Extended-Release Niacin Treatment of the Atherogenic Lipid Profile and Lipoprotein(a) in Diabetes

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We tested the hypotheses that extended-release niacin is effective for the separate treatments of abnormalities in low-density liprotein (LDL) size, high-density lipoprotein (HDL)-2, and lipoprotein(a) [Lp(a)] without potential negative effects on glycated hemoglobin levels. The lipids that constitute the atherogenic lipid profile (ALP), such as triglycerides, small, dense LDL-cholesterol particle concentration, LDL particle size, total HDL-cholesterol (HDLc), HDL-2, and HDL-2 cholesterol concentration, as well as total LDL-cholesterol (LDLc) and Lp(a), were measured in 36 diabetic patients with primary abnormalities of LDL particle size (n = 25), HDL-2 (n = 23), and/or Lp(a) (n = 12) before and after extended-release niacin treatment. LDL particle size and HDL-2 were measured using polyacrylamide gradient gel electrophoreses and Lp(a) was measured by enzyme-linked immunosorbent assay (ELISA). After extended-release niacin, LDL peak particle diameter increased from 25.2 ± 0.6 nm to 26.1 ± 0.7 nm ($P < .0001$); small, dense LDLc concentration decreased from 30 ± 17 mg/dL to 17 ± 10 mg/dL ($P < .0001$); total HDLc increased from 42 ± 9 mg/dL to 57 ± 16 mg/dL ($P < .0001$); HDL-2 as the percent of total HDLc mass increased from 34% ± 10% to 51% ± 17% ($P < .0001$); and Lp(a) decreased from 37 ± 10 mg/dL to 23 ± 10 mg/dL ($P < .001$). Mean hemoglobin A_{1c} level was improved during treatment from 7.5% ± 1.6% to 6.5% ± 0.9% ($P < .0001$). A subset of patients who had no change in hemoglobin A_{1c} levels before and after treatment (6.8% ± 1% *v* 6.7% ± 1%; not significant) showed identical lipid changes. Twenty-two percent of patients were unable to tolerate extended-release niacin due to reversible side effects. These data indicate that in diabetic patients, extended-release niacin (1) is effective for separately treating diabetic dyslipidemias associated with abnormal LDL size, HDL-2, and Lp(a) independently of glycated hemoglobin levels; (2) must be used with modern and aggressive oral hypoglycemic agents or insulin treatment; and (3) is a major drug for the treatment of diabetic dyslipidemias because of its broad spectrum of effectiveness for the ALP and Lp(a).

CARDIOVASCULAR DISEASES mediate 80% of the mortality in diabetes, and asymptomatic diabetic patients have similar rates of cardiovascular mortality as nondiabetic individuals who have already had a first cardiovascular event. Thus, diabetes has been elevated to a coronary heart disease risk equivalent in the new National Cholesterol Education Program Program (NCEP) guidelines.[1] Recent studies also show high diabetes mortality rates after a first cardiac event, with 25% mortality by 1 month and nearly 50% after 1 year.[2] Recent randomized and masked interventional trials of diabetic dyslipidemias have shown remarkable reductions in coronary mortality.[3,4] Treatment of diabetic dyslipidemias with hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors can reduce relative mortality rates by 25% to 55%, but a substantial number of patients continue to have coronary mortality.

Diabetic dyslipidemias are characterized by elevation of serum triglycerides, reduction of total high-density lipoprotein cholesterol (HDLc) and HDL fraction 2 (HDL-2), reduced average low-density lipoprotein (LDL) size, and a preponderance of small, dense LDL particle mass.[5] These abnormalities comprise the atherogenic lipid phenotype or profile (ALP) and are highly prevalent. From our preliminary evaluation of 130 diabetic patients, when the ALP is combined with abnormalities of lipoprotein(a) [Lp(a)], 85% of type 2 diabetic patients are affected.[6,7] Abnormalities of LDL and HDL particle size are each present in more than 60% of type 2 diabetic patients.[6,7] Elevation of Lp(a) is present in 40% of type 1 diabetic patients, whereas the ALP is present in only 15% to 20% of type 1 patients.[7] In nondiabetic subjects, abnormalities of LDL size and Lp(a) each are associated with up to a 3-fold increase in the rate of cardiovascular events and HDL-2 levels are inversely correlated with the severity of coronary disease and its progression.[8-13] Thus, it is likely that the high prevalence and toxicity of the ALP and Lp(a) contribute to increased rates of cardiovascular death in both types of diabetes.

Currently, there is neither consensus nor guidelines regarding the treatment of abnormalities of LDL or HDL particle size or Lp(a) in diabetic or nondiabetic subjects. Although recent NCEP treatment guidelines recognized that these newer dyslipidemias are associated with a metabolic disorder characterized as an "emerging" risk factor, no diagnostic or treatment criteria were presented.[1]

Niacin has been shown to reduce cardiovascular mortality and is the only drug class documented to substantially enhance LDL and HDL particle size and Lp(a) levels in nondiabetic individuals.[14-19] An improvement in LDL particle size is also strongly associated with increased coronary vessel lumen width and other coronary vessel surrogates.[19,20] We have recently reported data showing similarly successful lipid treatment using high-dose rapid-release niacin in diabetic patients.[21,22] Nonetheless, niacin products have not gained wide acceptance for the treatment of diabetic dyslipidemias and are considered to be second-line agents to be used with caution because of a variety of adverse effects, including deteriorating blood glucose control.[23] These concerns were initiated before the development of newer and more effective treatment options and strategies to control hyperglycemia.[24] We have shown that successful treatment of the diabetic dyslipidemias with rapid-release niacin can occur without negatively affecting glucose control.[21,22]

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Prior to large, randomized, controlled and masked extended-release niacin interventions in diabetes, it should be ascertained whether extended-release niacin can be used to move (1) LDL size, HDL-2, and Lp(a) dyslipidemias into their recommended ranges, or (2) the traditional dyslipidemias to currently recommended guidelines. Further, the doses of extended-release niacin required need to be determined and strategies to avoid excessive hyperglycemia created. These goals are best met by preliminary, open-label, and flexible dosing studies. These points are emphasized by the recently published placebo-controlled, randomized and masked study of rapid-release niacin treatment in moderately hyperglycemic diabetic patients.[25] In this study, the mean total HDLc level was increased by 29% and into the range recommended by the current NCEP and American Diabetes Association (ADA) guidelines. However, because a niacin dosage reduction strategy was used to maintain constant blood glucose control, and due to the choice to employ traditional lipid measurements, several questions remain. A more recent preliminary report, again in a large, controlled and randomized trial, showed only minimal to modest alterations of the ALP parameters when a relatively low dose of extended-release niacin was used.[26] Thus, we ask the following questions in diabetic patients: (1) can extended-release niacin normalize mean levels of LDL size, HDL-2 percent and other ALP lipids, and Lp(a); (2) what is the required dose of extended-release niacin; (3) is extended-release niacin intolerance increased in diabetes; and (4) what is the effect of extended-release niacin on hemoglobin A_{1c} using increased antihyperglycemic medications rather than niacin reduction strategies to maintain glycemia?

MATERIALS AND METHODS

Subjects

Forty-six diabetic patients with abnormalities of the APL, defined by LDL peak particle diameter $\leq$ 26.3 nm, HDL-2 less than 40% of total HDLc, and Lp(a) $\geq$ 25 mg/dL, were evaluated at the Diabetes Research Center. These criteria were selected using the following rationale. For LDL size, the cut-off level for absence of cardiovascular events is greater than 26.3 nm[8-10]; a LDL size of greater than 26.3 nm has been previously recommended as the upper normal cut-off level.[5,10,27] We have also evaluated 68 asymptomatic normal subjects and found a mean LDL particle size of 27.3 $\pm$ 1.1 nm (2 SD), which indicates a lower range cut-off of 26.2 nm. The selection of HDL-2 less than 40% was based on the recommendation of Berkeley HeartLab (San Mateo, CA) recommendation, as well as a mean level of HDL-2 level in our group (n = 68) of 47% $\pm$ 22% (1 SD). Thus, an HDL-2 less than 40% represents a stringent value well within the normal range and near the mean normal value. Regarding Lp(a) greater than 25 mg/dL, this level has been previously recommended.[27]

All subjects provided written informed consent. Thirty-six patients were evaluable for dyslipidemic outcomes, whereas 10 were not evaluable due to drug-related side effects (see Results). The evaluable diabetic group consisited of 30 men and 6 women. There were 19% type 1 and 81% type 2 patients. Mean age was 59 $\pm$ 11 years (range, 34 to 80). Mean body mass index was 28 $\pm$ 4 kg/m^2 and mean body weight was 84 $\pm$ 16 kg; there was no change in these 2 parameters before and after treatment. Mean duration of diabetes for type 1 patients was 23 $\pm$ 5 years and for type 2 patients, 10 $\pm$ 9 years.

Research Design

Hypotheses. We made the following hypotheses: (1) Extended-release niacin can improve LDL size abnormalities associated with diabetes. (2) Extended release niacin can improve HDL-2 percentage abnormalities associated with diabetes. (3) Extended-release niacin can improve Lp(a) abnormalities associated with diabetes. (4) High-dose extended-release niacin treatment is not associated with a deterioration of glycemic control.

Patients. This open-label, uncontrolled, dosing and efficacy study used retrospective chart review analyses after aggressive antilipid treatment. Patients' lipid panels and treatments were routinely available to all patients and physicians in the United States. Results obtained before and after extended-release niacin treatment were compared. All subjects took extended-release niacin (Niaspan; KOS Pharmaceuticals, Miami FL) as outpatients, once daily. Initial doses were 500 to 750 mg, consumed 1 to 2 hours after dinner, with continuous escalation of doses over a period of 1 to 4 months. Detailed instructions were given regarding the timing of the extended-release niacin dose; timing was further customized for each patient if side effects were significant. In some patients, transient side effects of niacin were alleviated by 1 or 2 325-mg aspirin tablets 30 to 60 minutes before anticipated symptoms. This aspirin dose replaced the daily dosing for cardiovascular event prevention. Though common, flushing and pruritis usually resolve spontaneously after 5 to 10 days of continuous stable dosing. Since these symptoms appear related to prostaglandin D2, aspirin given as described above, or twice daily, or in a slow-release form once daily can be given to alleviate them.[28] Symptomatic patients were also asked to avoid alcohol, caffeine, spicy foods, or hot showers or baths during the time periods when symptoms are anticipated.

Dosing of extended-release niacin was assessed only by observing outcomes of LDL size, HDL-2 percentage, and/or Lp(a) levels after a minimum of 6 to 8 weeks on a fixed dose. Extended-release niacin doses were increased accordingly to achieve a normal or best possible value for these 3 lipid variables using goals of greater than 26.3 nm for LDL particle size, greater than 40% for HDL-2, and less than 25 mg/dL for Lp(a). To achieve these aims, doses of extended-release niacin exceeded that recommended by the manufacturer. Patients were asked to routinely monitor their blood glucose levels 2 to 4 times daily, ie, before meals and at bedtime during niacin use. Attempts were made when appropriate to modify niacin-induced hyperglycemia by increasing oral hypoglycemic agents or insulin dosages. This active and aggressive titration of oral agents and/or insulin was essential to maintain optimal glycemic status. None of the patients received thiazolidinediones, fibrates, cerivastatin, or atorvastatin during the observation period. Patients were permitted use of simvastatin or pravastatin at 20 or 40 mg daily. Statin doses were not altered immediately before or during extended-release niacin use. Since most patients in this study, both before and after treatment, were using pravastatin or simvastatin ($\leq$40 mg/d) for prevention of coronary events, we evaluated 130 randomly selected diabetic patients cross sectionally for total LDLc, LDL size, and small, dense LDLc concentration differences to insure these drugs did not effect the main outcome variables. For those subjects using a statin (n = 29), LDL particle size was 25.8 $\pm$ 1.0 nm (1 SD) and small, dense LDLc concentration was 21 $\pm$ 10 mg/dL, whereas for those subjects not using statins (n = 101), LDL particle size was 25.9 $\pm$ 1.0 nm and small, dense LDL concentration was 22 $\pm$ 20 mg/dL (P not significant for both parameters). Similar data have been found with fluvastatin in nondiabetic subjects.[29] Total LDLc levels in the same groups were 121 $\pm$ 44 mg/dL for those not using a statin and 104 $\pm$ 27 mg/dL for those using a statin ($P < .1$).

Biochemical analyses. Plasma samples for lipid and lipoprotein analyses were prepared from EDTA-treated blood within 30 minutes at 4°C and then frozen at -80°C until analysis. Triglyceride and lipoprotein cholesterol values (total LDLc and HDLc) were measured enzy-

matically (Cholestech Instruments, Hayward, CA). Lp(a) concentration was determined using an enzyme-linked immunosorbent assay (ELISA) kit [Macra Lp(a) Terumo Diagnostics Division]. Normal Lp(a) levels have previously been identified at less than 25 mg/dL.[10,11,27]

Identification and densitometric measurements of LDL species were performed after 2% to 16% polyacrylamide gradient gel electrophoresis (Alamo gels, San Antonio, TX) of plasma samples as previously described in detail.[30] Since densitometric assays may have wide data variation at lower optical densities, and are dependent on size standards, sample quantity must be sufficient; 4 standards are used for LDL and 5 standards for HDL gels. For all assays we used quadruplicate separate gel determinations. We used the lipid staining agent, Sudan black, in order to avoid heating the gels. Duplicate densitometric scanning is unnecessary using this system. Normal levels of LDL peak particle diameter have been previously described to be greater than 26.3 nm.[5,10,27,30] The intra- and interassay coefficients of variation were 0.6% and 0.8%, respectively, which are similar to that previously reported using Alamo gels.[31] Accuracy of peak particle diameter was estimated to be ±0.3 nm. To estimate small, dense LDLc concentration, the combined percentage of fractions IIIA and B plus IVA and B, from the total of 7 LDL fractions resolved by gel electrophoresis, was multiplied by the total LDLc concentration measured by the technique described above. Sudan black staining in LDL particles reflects about 61% total cholesterol.[32,33] Thus, by estimating total LDLc, multiplying by total percentages of fractions III and IV, and then multiplying by 0.61, one can estimate small, dense LDLc concentration. Using these calculations, normal mean small, dense LDLc concentration was 7 ± 4 mg/dL (range, 2 to 16 mg/dL; n = 38) in subjects (1) with no personal or family history of diabetes or early heart disease, (2) who are asymptomatic, (3) have a mean age of 33 ± 10 years, (4) comprised of 30 women and 8 men, (5) have a total LDLc of ≤ 160 mg/dL (mean, 113 ± 30 mg/dL), and (6) have a LDL peak particle diameter ≥ 26.4 nm. The rationale was applied that abnormally high total LDLc and low LDL size both predispose to coronary disease, and thus to determine the truly normal small, dense LDLc concentration, subjects used in the analysis should clearly not have had LDL series values leading to cardiac risk. Normal small, dense LDLc concentration levels determined using these criteria can be used as a treatment goal. Our normal levels of small, dense LDLc concentration were substantially lower than those recently reported of 30 mg/dL using ultracentrifugation methods in 10 control subjects (mean age, 30 years) comprised of 9 men and 1 woman, where no LDL size qualification was used[34] In 2 other reports using ultracentrifugation, normal subjects more closely resembling our subjects for gender and age with triglyceride levels less than 115 mg/dL, but without LDL size measurements, had a mean calculated small, dense LDLc concentration of 12 and 14 mg/dL.[35,36] The latter values are identical to those of our normal group (mean, 15 mg/dL) prior to deleting subjects based on LDL size. Among 11 diabetic patients in a prior report using ultracentrifugation, our values are about 50% lower, probably due to the higher mean total LDLc of 163 mg/dL versus 112 in our diabetic group, and higher mean triglyceride levels of 259 mg/dL versus 207 in our group.[34] When our diabetic patients are compared to patients with combined hyperlipidemia using ultracentrifugation, our values are virtually identical.[33]

To estimate the HDL-2 percentage, the combined percentage of 2a and 2b was determined by densitometry from the total of 5 resolved HDL fractions using 4% to 30% polyacrylamide gradient gel electrophoresis. Quadruplicate different gel runs were made for each sample. The intra- and interassay coefficients of variation were 3.9% and 4.9%, respectively. To estimate the HDL-2 cholesterol concentration, the combined percentage of 2a and 2b was determined and multiplied by the total HDLc concentration and then multiplied by 0.41. Sudan black staining in HDL particles represents about 41% cholesterol species.[32,33] Using this method, in subjects who (1) have no personal or family history of diabetes or early heart disease, (2) are asymptomatic, (3) have a mean age of 34 ± 9 years, (4) comprised 18 women and 6 men, (5) have total HDLc ≥ 45 mg/dL, and (6) have HDL-2 levels ≥ 40% of the total HDLc concentration, the mean HDL-2 cholesterol concentration is 18 ± 8 mg/dL (range, 10 to 42 mg/dL; n = 24). Normal levels of HDL-2 have previously been described to be ≥ 40% of the total HDLc concentration,[5,10] and our levels of HDL-2 cholesterol concentration are similar to those recently reported in adolescents using nuclear magnetic resonance technology.[37] Hemoglobin A_{1c} was measured using DCA 2000 (Abbott Diagnostics, Pittsburgh, PA) and Bio-Rad Variant (BioRad, Richmond, CA) assays with all data normalized to the Diabetes Control and Complications Trial (DCCT) format.

Statistical analyses. All data are presented as means ± 1 SD unless otherwise stated. Paired and unpaired *t* tests were used to determine significance.

RESULTS

Forty-six diabetic subjects receiving extended-release niacin treatment underwent periodic evaluations for LDL size, HDL-2, and/or Lp(a) abnormalities. Ten subjects (22%) were unable to tolerate niacin due to previously described reversible side effects such as bleeding ulcer (n = 1); blood glucose instability (n = 1); emesis (n = 1); visual blurring (n = 1); flushing, itching, or rash (n = 5); and/or liver enzyme elevations (n = 1). Thus, 36 dyslipidemic subjects (78%) who could tolerate and adhere to the extended-release niacin treatment protocol were evaluable for dosing and efficacy. The mean dose was 2,819 ± 821 mg/d (range, 1,000 to 4,000) taken once daily. There were no treatment differences between type 1 and 2 diabetes patients.

To determine the effect of extended-release niacin on LDL particle size, 25 patients were evaluated whose LDL peak particle diameter was ≤ 26.3 nm. As shown in Table 1, mean triglyceride levels were reduced nearly 48%, total LDLc was reduced by 18%, LDL peak particle diameter was increased by 0.9 nm, and small, dense LDLc was decreased by 44%. Triglyceride and total LDLc levels were moved well into the recommended ranges of the new NCEP and ADA guidelines. LDL size and small, dense LDLc, although showing marked improvements, remained just above our recommended range (see Methods), despite relatively large doses of extended-release niacin. If one selects the arbitrary criteria of less than 1% improvement in LDL peak particle diameter, or the latter remaining at less that 25.0 nm, as inadequate treatment after extended-release niacin, 5 of the 25 individuals (20%) were nonresponders, with LDL size changing from 24.8 to 25.1, 25.7 to 25.6, 26.1 to 26.2, 25.1 to 25.1, and 26.1 to 26.2 nm before and after 3,600 mg of extended-release niacin daily for each patient. These 5 nonresponders were known to be taking extended-release niacin appropriately since triglycerides, total LDLc, total HDLc, and/or HDL-2 levels responded substantially. Although these patients were refractory to LDL size change, one subject had a 66% reduction in small, dense LDLc and the other 4 had a concentration within 5 mg/dL of the post-niacin mean for the group.

Among those 23 patients with HDL-2 levels less than 40% who received extended-release niacin, Table 1 shows a 46% reduction in triglyceride levels, a greater than 36% increase in total HDLc, and a 47% increase in HDL-2. HDL-2 cholesterol

Table 1. The Effect of Niaspan on the Atherogenic Lipid Profile

	Before Niaspan	After Niaspan	*P*
LDL peak particle diameter and related lipids (n = 25)			
Triglycerides (mg/dL)	207 ± 98	108 ± 73	<.0001
Total LDLc (mg/dL)	112 ± 33	92 ± 32	<.01
LDL peak particle diameter (nm)	25.2 ± 0.6	26.1 ± 0.7	<.0001
Small, dense LDLc (mg/dL)	30 ± 17	17 ± 10	<.0001
HDL2 and related lipids (n = 23)			
Triglycerides (mg/dL)	185 ± 96	100 ± 76	<.0001
Total HDLc (mg/dL)	42 ± 9	57 ± 16	<.0001
HDL2 (%)	34 ± 10	50 ± 17	<.0001
HDL-2 cholesterol (mg/dL)	7 ± 3	14 ± 8	<.0001

doubled during treatment. If one arbitrarily considers a less than 15% increase in HDL-2 as inadequate, 4 individuals (17%) were nonresponders to extended-release niacin since HDL-2 levels before and after treatment were 38% and 32%, 34% and 38%, 35% and 34%, and 30% and 15% despite a mean daily dose of 3,000 mg. These patients were taking adequate doses as indicated by the substantial changes in triglycerides, small, dense LDLc mass, total LDLc, and/or total HDLc levels. In this refractory group, HDL-2 cholesterol was also nonresponsive with post–extended-release niacin levels near the pre-niacin level of 7 mg/dL.

To determine Lp(a) responses to extended-release niacin in the 12 diabetic patients with Lp(a) levels greater than 25 mg/dL, mean pre-niacin levels of 37 ± 10 mg/dL were reduced to 23 ± 10 mg/dL ($P < .001$). If one considers a less than 20% reduction of Lp(a) to be indicative of nonresponsiveness to niacin, there were 2 nonresponders (17%). Both patients had substantial responses to niacin of total LDLc, total HDLc, and/or triglycerides.

Evaluating whether extended-release niacin therapy in the 36 evaluable patients had a negative effect on hemoglobin A_{1c} levels, the pre-niacin mean hemoglobin A_{1c} level was 7.5% ± 1.6%, whereas after niacin treatment, it was 6.5% ± 0.9% ($P < .0001$). Since the ALP and Lp(a) improvement could be due to improved glycemic control, subjects were selected who had no significant change in hemoglobin A_{1c}, ie, mean levels of 6.8% ± 1% prior to and 6.7% ± 1% after extended-release niacin. In this subgroup, shown in Table 2, LDL size and other lipid parameter changes were similar to those in the total group reported in Table 1. Similar results were observed for HDL-2 and Lp(a) (Table 2). Thus, in this study, changes in the ALP during niacin therapy were not secondary to concomitant improvement in glycemia as estimated by glycated hemoglobin.

Finally, we evaluated changes in hypoglycemic medication doses before and during high-dose extended-release niacin treatment. Among the patients with stable hemoglobin A_{1c} (n = 14), 4 required no change, 6 required an increase in oral hypoglycemic agents, and 8 needed an increase in insulin dosage. Some patients were using combination oral agents and insulin. All 22 patients with a greater than 1% reduction in hemoglobin A_{1c} levels required additional medications: 45% oral agents and 75% insulin.

DISCUSSION

We have shown that extended-release niacin at does of 1,000 to 4,000 mg/d results in major improvements in mean levels of LDL and HDL particle sizes, small, dense LDLc, and HDLc and Lp(a) abnormalities associated with diabetes. Further, this treatment also corrects abnormalities of triglycerides, total LDLc, and total HDLc to current NCEP and ADA recommendations, despite the fact that these latter parameters were not used as our treatment goals.[1,23] Our results were also obtained without a deterioration of glycemic control. Finally, these ALP results confirm similar observations in nondiabetic subjects treated with niacin, as well as our prior studies using rapid-release niacin in diabetic subjects.[15-19,21,22]

Since both small, dense LDLc concentration and LDL peak or average particle diameter are important determinants of LDL content in endothelial plaque, it is important to increase not only the average size of LDL particles, but also, and perhaps more importantly, to reduce small, dense LDLc particle con-

Table 2. Patients With No Hemoglobin A_{1c} Change Before and After Treatment

	Before Niaspan	After Niaspan	*P*	n
Hemoglobin A_{1c} (%)	6.8 ± 1	6.7 ± 1	<.3	14
Triglycerides (mg/dL)	207 ± 104	111 ± 84	<.001	14
Total LDLc (mg/dL)	112 ± 24	89 ± 34	<.01	14
LDL peak particle diameter (nm)	25.3 ± 0.7	26.2 ± 0.8	<.001	14
Small, dense LDLc (mg/dL)	28 ± 15	14 ± 7	<.001	14
Total HDLc (mg/dL)	42 ± 9	62 ± 17	<.001	10
HDL-2 (%)	35 ± 8	50 ± 19	<.01	10
HDL-2 cholesterol (mg/dL)	7 ± 3	15 ± 10	<.1	10
Lp(a) (mg/dL)	36 ± 6	27 ± 11	<.1	6

centration. When comparing cardiac event risks, abnormal LDL size confers up to 3 times excess risk, whereas LDL particle concentration confers as much as 7 times the risk.[8,9,38] Small, dense LDLc concentration is a function not only of average LDL particle size, but also of total LDLc concentration. For example, if LDL particle size remains relatively unchanged after a specific treatment, and total LDLc concentration is sufficiently reduced, small, dense LDLc concentration will decrease as we and others have recently shown.[33,34,39-41] In the current study, extended-release niacin had a significant effect on LDL size; however, mean levels of small, dense LDLc mass remained substantially above the normal mean and minimally above the normal range levels. This is because extended-release niacin moves the average particle size toward normal, without reducing total LDLc concentration sufficiently to reduce mean small, dense LDLc concentration into the normal range. The effects of niacin on total HDLc, HDL-2, and Lp(a) also were relatively ideal at the doses used. Thus, extended-release niacin normalizes the mean levels of 4 of the 6 ALP abnormalities and Lp(a) without a negative impact on hemoglobin A_{1c}, assuming hyperglycemia is addressed appropriately. If only the responder patients are considered, extended-release niacin normalizes all values. Thus, for clinical purposes, 68% of diabetic patients are tolerant and responsive to extended-release niacin and will have virtual normalization of mean LDL and HDL particle size and/or concentration and Lp(a) levels.

The mechanisms of niacin action to mediate such a broad spectrum of action are complex and incompletely understood. Niacin's action begins by diminishing release of free fatty acids from adipose tissue, thus decreasing hepatic uptake and conversion to triglyceride, and ultimately very-low-density lipoprotein-1 (VLDL1) in diabetes.[42] By reducing intrahepatic triglyceride synthesis, niacin also enhances intrahepatic apolipoprotein B catabolism, thereby decreasing trigylceride packaging into VLDL synthesis and secretion.[42] Niacin derivatives also block the intrahepatic conversion of VLDL2 to VLDL1, further abrogating hepatic VLDL1 synthesis and secretion.[43] The cumulative effects of these niacin actions to reduce hepatic VLDL1 secretion potently decreases the formation of small, dense LDL, since the latter is derived from a VLDL1-dependent pathway.[44] Niacin also appears to decrease the activity of hepatic lipase, an important enzyme in the formation of small, dense LDL precursors and the direct conversion of precursor molecules to small, dense LDL.[44,45] Since VLDL1 and hepatic lipase are also involved in HDL-2 remodeling to smaller, more dense molecules, niacin has potent effects on elevating HDL-2 levels.[44] Niacin is also reported to selectively decrease hepatic removal of HDL-apolipoprotein AI, but not HDL cholesteryl ester, thus recycling HDL-apolipoprotein AI for further reverse cholesterol transport and other HDL functions to reduce atherogenesis.[42] These combined niacin actions increase both total HDLc and HDL-2. How niacin works to reduce Lp(a) is less well understood, but this action is clearly not related to profound lowering of total LDL levels, since atorvastatin does not reduce Lp(a) levels in diabetes.

For intolerant or nonresponsive patients, alternative treatments must be evaluated. The choice of agents to effectively treat ALP abnormalities to NCEP or ADA guidelines and to recommended levels of HDL and LDL particle concentration and size and Lp(a) is limited .[46] Recent data show atorvastatin, fibrates, and thiazolidinediones also to be useful for causing changes in LDL particle size or concentration as well as HDL size in diabetic patients, although the improvements caused by thiazolidinedione are rather modest and none of the above agents improve Lp(a) levels.[39,47-51] Furthermore, detailed results for LDL size, small, dense LDLc concentration, HDL-2, and/or Lp(a) using resins and nonatorvastatin HMG CoA reductase inhibitor drugs have not been not reported for diabetic patients. The cross-sectional data reported here suggest that some HMG CoA reductase inhibitors are not associated with improvement in LDL size or small, dense LDLc concentration in diabetes, whereas low-dose atorvastatin markedly decreases small, dense LDL mass in nondiabetic subjects with combined hyperlipidemia.[33] Simvastatin has also been shown to substantially reduce small, dense LDL mass in nondiabetic patients, which highlights the differences between the treatment of diabetic and nondiabetic subjects.[52] Insulin also improves LDL size modestly, but this effect may be due to improved glycemic control.[36] Thus, caution is advised when comparing ALP treatments in diabetic and nondiabetic subjects.

Although the HMG CoA reductase inhibitors have been shown to decrease cardiovascular mortality in diabetes, the improvement noted is most likely due to its anti-inflammatory properties,[53] since these agents, in doses commonly used, do not substantially reverse the diabetic dyslipidemic abnormalities of Lp(a)[38] or ALP parameters such as total HDLc,[3,54] triglycerides,[3,54] LDL size, or small, dense LDLc as reported here. These latter concerns are paradoxically not of current practical clinical importance, since a minority of diabetic patients have total LDLc measured, and when LDLc is measured and found to be increased, treatment guidelines are not achieved in more than 80% of cases.[55]

Although niacin products are thought to be contraindicated for diabetic patients due to deteriorating glycemic control,[23] our current and prior studies document that despite relatively high doses of extended- or rapid-release niacin, hemoglobin A_{1c} levels can actually fall if they were elevated prior to niacin treatment or can remain constant if they were ideal before niacin.[22] These observations were possible since some patients were already in excellent glycemic control prior to extended release niacin treatment, and in these subjects, hemoglobin A_{1c} levels remained unaltered (Table 2). Other patients were in less than ideal control, and despite high-dose extended-release niacin treatment, subjects experienced reduced hemoglobin A_{1c} levels, secondary to aggressive glycemic control. We have previously reported our strategy to increase medications for glycemic control in the 80% to 100% of patients who need more intensive blood glucose control secondary to increasing niacin therapy.[22,46] Our strategy is different from that reported in the recent Arterial Disease Multiple Intervention Trial (ADMIT), where niacin doses were lowered to maintain hemoglobin A_{1c} levels.[25] We have 2 concerns with the latter approach. First, the hemoglobin A_{1c} levels cannot be reduced and, second, lowering the niacin dose may decrease dyslipidemic effectiveness, although this was not the case in the ADMIT study. Our strategy of increasing hypoglycemic agents and niacin products should provide improved dyslipidemic and

glycemic control. The effective extended-release niacin doses for diabetic patients appear to be substantial for treating ALP and Lp(a). Although dose-response studies for ALP and Lp(a) have not been performed, a recent preliminary indicated that 1,500 mg/d of extended-release niacin is substantially less effective than the doses used in the current stud.[26] Dosing must be individualized depending on the severity of patients' dyslipidemias, and doses should be tritrated to achieve the recommended level for the most difficult to treat lipid parameters. These concepts are important in the context of randomized, large and masked clinical trials of diabetes, where both niacin and hypoglycemic drug dosing must be aggressive.

When one compares our diabetes-associated extended-release niacin data with those recently published in another diabetic patient study using rapid-release niacin, it appears that glycemic control may play a role in the effectiveness of niacin.[25] Thus, in patients with mean hemoglobin A_{1c} levels in the 7.6% range, triglycerides and total HDLc are improved by only 20% and 30%, respectively. In our study, where mean hemoglobin A_{1c} levels were maintained at 6.5%, triglycerides and total HDLc both improved by about 50% and 36%, respectively, despite similar niacin doses in each study. Furthermore, HDL-2 percentages were increased 55% in a nondiabetic population using 3,000 mg of rapid-release niacin.[56] These results are similar to the current data with the extended-release formation and our prior data with rapid-release niacin at near normal hemoglobin A_{1c} levels.[21,22] Since our patient group with elevated hemoglobin A_{1c} levels prior to extended-release niacin treatment had similar lipid reductions to our group that started with ideal levels, the threshold for this hypoglycemic effect on lipid lowering may be 7.5% to 8.5%, as judged from our studies and the ADMIT trial.[21,22,25] Thus, an important interpretation of these data may be that when aggressive niacin therapy is combined with intensification of glycemic therapy, the lipid responses to niacin products may be enhanced. Some caution reagrding this conclusion is justified, because the ADMIT trial patients (1) used a twice-daily dosing regimen of niacin rather than 3 times daily dosing, (2) represented a different and larger patient population, and (3) received less aggressive glycemic treatment. These data underscore the need for aggressive treatments and the interactivity of both the dyslipidemic and glycemic risk factors.

Intolerance to extended-release niacin is substantial: 22% of the individuals in this open-label trial were unable to continue the drug, despite using aspirin and detailed patient counseling. This represents an improvement over rapid-release niacin in our experience, since we found 35% of patients unable to continue treatment.[21,22] The prrevalence of intolerance to extended-release niacin in our study is higher than the 10% to 15% reported in larger, controlled trials.[15,16,56] Our results may be due to a higher mean dose of extended-release niacin. Hepatotoxicity in this group appears to be low, since only 1 patient had to withdraw, due to mild and reversible liver function abnormalities. When we examine high-dose rapid- and extended-release niacin products in our prior study plus this current study, 4 of 111 patients had to withdraw due to hepatotoxicity.[22] There is evidence that some slow-release niacin products actually enhance hepatotoxicity due to preferential conversion to a toxic metabolite.[57] Niaspan is relatively free from this effect, which may explain the relatively lower mild hepatotoxicity observed in the current study when compared to our niacin results.[22] It should be stressed that the dose of extended-release niacin used in the current study exceeds that recommended by the manufacturer, and that the full potential of adverse effects can only be determined by studies on a larger number of subjects. Also, some patients, although responsive to niacin in 1 component of the ALP, were nonresponders for 1 or more other components. The reason for this observation is unclear, but it is interesting since in these subjects, the usual tight linkage of each ALP component is violated. The HDL-2 nonresponders in the current study showed severely depressed HDL-2 cholesterol concentration, whereas the LDL size nonresponders had nearly normal small, dense LDLc concentration. Thus, nonresponsiveness of LDL size does not necessarily infer high levels of small, dense LDLc particle concentration. These results in the nonresponders suggest altered metabolic pathways from VLDL1 to small, dense LDL or HDL2.

In conclusion, extended-release niacin has a broad and potent treatment spectrum for treating diabetic dyslipidemias, such as the ALP and Lp(a), in those 68% of patients who can tolerate the drug and who are responsive.

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