Does Glycemic Control of Type II Diabetes Suffice to Control Diabetic Dyslipidemia?

A Community Perspective

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OBJECTIVE— To assess the extent to which glycemic control by itself results in satisfactory control of diabetic dyslipidemia.

RESEARCH DESIGN AND METHODS— A population-based case series consisting of 386 Mexican Americans and 94 non-Hispanic whites with non-insulin-dependent (type II) diabetes was studied. All subjects answered questions about their medical history and care received and underwent a standardized oral glucose tolerance test and measurements of fasting serum lipid and lipoprotein concentrations. Three definitions of dyslipidemia were used: total cholesterol >6.20 mM (240 mg/dl), triglyceride >2.82 mM (250 mg/dl), and high-density lipoprotein cholesterol <0.90 mM (35 mg/dl).

RESULTS— Despite having removed subjects receiving lipid-lowering drugs, diabetic subjects who had been previously diagnosed and were under medical care exhibited a lower prevalence of hypertriglyceridemia than those who were newly diagnosed at the time of their survey visit, suggesting that conventional management was associated with a reduced frequency of this dyslipidemia. Among previously diagnosed cases, the prevalence of dyslipidemia rose with worsening glycemic control but there was little association with type of therapy (diet only, oral agents, or insulin) or frequency of physician visits. In general, the prevalence of dyslipidemia in diabetic subjects remained higher than in nondiabetic subjects, despite hypoglycemic therapy.

CONCLUSIONS— The results suggest that glycemic control by itself does not suffice to control diabetic dyslipidemia and that significant numbers of diabetic subjects will need direct lipid management. Clinical trials are urgently needed to define the optimum management strategy for diabetic dyslipidemia.

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Numerous studies have documented that cardiovascular disease (CVD), particularly ischemic heart disease, is the leading cause of death and a major cause of morbidity and functional disability in patients with non-insulin-dependent (type II) diabetes mellitus as it is in the general population (1–3). Whereas the principal risk factors for the microvascular complications of diabetes are the degree and duration of hyperglycemia (4–9), these are not the main risk factors for macrovascular complications (2,4,10–13). Instead, the risk factors for macrovascular complications are the same as those that operate to produce CVD in the nondiabetic population, i.e., cholesterol level, blood pressure, and cigarette smoking (10,14). Despite this, most authorities emphasize glycemic control as the first line of defense in the treatment of diabetic dyslipidemia. (In this paper, we will use the term *diabetic dyslipidemia* to refer to the hypertriglyceridemia, low high-density lipoprotein (HDL), and occasional low-density lipoprotein (LDL) elevations commonly found in diabetic patients.) For example, both the American Diabetes Association (ADA; 15) and the National Cholesterol Education Program (NCEP; 16) recommend glycemic control as the first step in controlling diabetic dyslipidemia. Moreover, it appears that physicians are inclined to follow this policy. In San Antonio, Texas, for example, whereas 50–70% of previously diagnosed diabetic subjects were under treatment with either oral agents or insulin, <10% of those with dyslipidemia were receiving lipid-lowering agents (17). Although no one questions the importance of glycemic control, the ADA has recently published a Consensus Statement, which emphasizes that many diabetic patients may need additional therapy directed specifically at their lipid abnormalities, including the use of lipid-lowering drugs when necessary (18).

There is no doubt that the principal modalities of glycemic control can improve lipid profiles in selected diabetic

patients. Thus, diet (19–22), oral antidiabetic agents (22–25), and insulin (23,26–28) have all been shown to produce favorable changes in diabetic dyslipidemia, particularly reductions in very-low-density lipoprotein (VLDL) cholesterol. However, most of these studies were relatively small and involved selected groups of patients. What is not known and what is relevant from a public health standpoint is: How often does the glycemic control strategy work in the general diabetic population? Specifically, what percentage of diabetic subjects can realistically be expected to achieve satisfactory glycemic control, and of these, what percentage will then need no further attention to their lipid profiles? These are the questions that we have attempted to answer in this article.

RESEARCH DESIGN AND METHODS

— The diabetic subjects analyzed herein were drawn from the cohort enrolled in the San Antonio Heart Study, a population-based study of diabetes and CVD in Mexican Americans and non-Hispanic whites. More than 5100 individuals, 60% of whom were Mexican American, have been enrolled in this study since 1979. The study design, sampling procedures, field procedures, and response rates of the San Antonio Heart Study have been described in detail in previous publications (17,29–31). Briefly, households were randomly sampled from three types of neighborhoods: low-income barrios, middle-income transitional neighborhoods, and high-income suburbs. All 25- to 64-yr-old men and nonpregnant women residing in the selected households were considered eligible for the study and invited to undergo a medical examination in a mobile clinic located in their neighborhood. Response rates ranged from 60 to 75% in the various neighborhoods. All participants underwent a standard oral glucose tolerance test, and diabetes was diagnosed according to the plasma glucose criteria of the National Diabetes Data Group (32). In addition, individuals who gave a history of diabetes and who reported current therapy with oral antidiabetic agents and/or insulin were considered to have diabetes regardless of their plasma glucose concentrations. A total of 386 Mexican Americans and 94 non-Hispanic whites met these criteria for diabetes. One hundred seventy-nine Mexican Americans and 58 non-Hispanic whites were diagnosed for the first time at their survey visit. These individuals will be referred to as *newly diagnosed* and the remaining diabetic subjects will be referred to as *previously diagnosed*. The combined group of patients thus constitutes a population-based case series and should be reasonably representative of typical diabetic patients in our community. Height and weight were measured on all participants and body mass index (BMI; kg/m^2) was calculated as an index of adiposity. Insulin-taking diabetic subjects who had BMI <30 kg/m^2 and whose age of diabetes onset was <40 yr were considered to have possible insulin-dependent diabetes (n = 16) and were excluded from our analyses. Also, because the emphasis in this article is on the relationship between glycemic control and prevalence of dyslipidemia, patients who reported treatment with lipid-lowering medications (n = 12) were also excluded from the analyses. Occasional missing values on selected variables further reduced the number of subjects in

Table 1—*Age-adjusted prevalence (%) of dyslipidemia (3 definitions) in diabetic and nondiabetic subjects according to sex and ethnicity*

	Mexican American				non-Hispanic white			
	Nondiabetic	Diabetic	Prevalance ratio	Age-adjusted *P* value for effect of diabetes	Nondiabetic	Diabetic	Prevalance ratio	Age-adjusted *P* value for effect of diabetes
Men								
N	1198	143			778	39		
Total cholesterol >6.20 mM*	21.3	21.8	1.02	0.89	21.2	25.2	1.19	0.56
Triglyceride >2.82 mM†	15.4	29.4	1.91	<.001	14.0	25.5	1.82	0.06
High-density lipoprotein cholesterol <0.90 mM‡	24.3	37.8	1.56	.001	23.1	45.9	1.99	0.003
Women								
N	1621	221			966	44		
Total cholesterol >6.20 mM§	20.2	29.3	1.45	.005	22.9	24.1	1.05	0.85
Triglyceride >2.82 mM‖	6.5	20.6	3.17	<0.001	5.6	16.9	3.02	0.003
High-density lipoprotein cholesterol <0.90 mM¶	8.0	21.6	2.70	<0.001	4.6	17.5	3.80	0.002

*P = 0.58, †P = 0.13, ‡P = 0.97, §P = 0.55, ‖P = 0.05, ¶P = 0.008, for main effects of ethnicity on diabetes status.

Table 2—*Age-adjusted prevalence (%) of dyslipidemia in newly and previously diagnosed diabetic subjects according to severity of fasting glycemia*

	MEN		WOMEN	
	NEWLY DIAGNOSED	PREVIOUSLY DIAGNOSED	NEWLY DIAGNOSED	PREVIOUSLY DIAGNOSED
N				
MILD	52	24	78	46
MODERATE	27	31	22	44
SEVERE	13	31	23	51
FASTING GLUCOSE*				
MILD	6.21 mM	6.25 mM	6.12 mM	6.42 mM
MODERATE	9.31 mM	9.42 mM	9.20 mM	9.22 mM
SEVERE	13.33 mM	13.99 mM	14.81 mM	14.31 mM
TOTAL CHOLESTEROL >6.20 mM				
MILD	25.7	19.4	22.9	22.6
MODERATE	18.1	13.4	37.9	37.6
SEVERE	37.6	29.6	31.6	31.3
P FOR MAIN EFFECT OF DIAGNOSIS STATUS	$P = 0.30$		$P = 0.88$	
TRIGLYCERIDE >2.82 mM				
MILD	27.2	11.9	15.8	12.0
MODERATE	43.2	21.5	26.6	20.9
SEVERE	54.1	29.8	32.7	26.1
P FOR MAIN EFFECT OF DIAGNOSIS STATUS	$P = 0.005$		$P = 0.38$	
HIGH-DENSITY LIPOPROTEIN CHOLESTEROL <0.90 mM				
MILD	37.5	42.8	18.1	19.0
MODERATE	31.8	36.8	16.4	17.2
SEVERE	43.8	49.4	23.4	24.4
P FOR MAIN EFFECT OF DIAGNOSIS STATUS	$P = 0.82$		$P = 0.90$	

*Mild <7.78, moderate 7.78–11.1, severe >11.1 mM.

several of the tables. The study was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio, and all subjects gave informed consent.

All subjects completed a detailed medical history questionnaire, which included questions on their type of antidiabetic therapy (diet only, oral agents, and/or insulin) and frequency of physician visits within the preceding year. These items were used as indicators of the intensity of therapy. Three definitions were used for dyslipidemia: total cholesterol (TC) concentration >6.20 mM (240 mg/dl), triglyceride (TG) concentration >2.82 mM (250 mg/dl), and high-density lipoprotein (HDL) cholesterol concentration <0.90 mM (35 mg/dl). (Although it could be argued that sex-specific cutoffs should be used for low HDL cholesterol, we followed the NCEP guidelines (16) that specify an HDL cholesterol of <0.9 mM (<35 mg/dl) as indicative of high cardiovascular risk for both men and women.) Severity of fasting glycemia was categorized as: mild <7.78 mM (140 mg/dl), moderate 7.78–11.1 mM (140–200 mg/dl), and severe >11.1 mM (200 mg/dl).

The prevalences of dyslipidemia were age-adjusted by multiple logistic regression (33). In all tables, the predicted prevalence at age 53 yr is presented because this was the approximate mean age for the total sample of diabetic subjects. In Table 1, four logistic regression models were used, one for each sex-ethnic group. In each model, dyslipidemia was the dependent variable and age and diabetes status were the independent variables, and the main effect of diabetes status was tested. The sexes were then combined and a second series of logistic regression models was run with ethnicity added as an independent variable to test for the main effect of ethnicity. In Table 2, the effect on dyslipidemia prevalence of being either newly or previously diagnosed is presented. Because newly diagnosed diabetic subjects appeared to have milder disease (as evidenced by lower levels of glycemia, perhaps reflecting more recent disease onset), these analyses were stratified according to glycemic level (characterized as mild, moderate, or severe). Multiple logistic regression was again used to estimate the predicted prevalence of dyslipidemia at age 53 yr for newly

Table 3—*Age-adjusted prevalence (%) of dyslipidemia in previously diagnosed diabetic subjects according to sex and type of therapy*

	Men					Women				
	Type of therapy			Age-adjusted P value for effect		Type of therapy			Age-adjusted P value for effect	
	Diet only	Oral agents	Insulin	Pills vs. diet	Insulin vs. diet	Diet only	Oral agents	Insulin	Pills vs. diet	Insulin vs. diet
N	30	46	11			49	70	25		
Age (yr)	54.3	52.7	57.2	0.39	0.22	52.5	53.6	54.0	0.58	0.47
Body mass index (kg/m^2)	29.0	29.5	32.5	0.80	0.056	31.5	31.0	36.6	0.89	0.001
Total cholesterol >6.20 mM	20.1	21.7	18.5	0.87	0.91	30.6	32.7	27.8	0.81	0.80
Triglycerides >2.82 mM	27.0	19.3	28.8	0.44	0.91	19.8	21.3	20.2	0.85	0.97
High-density lipoprotein cholesterol <0.90 mM	51.2	29.8	84.2	0.07	0.06	21.1	24.3	12.8	0.67	0.40

and previously diagnosed diabetic subjects at each level of glycemia. These analyses were performed separately for men and women and the main effect of diagnosis status was tested. Among previously diagnosed diabetic subjects, age-adjusted dyslipidemia prevalences were calculated according to type of therapy (Table 3) and frequency of physician visits in the preceding year (Table 4). Each of these independent variables was entered as a categorical variable to compute the predicted prevalence at age 53 yr for each level of the variable. In Table 4, the models were then rerun with frequency of physician visits entered as a continuous variable to test for the linear effect of this variable.

RESULTS — Table 1 shows the age-adjusted prevalence of dyslipidemia according to the three definitions in diabetic and nondiabetic Mexican-American and non-Hispanic white men and women. Diabetic subjects consistently had higher prevalences of hypertriglyceridemia and low HDL cholesterol. These differences were statistically significant in seven of eight comparisons. In Mexican-American women, the prevalence of hypercholesterolemia was also significantly higher among diabetic than nondiabetic subjects. The effect of diabetes on dyslipidemia was greater in women than men as previously reported by us (34) and others (35). There were no statistically significant ethnic differences in men, although in women the ethnic differences in both hypertriglyceridemia and low HDL were statistically significant.

Because there were no significant ethnic differences in dyslipidemia prevalence among diabetic subjects, we pooled the two ethnic groups to simplify the presentation and to increase statistical

Table 4—*Age-adjusted prevalence (%) of dyslipidemia in previously diagnosed diabetic subjects according to sex and frequency of physician visits*

	Men					Women				
	Physician visits/yr				Age-adjusted P value for effect of number of visits	Physician visits/yr				Age-adjusted P value for effect of number of visits
	0	1–2	3–4	>4		0	1–2	3–4	>4	
N	21	15	17	29		20	24	28	69	
Age (yr)	54.2	51.9	54.5	54.3	0.72	53.4	51.3	56.2	52.4	0.88
Body mass index (kg/m^2)	29.0	28.4	29.8	31.0	0.12	31.4	31.7	30.2	33.3	0.21
Total cholesterol >6.20 mM	24.0	13.1	23.9	17.5	0.73	19.9	25.3	24.2	39.3	0.06
Triglycerides >2.82 mM	19.1	26.6	17.7	27.7	0.58	5.0	19.8	19.0	27.1	0.05
High-density lipoprotein cholesterol <0.90 mM	57.6	46.2	17.9	48.7	0.40	24.6	10.8	17.2	25.2	0.45

Table 5—*Comparison of age-adjusted dyslipidemia prevalence in nondiabetic subjects and least severe and most intensively managed diabetic subjects*

	Nondiabetic		Previously diagnosed diabetic		
	Mexican American	Non-Hispanic white	Least severe (fasting plasma glucose <7.78 mM)	Insulin treated	>4 Physican visits/yr
Men					
Total cholesterol >6.20 mM	21.3	21.2	19.4	18.5	17.5
Triglycerides >2.82 mM	15.4	14.0	11.9	28.8	27.7
High-density lipoprotein cholesterol <0.90 mM	24.3	23.1	42.8	84.2	48.7
Women					
Total cholesterol >6.20 mM	20.2	22.9	22.6	27.8	39.3
Triglycerides >2.82 mM	6.5	5.6	12.0	20.2	27.1
High-density lipoprotein cholesterol <0.90 mM	8.0	4.6	19.0	12.8	25.2

power (Tables 2–5). Table 2 shows the prevalence of dyslipidemia in newly and previously diagnosed diabetic subjects according to level of glycemia. Hypertriglyceridemia prevalence was lower in previously diagnosed diabetic subjects and this deficit was statistically significant in men. Previously diagnosed men also appeared to have somewhat less hypercholesterolemia, although this difference was not statistically significant. In none of the other comparisons, however, was there an advantage among the previously diagnosed diabetic subjects. In both newly and previously diagnosed diabetic subjects, the prevalence of hypertriglyceridemia declined in a stepwise fashion with progressively better glycemic control. Similar associations were not consistently observed for the other types of dyslipidemia, however.

Table 3 shows no significant trends in the prevalence of dyslipidemia according to type of antidiabetic therapy. Table 4 shows the prevalence of dyslipidemia according to the frequency of physician visits in the preceding year. In men, no consistent trends were observed. In women, however, there was a significant trend toward more hypertriglyceridemia with increasing frequency of physician visits. A similar trend, albeit only of borderline significance, was seen for hypercholesterolemia. Neither of these trends could be attributed to rising obesity because this variable showed no association with the frequency of physician visits.

In Table 5, we combined the data from Tables 1 to 4 to compare the prevalence of dyslipidemia in the least severe (fasting glycemia <7.78 mM) and most intensively managed (insulin treatment and >4 physician visits/yr) diabetic subjects to that in nondiabetic subjects. Diabetic subjects consistently experienced more hypertriglyceridemia and low HDL cholesterol than nondiabetic subjects. These data suggest that regardless of the intensity or success of interventions directed at lowering blood glucose, diabetic subjects persist in having an excess prevalence of dyslipidemia.

CONCLUSIONS— In general, the results presented in this paper provide some evidence of a beneficial effect of conventional therapy on the prevalence of diabetic dyslipidemia, particularly hypertriglyceridemia, although this improvement still leaves diabetic subjects with higher dyslipidemia prevalences than are observed in the nondiabetic population. Even after having excluded subjects treated with lipid-lowering medications (n = 12), the previously diagnosed diabetic subjects exhibited less hypertriglyceridemia than the newly diagnosed diabetic subjects (statistically significant in men) (Table 2). There was also less hypercholesterolemia in previously diagnosed men, although this difference was not statistically significant. The prevalence of low HDL cholesterol was similar in newly and previously diagnosed diabetic subjects. Even with the improvements noted in the previously diagnosed diabetic subjects, their prevalences of dyslipidemia remained higher than in nondiabetic subjects. Among both newly and previously diagnosed diabetic subjects, the prevalence of hypertriglyceridemia tended to increase with worsening glycemia but there appeared to be little association between dyslipidemia prevalence and either type of therapy or frequency of physician visits in the preceding year. However, note that the sample size in certain subgroups is quite small. Thus, failure to achieve statistical significance could in some cases reflect a type II error.

A further limitation of these data is that they are cross sectional, thus making it difficult to distinguish cause and effect. For example, mild hyperglycemia

could reflect either therapeutic success or an intrinsically less severe disease process. Similarly, intensity of therapy could reflect either an aggressive physician or a sicker patient. By contrast, a low frequency of physician visits could reflect either an apathetic physician or an apathetic patient. Nevertheless, our results seem to imply that there is no combination of glycemic level, type of therapy, or frequency of physician visits that will return the prevalence of dyslipidemia in diabetic subjects to that observed in nondiabetic subjects. For example, in Table 5, even if we substitute less intensively managed patients (diet only therapy and <1 physician visit/yr) under the assumption that such patients have milder disease (rather than less aggressive management), the pattern of excess dyslipidemia prevalence in the diabetic subjects persists. (The data for these substitutions can be found in Tables 3 and 4.)

It might be argued that the level of glycemic control achieved in a community setting falls short of the optimum level and that had better control been achieved, the prevalence of dyslipidemia might have been reduced further, perhaps to levels seen in the nondiabetic population. More vigorous dietary management, for example, or more aggressive insulin therapy might have produced more satisfactory levels of glycemic control. However, other studies suggested that hyperinsulinization may be an independent risk factor for CVD (36–38), which raises the question of whether more aggressive efforts at glycemic control by this modality might actually be counterproductive. Conceivably, the benefits of more aggressive insulin therapy on the prevalence of dyslipidemia might be partially or wholly offset by an adverse effect of hyperinsulinization on cardiovascular risk.

The results presented herein point to the urgent need for large-scale randomized clinical trials to test the efficacy of various strategies for controlling dyslipidemia on reducing the risk of CVD in diabetic subjects. All current lipid-lowering trials have systematically excluded diabetic subjects. The distinctive metabolic abnormalities of diabetic patients make it necessary to replicate these trials in this patient population. We recently discussed the theoretical considerations suggesting that glycemic control might favorably alter lipid profiles in type II diabetic patients (39). On the other hand, the possible atherogenic effects of hyperinsulinization (36–38) raise concerns about overly aggressive hypoglycemic therapy. In fact, the only clinical trial that tested the effects of glycemic control on cardiovascular end points in diabetic patients (i.e., the University Group Diabetes Program) gave a negative result (40), compatible with the idea that offsetting influences might have been at work. Only clinical trials can define the relative trade-offs between more aggressive glycemic control versus direct pharmacological management of dyslipidemia. For example, nicotinic acid is a potent drug for managing dyslipidemia, which in nondiabetic subjects has been shown to reduce not only the incidence of ischemic heart disease but total mortality as well (41). However, its potential for raising blood glucose levels means that its use in diabetic subjects may necessitate escalating the hypoglycemic regimen (42). The Consensus Statement of the ADA recommends that clinical trials on controlling cardiovascular risk factors in diabetic subjects be undertaken as an urgent priority (18). Our results support this recommendation.

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