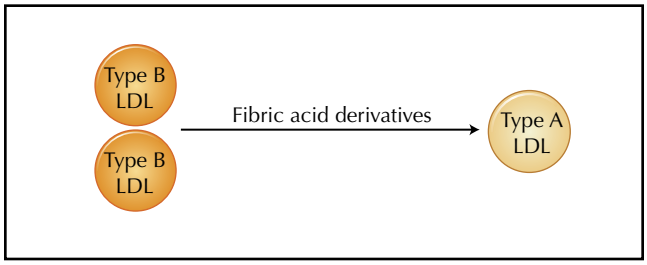

Figure 4. Fibrates and low-density lipoprotein (LDL) subclass.

while employing the same pharmacologic agent. The initial trial randomized 10,001 patients to receive either 80 mg/d of atorvastatin or 10 mg/d of atorvastatin. The original cohort of the TNT trial demonstrated significant clinical benefit with the aggressive pharmacologic regimen. A diabetic subgroup, which was composed of 1501 individuals, was also analyzed for the possible relative risk reduction associated with more aggressive therapy. The lipid criteria required that LDL levels be less than 130 mg/dL in the group to receive the standard therapy (10 mg/d of atorvastatin). The primary end point was the time to first major cardiovascular event, which was defined as a composite that encompassed fatal or nonfatal myocardial infarction, fatal or nonfatal cerebrovascular accident, or resuscitated cardiac arrest. Aggressive therapy in the diabetic subgroup resulted in a significant difference in the achieved lipid values. Atorvastatin at 80 mg/d resulted in an LDL cholesterol of 77 mg/dL compared with 99 mg/dL in the less aggressive group. The reduction in LDL cholesterol achieved by atorvastatin was correlated with a 25% reduction in the primary end point, which was statistically significant, emphasizing the cardiovascular benefits associated with aggressive lipid lowering.

Atorvastatin Study for the Prevention of Coronary Heart Disease End Points in Non–insulin-Dependent Diabetes Mellitus (ASPEN)

The ASPEN trial was designed to further substantiate the role for aggressive lipid management in diabetic subjects [21]. The ASPEN trial randomized 2410 diabetic subjects who were free of known atherosclerosis (primary prevention) or had documented vascular disease (secondary prevention). The randomization lipid criteria varied depending on the presence or absence of clinically documented coronary artery disease. Individuals with established coronary atherosclerosis were required to demonstrate an LDL cholesterol level of less than 140 mg/dL at the time of randomization. Subjects who were clinically free of atherosclerosis could be randomized as long as the LDL cholesterol was less than 160 mg/dL. Atorvastatin, 10 mg/d, was compared with placebo for a period of 4 years. A composite primary end point was utilized and defined as fatal or nonfatal myocardial infarction, nonfatal cerebrovascular accident, resuscitated cardiac arrest, unstable angina requiring hospitalization, or revascularization. LDL cholesterol was reduced by 29% with atorvastatin therapy. A trend to improvement in the primary end point was demonstrated (10% relative risk reduction), although it did not reach statistical significance. However, the group who would qualify as secondary prevention demonstrated an 18% reduction in the primary end point compared with only 3% in primary prevention. The results of the ASPEN trial were unexpected in light of the previous studies and may partially be explained by a change in the trial design. The ASPEN study was originally intended to test the role of atorvastatin therapy in diabetic subjects with documented atherosclerosis. However, the treatment guidelines for diabetes patients in the National Cholesterol Education Program Adult Treatment Panel III were published during the trial and recommended more aggressive LDL goals (< 100 mg/dL) in diabetes patients. The protocol was subsequently amended to comply with the new guidelines and subjects were advised to begin active therapy to achieve guidelines, which resulted in a significant reduction in the number of subjects who completed the double-blind treatment on the assigned regimen.

Heart Protection Study (HPS)

The HPS trial [22] was a very large (20,536 subjects) study that was designed to study the effects of simvastatin therapy in populations who had been under-represented in previous trials (diabetes patients, women, noncoronary vascular disease, and the elderly) [22]. A large diabetic subgroup consisting of 5963 subjects was analyzed in a predefined manner. The patients were randomized to receive 40 mg/d of simvastatin or placebo. Simvastatin therapy was clinically efficacious in the diabetic cohort and reduced LDL cholesterol by 35 mg/dL. The reduction in LDL cholesterol induced by simvastatin was correlated with a significant reduction in clinical events. Coronary event rates were reduced by 22% in the diabetic subgroup. Similar improvement was demonstrated in the risk of development of a cerebrovascular accident or necessity for revascularization. The clinical benefits were analyzed and determined to be independent of the degree of glycemic control or baseline LDL cholesterol. The relative risk reduction was identical if the baseline LDL was less than 100 mg/dL, 100 to 130 mg/dL, or greater than 130 mg/dL. The results of the HPS underestimate the clinical value of simvastatin, as a significant proportion of the control group had been begun on statin therapy at the termination of the trial. The HPS trial demonstrated the significant benefits of simvastatin therapy in diabetic patients and emphasized the role of hypolipidemic therapy.

Fibric acid derivatives

Fibric acid derivatives would theoretically provide optimal therapy in diabetic dyslipidemia due to the frequent presence of hypertriglyceridemia, low HDL, and small, dense LDL (ie, the lipid triad), which all may benefit from the use of these agents.

Helsinki Heart Study (HHS)
The Helsinki Heart Study [23] was one of the original lipid-lowering trials in primary prevention. The HHS evaluated 4081 subjects who were free of clinically evident coronary artery disease. The participants in the HHS were randomized on the basis of a non–HDL cholesterol level of greater than 200 mg/dL. Unfortunately, a large number of the subjects in the HHS did not demonstrate the lipid profile that would respond ideally to fibric acid therapy (lipid triad). Subjects were randomized to gemfibrozil therapy or placebo over a 5-year period. The administration of gemfibrozil significantly reduced cardiovascular mortality, although the absolute reduction was relatively modest and no reduction in total mortality was achieved. The benefit of gemfibrozil therapy was relatively greater in a subgroup (10% of the entire HHS cohort) characterized by hypertriglyceridemia and low HDL. Additionally, a small number (n = 135) of subjects in the HHS were diabetic and these individuals had an increased incidence of fatal and nonfatal myocardial infarction relative to subjects with a normal glucose level (7.4% vs 3.3%). Gemfibrozil therapy resulted in a statistically nonsignificant trend to a reduction in cardiovascular event rates in diabetic subjects (3.4% vs 10.5%). The role of gemfibrozil in diabetic subjects was not a prespecified end point and the study was not powered for proper evaluation. However, the beneficial trend indicated a potential role for fibric acid therapy in diabetic subjects and led to the design of adequately powered studies to evaluate the role of fibric acid therapy in diabetic subjects.

The Veteran's Affairs HDL Intervention Trial (VA-HIT)
The VA-HIT study [24] evaluated the potential benefits of gemfibrozil in 2531 men who had suffered an acute myocardial infarction (secondary prevention). The HHS trial had employed non–HDL cholesterol as the qualifying lipid parameter for randomization. In contrast, the VA-HIT trial was based on the presence of low HDL cholesterol levels and required a baseline value of less than 40 mg/dL for inclusion. Additionally, gemfibrozil exerts its predominant effect on triglycerides and HDL rather than LDL. Subjects with LDL levels above 140 mg/dL were not included in the VA-HIT trial. The primary end point in the VA-HIT trial was fatal and nonfatal myocardial infarction. Gemfibrozil therapy resulted in a reduction in circulating triglycerides of 31%, which was accompanied by an increase in HDL of 7%. The circulating levels of LDL cholesterol were not reduced by gemfibrozil therapy, although previous studies had demonstrated an alteration of LDL particles with reduced levels of small, dense LDL (Fig. 4). The alteration of the lipid parameters induced by gemfibrozil resulted in a statistically significant reduction in the primary end point of 22%. Despite the quantitatively greater relative reduction in triglyceride levels, the clinical benefit was determined to be related to the increase in HDL. The population in the VA-HIT trial was characterized by a 30% prevalence of diabetes mellitus. Gemfibrozil therapy in the diabetic subgroup resulted in a relative risk reduction in the primary end point of 32% compared with 18% in a nondiabetic group [25]; however, the trend was not statistically significant. Nonfatal myocardial infarction was essentially equal in the diabetic and nondiabetic populations. However, fatal myocardial infarction and stroke were both reduced by gemfibrozil therapy in the diabetic subgroup.

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)
The potentially beneficial effects of gemfibrozil in the diabetic subgroup of the VA-HIT trial prompted the design of a larger trial, specifically addressing the role of fenofibrate therapy in a large cohort of diabetic subjects. The FIELD trial [26] randomized 9795 subjects with type 2 diabetes who were not on statin therapy at the beginning of the study. The trial included subjects who could be classified both as primary prevention (7664) and secondary prevention (2131). The primary end point was fatal and nonfatal myocardial infarction occurring over the 5-year duration of the trial. Fenofibrate therapy resulted in a significant improvement in lipid parameters, which became attenuated as the trial progressed. Fenofibrate therapy resulted in a reduction of total cholesterol of 11%, LDL cholesterol of 12%, triglyceride reduction of 29%, and an increase in HDL cholesterol of 5% during the first 4 months of the trial. Fenofibrate therapy in this large group of diabetic subjects demonstrated a nonsignificant trend to benefit (11% relative risk reduction) in the primary end point. However, subjects were allowed to begin concomitant therapy during the trial and a higher percentage of the placebo group was placed on supplemental statin therapy, which may have partially explained the failure to reach statistical significance. Combination therapy utilizing fenofibrate and statin therapy has been demonstrated to improve lipid parameters and mixed dyslipidemia. However, the role of this combination in reduction of cardiovascular events has not been addressed in prospective clinical trials. The Action to Control Cardiovascular Risk in Diabetics (ACCORD) trial will employ combination therapy involving a fenofibrate and statin combination to test the potential benefits of hypolipidemic agents with differing mechanisms of action as a means to reduce cardiovascular risk in diabetic subjects.

Conclusions

Diabetes is a highly prevalent disease in the United States, and the incidence of both diabetes and conditions that predispose to its development (eg, obesity) is increasing. Cardiovascular disease is a major cause of morbidity

and mortality in diabetes mellitus. Insulin resistance is frequently demonstrable in a variety of cardiovascular risk factors such as obesity, dyslipidemia, and hypertension, which imply shared pathways. Major attempts to reduce cardiovascular morbidity and mortality in type 2 diabetes had previously focused on the correction of the carbohydrate abnormality. The results of major clinical trials such as the UKPDS demonstrated a nonstatistically significant trend to reduction in macrovascular end points. Improvements in LDL and HDL were correlated with a reduction in cardiovascular events. However, clinical optimization of the glucose abnormality in diabetes should be a therapeutic goal. Utilizing a different population from the UKPDS (type 1 diabetes), the Diabetes Control and Complications trial (DCCT) [27] demonstrated a reduction in macrovascular (fatal or nonfatal myocardial infarction and stroke) events with intensive diabetes therapy that was aimed at achieving normoglycemia. Additionally, lifestyle modification may prevent the onset of diabetes or significantly reduce the risk in established diabetes. Thus, lifestyle modifications should be a primary cornerstone in the prevention and management of the diabetic subject. Lifestyle modifications have been compared with insulin sensitizers (metformin) in a placebo-controlled evaluation. Lifestyle modification decreased the incidence of diabetes by 58% compared with a 31% reduction with metformin [28].

The role of dyslipidemia and diabetes had previously been downplayed as total cholesterol was frequently normal. However, abnormalities in major lipoproteins are demonstrable in type 2 diabetes (low HDL cholesterol, elevated triglycerides, and small, dense LDL) and have been termed the lipid triad. The role of modification of circulating lipoproteins in prospective clinical trials has been evaluated with both statins and fibric acid derivatives. Statin therapy has been demonstrated to be effective in reducing cardiovascular end points in several trials employing differing patient populations and therapeutic strategies (eg, HPS, CARDS, TNT). Despite the theoretical advantage of fibric acid derivatives in managing subjects with the lipid triad, the results from the clinical trials involving these agents have been controversial. Gemfibrozil therapy demonstrated a trend to benefit in a subgroup analysis of the diabetic cohort of VA-HIT. However, the large-scale FIELD trial demonstrated a nonsignificant trend to benefit. The currently available clinical data support the use of aggressive statin therapy in subjects with diabetes. The role of fibric acid derivatives may be relegated to combination therapy, which is currently being addressed in the ACCORD study.

Disclosure

No potential conflict of interest relevant to this article was reported.

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