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The effects of extended-release niacin on carotid intimal media thickness, endothelial function and inflammatory markers in patients with the metabolic syndrome

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The authors have declared that they have no interests which might be perceived as posing a conflict or bias.

SUMMARY

Background: Niacin is an agent that significantly increases high-density lipoprotein cholesterol (HDL-C), but its effects on surrogate markers of atherosclerosis and inflammatory markers are less clear. We studied the effects of niacin on carotid intimal media thickness (IMT), brachial artery reactivity as well as markers of inflammation and the metabolic profile of patients with metabolic syndrome. **Methods and results:** Fifty patients with the metabolic syndrome (Adult Treatment Panel (ATP) III criteria) were randomised to either extended-release niacin (1000 mg/day) or placebo. After 52 weeks of treatment, there was a change of carotid IMT of $+0.009 \pm 0.003$ mm in the placebo group and -0.005 ± 0.002 mm in the niacin group ($p = 0.021$ between groups). Endothelial function improved by 22% in the group treated with niacin ($p < 0.001$), whereas no significant changes were seen in the placebo group. High sensitivity C-reactive protein decreased by 20% in the group treated with niacin for 52 weeks ($p = 0.013$). Niacin increased HDL-C ($p < 0.001$) and decreased low-density lipoprotein cholesterol and triglycerides ($p < 0.001$) significantly, and there were no adverse effects on fasting glucose levels after 52 weeks of treatment. **Conclusion:** Extended-release niacin therapy effects a regression in carotid intimal medial thickness and improvement in metabolic parameters (increased HDL and reduced triglycerides). Furthermore, extended-release niacin may demonstrate an anti-atherogenic effect in the metabolic syndrome by improving endothelial function and decreasing vascular inflammation.

What's known
- There is an association with low HDL levels and increased incidence of cardiovascular disease.
- The incidence of the metabolic syndrome, which includes factors of dyslipidaemia, is increasing on a worldwide basis.
- Niacin therapy increases HDL and reduces triglyceride levels.

What's new
- Niacin therapy may have an anti-atherosclerotic effect by improving endothelial function and reducing inflammatory mechanisms.

Introduction

With the growing epidemic of obesity in developed countries, there has been enhanced awareness of the metabolic syndrome as an important risk factor for the development of diabetes mellitus and cardiovascular disease (1–3). While there has been controversy as to the exact definition, it seems clear that the metabolic syndrome is a well-delineated cluster of cardiometabolic risk factors, including central obesity, raised triglycerides, reduced high-density lipoprotein cholesterol (HDL-C), increased blood pressure and raised fasting plasma glucose (4,5). While insulin resistance appears to be the hallmark of the pathophysiology behind this process, there are parameters of dyslipidaemia seen in patients with metabolic syndrome (triglycerides > 150 mg/dl or 1.7 mmol/l; HDL-C < 40 mg/dl or 1.0 mmol/l in men and < 50 mg/dl or 1.2 mmol/l in women). This represents an important target for drug therapy with lipid-lowering agents (6). In addition, the association of metabolic syndrome to inflammation, critical in the atherosclerotic process, has been well documented (7,8).

Niacin remains the most effective agent in raising HDL-C, a well-established risk factor for atherosclerosis (9). However, recent data also suggests important effects of niacin on inflammation and endothelial function when added to existing statin therapy in patients with and without coronary artery disease (10–12). Similar anti-inflammatory effects of niacin were seen in patients with type 2 diabetes, where only about 50% were treated with statins (13). Furthermore, there is now direct evidence of the effects of niacin on progression of atherosclerosis through measurement of an established surrogate marker of clinical coronary events, carotid intima media thickness (cIMT) (14). In the ARBITER-2

study, investigators found a decreased progression of cIMT in patients with known coronary atherosclerosis already on statin therapy who were randomised to 1000 mg/day of extended-release niacin for 1 year (15). Nonetheless, recent data from a *post hoc* analysis of this study questions these anti-atherogenic effects of niacin in patients with insulin resistance as the positive effects on cIMT appeared to be only present in those with normal glycaemic states (16).

In the present study, we sought to determine in a prospective randomised manner, whether treatment with extended-release niacin (1000 mg/day) is associated with beneficial effects on cIMT, endothelial function, low-density lipoprotein cholesterol (LDL-C), HDL-C, triglycerides plus high-sensitivity C-reactive protein (hsCRP) levels.

Methods

Subjects

Men and women 18 years of age or older with the metabolic syndrome between September 2004 and September 2005 were enrolled into the study. Metabolic syndrome was defined according to the National Cholesterol Education Program III criteria and eligible subjects were required to meet at least three of the five criteria (4). Subjects were either unable or unwilling to take a statin and were excluded if they were on lipid-lowering therapy. Written informed consent was obtained in all patients. The study was conducted according to the Declaration of Helsinki as well as local institutional guidelines and was approved by the local institutional review board before implementation.

Study design

Subjects enrolled into the study were randomised in a double-blind manner and at a 1 : 2 ratio to either placebo or extended-release niacin (1000 mg/day, Slo-Niacin; Upsher-Smith Pharmaceuticals, Minneapolis, MN) and were treated for 52 weeks. Allocation concealment was maintained until the end of the study and subjects were instructed to take all medications in the morning. At the end of the study, pill counts were obtained to determine subjects' compliance with the protocol. A determination of > 80% pill use was noted to indicate subject compliance, and the compliance rate was 100% in both groups. The dose of niacin was chosen on the basis of previous findings in similar patient populations (13,15).

Carotid intima media thickness

Measurement of cIMT was accomplished using a 11/3 MHz Agilent probe using B-mode and an Agilent 5500 ultrasound machine with the subjects hyperextended at roughly 225° for imaging of the right carotid artery according to established protocols (17). After transverse imaging was performed for optimal image angle, longitudinal imaging was carried out on both the internal and common carotid arteries at the near and far walls. This was repeated in the left carotid artery at an extension of approximately 135°. To determine the peak systolic and diastolic flow velocities, spectral imaging and Doppler velocity waveforms were utilised. Both arteries were scanned for focal increases in IMT > 50% of surrounding walls to identify and size atherosclerotic plaques. The tests and measurements were recorded on super Video Home System (VHS) tape. Using B-mode ultrasound, the axial resolution was measured to be 0.27 mm with a precision of 0.04 mm, similar to previously reported findings (18). To reduce operator variability, measurements were made by the same technicians, under the guidance of the investigator. The intra-observer variability of IMT measurement was noted to be 0.01 ± 0.01 mm in studies at the common carotid artery far wall, similar to previously reported data determining intra- and interobserver variability.

Endothelial function

Endothelial function was measured non-invasively by using ultrasound to evaluate endothelium-dependent flow-mediated vasodilation (FMD) of the brachial artery. Measurements were performed according to the published guidelines (19). Briefly, subjects were positioned in the supine position with the arm in a comfortable position for imaging the brachial artery. A blood pressure cuff was placed on the forearm and a baseline rest image was acquired. Brachial artery was imaged above the antecubital fossa in the longitudinal plane. A segment with clear anterior and posterior intimal interfaces between the lumen and vessel wall was selected for continuous 2D grey-scale imaging. Blood flow velocity was estimated by time averaging the pulsed Doppler velocity signal obtained from a mid-artery sample volume. The cuff was then inflated to ≥ 50 mmHg above systolic blood pressure (SBP) to occlude arterial flow for 5 min. After cuff-deflation, the longitudinal image of the artery was recorded continuously from 30 s before and 2 min after cuff-deflation. A mid-artery pulsed Doppler signal was obtained on immediate cuff release and no later than 15 s after cuff-deflation to assess hyperemic flow velocity. After 15 min, nitroglycerin 0.4 mg was given sublingually and repeat images were obtained to determine endothelium-independent vasodilation. The diameter of the brachial artery was measured from longitudinal images in which the lumen–intima interface was visualised on both

the near (anterior) and far (posterior) walls. Once the image for analysis was chosen, the boundaries for diameter measurements were identified manually with electronic callipers (Medical Imaging Application Vascular Tools; Medical Imaging Application LLC, Coralville, IA). The average diameter was determined from at least three different diameter measurements determined along a segment of the vessel. Brachial artery diameter was measured at the same time in the cardiac cycle by use of ECG gating during image acquisition. The precision of our system is measured to be 0.004 mm, in the range of reported data from other laboratories (20,21). The FMD was typically measured as the change in poststimulus diameter as a percentage of the baseline diameter. In accordance with the guidelines (19), baseline diameter, absolute change and percentage change were recorded.

Laboratory measurements

Fasting plasma glucose levels were measured using the glucose dehydrogenase method after precipitation of proteins by trichloacetic acid. LDL and HDL-fractions were separated from fresh serum by combined ultracentrifugation and precipitation. Lipoprotein fraction cholesterol and triglycerides were measured enzymatically. hsCRP was measured by enzyme-linked immunosorbent assay.

Study end-points

The primary end-point of the study was changes in cIMT after 52 weeks of treatment. Secondary end-points included: (i) changes in FMD and (ii) changes in HDL-C, LDL-C and triglycerides.

Statistical analysis

All values are presented as mean ± standard deviation for continuous variables and as the percentage of total patients for categorical variables. Treatment groups were compared at baseline by using a Wilcoxon rank-sum test for continuous variables and a chi-squared model for categorical variables. The primary analysis was undertaken by paired-*t* test, followed by repeated-measures ANOVA incorporating age and gender as factors. A probability value of $p < 0.05$ was considered statistically significant, and all probability values were two-sided. Appropriate statistical power was given to detect a 15% relative change in cIMT over 52 weeks of treatment.

Results

Subject characteristics

A total of 50 subjects – 28 men and 22 women – with a mean age of 35.1 years (range: 21–45 years) were enrolled into the study. Of the 45 patients that completed the investigation, the mean SBP and diastolic blood pressure were 122.4 ± 20.0 mmHg and 71.8 ± 18.3 mmHg respectively (Table 1). The mean baseline fasting blood glucose was 102.7 ± 12.6 mg/dl (5.8 ± 0.7 mmol/l). Mean LDL-C, HDL-C and triglycerides were 126.6 ± 10.3 mg/dl (3.3 ± 0.3 mmol/l), 39.2 ± 5.3 mg/dl (1.0 ± 0.1 mmol/l) and 181.3 ± 31.4 mg/dl (2.0 ± 0.3 mmol/l) respectively. Waist circumference was 40.9 ± 3.0 inches (103.9 ± 7.6 cm). There were no significant differences between treatment groups with regard to demographics and baseline characteristics, except for age. In total, 45 subjects completed the study (30 niacin and 15 placebo). Niacin was discontinued in three cases because of nausea, flushing and myalgia. Two patients treated with placebo withdrew consent because of nausea.

Changes in LDL-, HDL-C and triglycerides after 52 weeks of treatment

Treatment with niacin was associated with a relative decrease in LDL-C of 17% from 125.7 ± 11.3 (3.2 ± 0.3 mmol/l) to 108 ± 15.4 mg/dl (2.8 ± 0.4 mmol/l) ($p < 0.001$), whereas in the placebo group, LDL-C was unchanged after 52 weeks of

Table 1 Baseline demographics and patient characteristics (completing study)

	Placebo group ($n = 15$)	Niacin group ($n = 30$)	
Age (years)	37.5 ± 9.6	34.6 ± 8.1	ns
Male/female	9/6	16/14	
SBP (mmHg)	121.2 ± 21.4	121.8 ± 19.7	ns
DBP (mmHg)	72.5 ± 17.7	71.0 ± 20.2	ns
Waist circumference (cm)	104.6 ± 8.3	101.6 ± 7.6	ns
Males	112.5	108.7	
Females	94.0	96.5	
Current tobacco use (%)	20.0	23.3	

SBP, systolic blood pressure; DBP, diastolic blood pressure; ns, not significant.

treatment (128.5 ± 7.8 mg/dl or 3.3 ± 0.2 mmol/l) at baseline; 127.8 ± 7.2 mg/dl or 3.3 ± 0.2 mmol/l) at 52 weeks, ns). HDL-C levels increased significantly by 24% in the niacin group (39.0 ± 5.7 mg/dl or 1.0 ± 0.2 mmol/l) at baseline to 48.5 ± 6.6 mg/dl or 1.2 ± 0.2 mmol/l) after 52 weeks, $p < 0.001$) and were unchanged after treatment with placebo (39.5 ± 4.7 mg/dl or 1.0 ± 0.1 mmol/l) at baseline and 38.5 ± 3.3 mg/dl or 1.0 ± 0.1 mmol/l after 52 weeks, ns). Triglycerides decreased significantly (Table 2) after 52 weeks of treatment with niacin from 183.2 ± 32.8 (2.1 ± 0.4 mmol/l) to 141 ± 27.8 mg/dl (1.6 ± 0.3 mmol/l) ($p < 0.001$), whereas in the placebo group no significant difference was detected (177.6 ± 29.2 mg/dl or 2.0 ± 0.3 mmol/l) at baseline, 178.9 ± 32.4 mg/dl (2.0 ± 0.4 mmol/l) after 52 weeks.

Blood glucose after 52 weeks of treatment

Fasting glucose was 102.2 ± 13.0 mg/dl (5.7 ± 0.7 mmol/l) at baseline (Table 2) and was not significantly different after 52 weeks in the placebo group [105.6 ± 13.9 mg/dl (5.9 ± 0.8 mmol/l), $p = 0.457$] and niacin group [104.1 ± 8.1 mg/dl (5.8 ± 0.5 mmol/l), $p = 0.447$]. There was no significant change in glycosylated haemoglobin levels after treatment in either group (data not shown).

Changes in hsCRP after 52 weeks of treatment

Mean hsCRP decreased by 20% in patients treated with niacin for 52 weeks ($p = 0.013$), whereas hsCRP was statistically unchanged after 52 weeks in the placebo group. This did result in a statistically significant change between the placebo and niacin groups ($p < 0.001$; Table 3).

Table 3 Changes in high-sensitivity C-reactive protein after 52 weeks of therapy in each group (values in mg/l)

	Placebo	Niacin
Baseline	2.04 ± 0.42	2.03 ± 0.42
52 weeks	2.07 ± 0.36	1.61 ± 0.41*†

*Differs ($p = 0.013$) from baseline. †Differs ($p < 0.001$) from placebo.

Changes in FMD and cIMT after 52 weeks of treatment

Endothelial function in placebo, as measured by per cent change in FMD, was not significantly changed after 52 weeks ($p = 0.25$). In contrast, FMD increased significantly by 22% after 52 weeks of treatment in the niacin group ($p < 0.001$; Table 4). When changes in FMD were compared between placebo and niacin, there was a statistically significant difference between the two study groups ($p = 0.007$). Of note, despite potential gender differences that have been previously documented with FMD, there was no significant difference in FMD based on gender in this study (mean FMD for males 4.521; mean FMD for females 4.700; $p = 0.24$).

After 52 weeks of treatment the mean cIMT increased from 0.694 ± 0.043 to 0.703 ± 0.042 mm in the placebo group, whereas in subjects treated

Table 4 Changes in flow mediated dilation (FMD) after 52 weeks of therapy in each group (values are percentage change in FMD)

	Placebo	Niacin
Baseline	4.64 ± 0.42	4.58 ± 0.57
52 weeks	4.81 ± 0.43	5.51 ± 0.59*†

*Differs ($p < 0.001$) from baseline. †Differs ($p < 0.001$) from placebo.

Table 2 Results at baseline and at 52 weeks

	Baseline	52 weeks	p-value
LDL in mg/dl (mmol/l)			
Placebo	127.4 ± 8.6 (3.3 ± 0.2)	127.8 ± 7.2 (3.3 ± 0.2)	0.686
Niacin	125.0 ± 11.8 (3.3 ± 0.3)	108.0 ± 15.4 (2.8 ± 0.4)	< 0.001
HDL in mg/dl (mmol/l)			
Placebo	38.8 ± 5.1 (1.0 ± 0.1)	38.5 ± 3.3 (1.0 ± 0.1)	0.390
Niacin	39.7 ± 6.3 (1.0 ± 0.2)	48.5 ± 6.6 (1.3 ± 0.2)	< 0.001
Triglycerides in mg/dl (mmol/l)			
Placebo	182.6 ± 30.4 (2.1 ± 0.4)	178.9 ± 32.4 (2.0 ± 0.418)	0.687
Niacin	177.7 ± 32.6 (2.0 ± 0.4)	141.0 ± 27.8 (1.6 ± 0.3)	< 0.001
Blood glucose in mg/dl			
Placebo	101.4 ± 14.1 (5.6 ± 0.7)	105.6 ± 13.9 (5.7 ± 0.7)	0.184
Niacin	103.6 ± 16.0 (5.6 ± 0.7)	104.0 ± 8.1 (5.6 ± 0.4)	0.566

Table 5 Changes in carotid intimal medial thickness (cIMT) after 52 weeks of therapy in each group

	Placebo	Niacin
Baseline	0.694 ± 0.043	0.700 ± 0.018
52 weeks	0.703 ± 0.042	0.695 ± 0.016
Regression in cIMT	13.3%	66.7%*

Patients with the metabolic syndrome were randomised to placebo or extended-release niacin (1000 mg po qd) for 52 weeks. cIMT was measured non-invasively by using B-mode ultrasound, as described in the Methods section. Values shown are in mm. *Value differs ($p = 0.006$) from placebo.

with niacin, cIMT decreased from 0.700 ± 0.018 to 0.695 ± 0.016 mm (Table 5). There was an increase in cIMT of +0.009 ± 0.003 mm in the placebo group and a regression of cIMT in the niacin group (−0.005 ± 0.002 mm, $p = 0.021$ between groups). Regression of cIMT, defined as a net decrease in mean cIMT at 12 months, was observed in two of 15 in the placebo group (13.3%), and 20 of 30 in the niacin group (66.7%; $p = 0.006$).

Discussion

While LDL-C remains the primary target of lipid-lowering therapy in the prevention of cardiovascular disease, there remains a significant number of events despite maximal therapy. Thus, the importance of targeting other lipid particles, such as HDL and triglycerides, which are associated with cardiovascular events, seems logical (22,23). Indeed, previously established agents that raise HDL-C, such as niacin, have shown important effects on relevant clinical end-points (24,25). In addition, the administration of niacin to patients with documented coronary artery disease was recently found to reduce the progression of cIMT (15). However, the use of niacin in patients with metabolic syndrome, an important precursor to both diabetes and cardiovascular disease, has not been well established. Furthermore, recent *post hoc* analysis from the ARBITER-2 trial raised questions about the safety of niacin treatment in patients with insulin resistance (16).

In this study, we confirmed the findings of some previous work and also answered some important questions about potential concerns regarding the use of niacin in a population of patients with metabolic syndrome but no overt coronary atherosclerosis. First, this study suggests a potential anti-inflammatory effect of niacin, as there was a significant reduction in CRP in patients treated with niacin. This has been also suggested previously in at least one study evaluating the use of extended-release niacin in patients with coronary disease (10). However, in the ARBITER-2 trial, there was no significant reduction in CRP in patients treated with niacin (15). The reason for this discrepancy is not clear, as both studies examined addition of extended-release niacin to patients with coronary vascular disease already on statins. Statins have now been established as having an important anti-inflammatory effect and reduce levels of CRP (26). Certainly, in our study, there may have been a more pronounced effect of niacin given the lack of statin use in these patients. Additionally, we used another commercially available form of extended-release niacin (Slo-Niacin) than the compound that was studied in the ARBITER-2 study (Niaspan). At least one other study in patients with overt diabetes mellitus and atherogenic dyslipidaemia found a trend towards a dose-related decrease in CRP in those treated with extended-release niacin for 15 weeks (13). Interestingly, the only other study to examine the effect of niacin on inflammatory markers in patients with metabolic syndrome did not find any effect on tumour necrosis factor-α, interleukin-6, soluble intracellular adhesion molecule (s-ICAM) or CRP, but did find significant increases in adiponectin and leptin (27). Similar to our study, no patients in this latter study were receiving any other drugs known to affect lipids. In trying to piece together the seemingly disparate results of these studies, one potential explanation is the different durations of treatment. With more sustained treatments of 52 weeks, as used in this study, it appears that there may develop a more significant anti-inflammatory effect that is not present with shorter treatment durations of 6 and 15 weeks, used in the above-mentioned studies.

This study also confirmed the findings on cIMT seen in the ARBITER-2 study. Specifically, treatment with extended-release niacin appears to have a sustained effect in reducing the progression of atherosclerosis. The mechanisms by which niacin is able to affect this change are not entirely understood. Recent data from the RADIANCE study suggested torcetrapib produces an even greater increase in HDL-C (52.4 mg/dl or 1.3 mmol/l to 81.5 mg/dl or 2.1 mmol/l) than that seen with niacin yet no appreciable difference in cIMT (28). Whether this lack of effect is related to detrimental effects specific to this class of agent, the mechanism by which they raise HDL levels or whether there is an alternative mechanism of niacin that prevents progression of atherosclerosis, are questions that have yet to be answered. Indeed, as novel therapies that target HDL are

developed and released, these will be important issues to consider.

There also appears to be a concomitant improvement in endothelial function with improvements in flow-mediated dilatation. There have been at least two trials that have shown beneficial effects on flow-mediated dilatation after treatment with niacin. The initial, small study of 21 patients with documented coronary atherosclerosis and low HDL had a significant improvement in flow-mediated dilatation after the 3-month treatment period (11). In addition, a more recent study in patients with atherosclerotic risk factors and low HDL, found that treatment with extended-release niacin for 3 months resulted in significant improvements in flow-mediated dilatation (12).

Furthermore, the present study did not find a significant increase in fasting glucose levels in those treated with niacin, a potential concern raised by previous investigators (16). The reason for this improvement may have to do with lower dosing of niacin and/or improved preparations. Thus, this study suggests that extended-release niacin can be used safely in this patient population, which has increased relevance when we consider the frequent presence of insulin resistance in patients with metabolic syndrome. Given the limited effect of statins on HDL-C, it may become increasingly important to target these lipid particles with alternative agents like niacin.

Nonetheless, there are several limitations to this study. First of all, this study had relatively small numbers of patients enrolled. Because of this limitation, there was no evaluation of discrete cardiovascular events. Second, this study had a relatively younger patient population than had been previously examined in other studies. What effect this could have on the results is not clear, but should be noted. Finally, patients treated with niacin were significantly younger at baseline than those treated with placebo. It would seem that if this had any effect on this study, it should have made it harder to show significant results, given the potentially healthier cohort in the niacin-treated arm.

To conclude, we have shown that extended-release niacin can be effectively used in patients with metabolic syndrome for a sustained period without ill effects on insulin resistance. In addition, this formulation of niacin has beneficial effects on inflammation, endothelial function and the progression of atherosclerosis in patients who are either unable or unwilling to take statin therapy. Given that it remains the most potent HDL raising agent available, it should be considered as important pharmacological therapy in patients with the metabolic syndrome.

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