Relationship between glycemic status and progression of carotid intima-media thickness during treatment with combined statin and extended-release niacin in ARBITER 2

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Background: We previously reported in a placebo-controlled study that extended-release niacin slowed the progression of carotid atherosclerosis when added to statin monotherapy. This analysis examines the relationship between glycemic status and the effects of niacin on common carotid intima-media thickness (CIMT) and HDL cholesterol.

Methods: Post-hoc, subgroup analysis of ARBITER 2, a randomized, placebo-controlled trial of once-daily extended-release niacin (1000 mg) added to background statin therapy in 167 patients (mean age 67 years) with known coronary heart disease. The primary analysis was a comparison of the primary endpoint, the change in CIMT, between participants with either normal glycemic status, diabetes mellitus (DM) or the metabolic syndrome (MS).

Results: Baseline cardiovascular risk variables were significantly worse in those with abnormal glycemic status, particularly among subjects with MS. Niacin increased HDL-C to a similar degree (~20%) across normals, DM and MS. Placebo-treated patients had the greatest CIMT progression, regardless of glycemic status. The lowest progression rate was observed in niacin treated patients with normal glycemic status. Among all niacin treated subjects, there was a significant linear relationship between change in CIMT and change in HDL-C ($r = –0.16$; $p = 0.05$), which was of similar magnitude in subgroups with normal glycemic status ($r = –0.23$; $p = 0.08$) and DM ($r = –0.22$; $p = 0.17$). In those with MS, there was no relationship between changes in HDL and CIMT, ($r = 0.11$; $p = 0.44$), whereas blood glucose was positive correlated to change in CIMT ($r = 0.30$; $p = 0.04$). In multivariable linear models controlling for MS characteristics and blood glucose changes, only the change in HDL independently predicted change in CIMT.

Conclusions: During niacin treatment, increases in HDL-C are related to changes in CIMT in the setting of both normal glycemic status and diabetes mellitus.

Keywords: atherosclerosis, risk factors, lipids, diabetes mellitus

Introduction

Atherogenic dyslipidemia, defined as low HDL-C, elevated triglycerides (TG), and increased levels of small-dense LDL-C contributes to the development of atherosclerosis and the risk of developing CHD among individuals with the metabolic syndrome (MS) and diabetes mellitus (DM) (Savage et al 2005). Thus the effect of niacin, which can favorably impact atherogenic dyslipidemia including increasing HDL-C concentrations by 20% or more (Guyton et al 1998), is of particular interest among these patient subgroups. ARBITER 2 was a double-blind, placebo controlled study of extended-release niacin (ERN; Niaspan® 1000 mg/d) on 12-month progression of carotid intima-media thickness (CIMT) among patients with known coronary heart disease, good control of their LDL-C during statin monotherapy, but moderately low HDL-C (Taylor et al 2004). The study found significant progression of carotid artery

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intima-media thickness (CIMT) among all placebo treated patients, whereas ERN resulted in a 21% increase in HDL-C and stabilized CIMT.

In the original report from ARBITER 2, a post hoc analysis suggested a possible attenuation of the atherosclerosis stabilization response to ERN among subjects with DM or MS. In this report, we explore this relationship further, specifically analyzing the relationships to CIMT progression within these subgroups and the relationship between the changes in CIMT and HDL-C.

Methods

Study population

This trial was a single center study conducted at Walter Reed Army Medical Center, a university-affiliated, suburban, tertiary care military medical center. The institution's Department of Clinical Investigation approved the study. Volunteer research subjects were recruited from the cardiology and general medicine services. The study included male and female patients, greater than 30 years old, with known coronary vascular disease. All subjects were required to be currently treated with a statin drug with documented LDL cholesterol below 130 mg/dL and HDL cholesterol below 45 mg/dL. Those with known intolerance to niacin, history of liver disease (cirrhosis, chronic hepatitis) or abnormal liver associated enzymes (>3 × the upper laboratory reference value) were excluded.

Randomization

After providing informed consent, subjects were randomized (allocation concealed) in a 1:1 fashion to either receive either extended release niacin (Niaspan) or matching placebo provided by Kos Pharmaceuticals, Inc. (Weston, FL, USA). Further details of the randomization procedures are as published (Taylor et al 2004). Study medication was initiated at a daily dose of 500 mg for 30 days, and then increased to 1000 mg for the duration of the 12-month study period. Study medication was taken at night with a recommendation it be co-administered with their usual daily dose of aspirin. All patients taking either vitamin C or vitamin E were strongly encouraged to discontinue their use of these supplements during the study to avoid possible interference with the response to niacin (Cheung et al 2001). Between December 2001 and May 2003, 167 patients were enrolled in the trial and the final follow-up was completed in May 2004. Patients were individually unblinded to their study medication assignment after completion of their 12-month endpoint assessment. The predefined primary endpoint of this study was the change in mean common carotid intima-media thickness after 1 year assessed within each study medication group using a paired t-test.

Cardiovascular medications and hypoglycemic medications were recorded from the patient history and the electronic medical record. Serial measurements of lipid concentrations, fasting blood glucose, and liver associated enzymes were performed. High-frequency ultrasound measurements of the common carotid artery intima-media thickness were performed at baseline and after 12 months. Further details of the analysis of CIMT and laboratory parameters are as previously reported (Taylor et al 2004).

The present analysis

The present analysis explores the relationship between the baseline presence of DM or MS, the assigned study drug (placebo and niacin) and the observed changes in CIMT (the primary endpoint of ARBITER 2). Diabetes mellitus and MS were determined using measurements from the baseline characteristics including historical variables, medications, and measured laboratory values. We defined DM using a composite definition including patient history, the use of hypoglycemic medications, or a fasting blood glucose ≥126 mg/dL. Among participants without DM, the MS was defined according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III guidelines using the baseline clinical and laboratory assessment (NCEP Writing Group 2001). This assessment occurred while the patients were taking their prescribed medications that included statin medications in all patients, and could also include antihypertensive medications or hypoglycemic agents.

Statistical analysis

This was a non-prespecified post-hoc subgroup analysis. Comparisons between patient categories (normal glycemic status, MS, and DM) were performed using Chi-square or ANOVA as appropriate. Bivariate correlations between the change in HDL-C and change in CIMT observed during trial were sought. We performed multivariable linear regression using the change in CIMT as the independent variable. Dependent variables including gender, metabolic syndrome variables and the change in HDL-C were entered into the model using both forward and backward entry. Models were tested for influential data points using leverage and colinearity diagnostics. The results of the model are reported as r values (partial correlations). All statistical analyses were

performed using SPSS software (version 13.0, SPSS Inc., Chicago, IL, USA). Values are reported as mean ± standard deviation, except where indicated. A 2-sided P value of ≤0.05 was considered statistically significant.

Results

The mean patient age was 67 ± 10 years and 91% were men. Known coronary heart disease was present in all 167 patients, with a prior history of myocardial infarction reported in 83 (49.7%), percutaneous coronary revascularization in 77 (46.1%), coronary bypass surgery in 68 (40.7%). Mean baseline lipid concentration included a total cholesterol 157 ± 27 mg/dL, LDL-C 89 ± 20 mg/dL, HDL-C 40 ± 7 mg/dL and triglycerides 161 ± 91 mg/dL. All patients were receiving statin drugs upon entry to the study with a mean duration of treatment of 4.8 ± 4.3 years. Most patients (n = 156, 93.4%) were being treated with simvastatin, and the majority (n = 160, 95.8%) were receiving a daily dose of 20 mg or above. All patients had non-insulin dependent diabetes mellitus. The proportion of subjects prescribed hypoglycemic medications including insulin, metformin, and sulfonylureas was similar in the niacin and placebo groups.

There were significant differences among baseline cardiovascular risk variables among patients with normal glycemic status, DM, and MS (Table 1). Past history and medications were generally similar in these groups, although those with DM were more commonly treated with angiotensin converting enzyme inhibitors. However, among measured cardiovascular risk variables, participants with metabolic syndrome had significantly higher blood pressure, triglycerides, BMI, and significantly lower HDL-C, compared with those with normal glycemic status and, for some variables, even those with DM (Table 2). Although this was in part related to the application of the definition of metabolic syndrome, it is notable that, in these individuals, metabolic syndrome was persistent, despite the frequent use of medications (eg, anti-hypertensive medications) to treat the metabolic syndrome components.

During treatment with the study drug, hypoglycemic medications were added to 2 subjects in the placebo group (one each, metformin, and sulfonylurea) versus 3 in the niacin group (insulin, n = 2; metformin n = 1). There was no significant difference between the placebo and ERN groups with respect to the change in fasting blood glucose values among subjects with either normal glycemic status, MS, or DM. Among either placebo or ERN treated subjects, similar changes in HDL-C were observed in all 3 groups (Table 3). Significant progression of CIMT was observed in all 3 placebo treated groups. In comparison, none of the ERN treated groups had significant CIMT progression. However, the difference in the change in CIMT between the placebo and ERN groups, although directionally similar, tended to be of lower magnitude in patients with DM or MS. In normal glycemic status, CIMT progression compared with placebo was reduced by 109% ($p < 0.05$), vs. 33% in metabolic syndrome and 53% in DM (p = NS for both comparisons with placebo) (Table 3 and Figure 1).

Table 1 Baseline characteristics of 167 patients randomly assigned to either placebo or extended-release niacin

	Placebo n = 80	Niacin n = 87	P
Male gender	74 (92.5)	78 (89.7)	0.52
Age, mean ± SD	68 ± 10	67 ± 10	0.64
Diabetes mellitus (n, %)	22 (27.5)	24 (27.6)	0.99
Hypertension (n, %)	61 (76.3)	64 (73.6)	0.69
Tobacco use (n, %)	5 (6.3)	12 (13.8)	0.23
Family history of coronary heart disease (n, %)	39 (48.8)	33 (37.9)	0.16
Metabolic syndrome	42 (52.5)	43 (49.4)	0.69
History of coronary heart disease			
Myocardial infarction	42 (52.5)	41 (47.1)	0.49
Percutaneous coronary revascularization	35 (43.8)	42 (48.8)	0.51
Coronary bypass surgery	28 (35.0)	40 (46.0)	0.15
Angina with documented ischemia	27 (33.8)	26 (29.9)	0.59
Medications			
Beta blocker	63 (78.8)	69 (79.3)	0.93
Aspirin	68 (85.0)	75 (86.2)	0.82
Angiotensin converting enzyme inhibitor	42 (57.5)	54 (62.1)	0.21
Insulin	8 (10)	9 (10.3)	0.94
Metformin	10 (12.5)	10 (11.5)	0.84
Sulfonylurea	9 (11.4)	8 (9.2)	0.64

Table 2 Measured baseline cardiovascular risk variables in subjects with normal glycemic status, metabolic syndrome, or diabetes mellitus

	Normal	Metabolic syndrome	Diabetes mellitus	ANOVA P
N	70	51	46	
LDL-C	91 ± 21	85 ± 15	89 ± 24	NS
HDL-C	43 ± 6	35 ± 4	40 ± 7	<0.001
TG	131 ± 62	181 ± 99	188 ± 104	0.001
Blood glucose	96 ± 12	101 ± 11	130 ± 44	<0.001
Systolic BP (mmHg)	127 ± 19	141 ± 20	135 ± 23	0.001
Diastolic BP (mmHg)	73 ± 12	78 ± 12	71 ± 14	0.012
Body Mass Index	27.8 ± 5.7	30.8 ± 5.3	30.6 ± 6.2	0.005
Waist girth (cm)	104 ± 15	112 ± 8	113 ± 16	0.001

On univariate analysis, there was a statistically significant inverse correlation between change in CIMT and change in HDL ($r = –0.16$; $p = 0.05$) which was of similar magnitude in the subgroups with normal glycemic status ($r = –0.23$; $p = 0.08$) and DM ($r = –0.22$; $p = 0.17$). No relationship between change in HDL-C and CIMT was observed in the MS subgroup ($r = 0.11$; $p = 0.44$). In multivariate models controlling for the DM or MS, and for the individual components of the metabolic syndrome, gender and change in HDL-C, only change in HDL-C was related (inversely) to change in CIMT (Table 3). In the subgroup of participants with MS, blood glucose level was positively correlated to change in CIMT ($r = 0.30$; $p = 0.04$). Controlling for the change in HDL-C, changes in BG were unrelated to the CIMT effects.

Discussion

ARBITER-2 was the first study to demonstrate the impact of combination therapy with statin and extended release niacin for the endpoint of CIMT in the setting of moderate increases in HDL-C (Taylor et al 2004). However, a blunting of the effect of ERN on CIMT appeared to be present in the subgroup of participants with either DM or MS, leading to concerns regarding therapeutic efficacy in this important subgroup. The present analysis shows the relationships between changes in HDL-C and CIMT were similar in those with either DM or normal glycemic status. However, among participants with persistent metabolic syndrome (defined as metabolic syndrome despite the use of medications to treat its components) in whom other cardiovascular risk factors were poorly controlled, the impact of raising HDL-C on CIMT appears to be blunted. This reinforces the multi-factorial nature of cardiovascular risk, for which the global control lipid and non-lipid risk factors is crucial.

Plasma levels of HDL-C, with its major apolipoprotein (apo) component apoA-I, are inversely associated with coronary heart disease (CHD) risk (Gordon et al 1989). As an emerging therapeutic target for primary prevention and secondary prevention of coronary heart disease, raising HDL-C is gaining increasing attention in recognition that the protection afforded by decreasing LDL-C, even to very low values, is incomplete (Cannon et al 2004; de Lemos et al 2004). A key function of HDL is its pivotal role in reverse cholesterol transport (RCT) (Zhang et al 2003), a dynamic process leading to the stabilization or regression of atherosclerotic plaque. Recent clinical evidence supporting this include the results of TromsØ study showed that elevated HDL levels were protective against plaque progression in right carotid artery (Johnsen et al 2005). In this study, transformation of the plaque mass into higher echogenicity was associated with reduced plaque growth. This finding is plausible because removal of lipids by HDL may decrease the echolucent proportion of the plaque and therefore make the regressed plaque more echogenic (fibrous) (Gronholdt et al 1998). In addition to the plasma level of HDL, the size

Table 3 Changes in HDL and carotid intima-media thickness with placebo or extended-release niacin among subgroups according to glycemic status

	Normal		Metabolic syndrome		Diabetes mellitus	
Study drug	Placebo	ERN	Placebo	ERN	Placebo	ERN
n	31	30	21	26	19	22
DHDL (mg/dL ± SD)	–1.1 ± 5.0	6.8 ± 12.2	1.6 ± 5.2	6.3 ± 5.6	–0.6 ± 3.0	6.4 ± 6.0
DCIMT (mm ± SEM)	0.044 ± .024	–0.004 ± .021	0.046 ± 0.012	0.031 ± 0.018	0.043 ± 0.017	0.020 ± 0.023

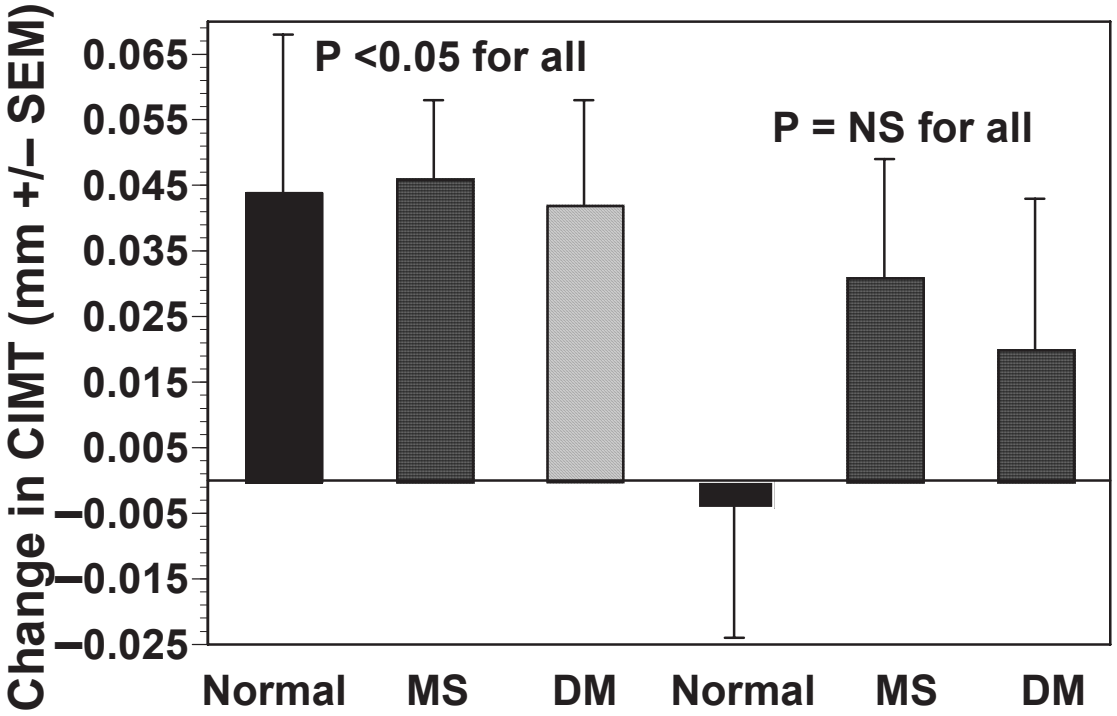

Figure 1 Carotid intima-media thickness (CIMT) change across 12 months in placebo and extended-release niacin treated patients in subjects with normal glycemic status, metabolic syndrome or diabetes mellitus.
Abbreviations: DM, diabetes mellitus; MS, metabolic syndrome; NS, nonsignificant.

and chemical composition of HDL affects its protective effect against atherosclerosis. In a HATS substudy, Schaefer and colleagues showed that treatment with niacin and simvastatin significantly increased the two large apoA-I-containing HDL subpopulations, α1 and pre α1. A significant inverse correlation ($r = –0.235$, $p < 0.01$) was noted between the changes in α1 HDL particle concentration and coronary artery stenosis progression (Asztalos et al 2003). In concordance with these observations, ARBITER 2 demonstrated for the first time an incremental independent effect of combination therapy with niacin and simvastatin to retard the progression of atherosclerosis in comparison to statin monotherapy. A significant, independent inverse correlation was found between the change in HDL-C and change in CIMT, which was notably of similar magnitude to that observed by Schaefer and colleagues.

Most patients with diabetes mellitus or metabolic syndrome have complex lipid disorders characterized by low HDL-C, high TG, high LDL-C, and small, dense LDL-C particles (Jacobs et al 2005). Combination therapy with niacin and a statin is an appropriate option for treating the cluster of lipid abnormalities in these patients because of their synergistic effect in increasing HDL-C, decreasing TG and LDL-C, and increasing LDL-particle size. In our study, similar changes in HDL-C were achieved in subgroups of normal glycemic status, DM and MS with combination therapy of niacin-simvastatin, suggesting the HDL-modulating effect of the combination therapy regimen was clinically equivalent in these three subgroups. However, although with similar directional trends, the smaller relative effect in retarding CIMT progression in DM and MS subgroups may be due to other poorly controlled cardiovascular risk factors, particularly in the subgroup with MS. The non-parallel effect between modulating HDL and retarding CIMT progression in these subgroups was further confirmed by correlation analysis. Although a similar magnitude of inverse correlation was observed between change in CIMT and change in HDL in the subgroups with normal glycemic status and DM, no relationship was observed in the MS subgroup. Differences among non-lipid factors between these subgroups and their interactions are likely critical, as shown by the positive correlation between blood glucose level and change in CIMT in MS subgroup.

Our results highlight the need to broadly identify and treat cardiovascular risk, including control of all lipid and

Table 4 Results of multivariate analysis of the relationships between change in CIMT

	Partial correlation	P
Change in HDL-C	–0.16	0.05
Gender	–0.09	0.29
Waist girth	–0.08	0.33
SBP	0.09	0.27
Baseline HDL-C	–0.12	0.15
Baseline TG	0.04	0.61
Baseline BG	–0.01	0.87

Abbreviations: BG, ; SBP, systolic blood pressure; TG, elevated triglycerides

non-lipid risk factors, concurrent with efforts to increase HDL-C. The present analysis was a non-prespecified subgroup analysis involving small subgroups, and thus requires cautious interpretation and is best regarded as hypothesis generating and requiring further study in dedicated clinical trials. Specifically, the original trial design was not powered to detect treatment-related differences on CIMT in either the DM or MS subgroups. Although the worse risk factor status among participants with the metabolic syndrome is in part based upon the application of the NCEP ATPIII definition, the individuals with persistent metabolic syndrome on pharmacotherapy for blood pressure and lipids distinguishes them as a higher risk subgroup and is a potential source of bias towards individuals with more severe metabolic syndrome. Thus, the results may not apply to individuals with de novo metabolic syndrome diagnosed off pharmacotherapy.

In conclusion, during niacin treatment, increases in HDL-C are related to changes in CIMT. Because the presence of other poorly controlled cardiovascular risk factors may blunt this effect, concurrent control of lipid and non-lipid risk factors is indicated. In particular, individualization of treatment plans based on risk stratification paradigms should be emphasized for dyslipidemic patients, especially patients with diabetes mellitus or metabolic syndrome. Large scale clinical trials focused on pre-specification of patient subgroups are warranted to determine the effect of niacin and other lipid-modulating agents on CIMT progression in patients with diabetes mellitus or metabolic syndrome.

Declaration

The opinions or assertions herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

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