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Effect of Extended Release Niacin on Serum Lipids and on Endothelial Function in Adults with Sick Cell Anemia and Low High-Density Lipoprotein Cholesterol Levels

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Abstract

Through bound apolipoprotein A-I (apoA-I), high density lipoprotein cholesterol (HDL-C) activates endothelial nitric oxide synthase, inducing vasodilation. Because patients with sickle cell disease (SCD) have low apoA-I and endothelial dysfunction, we conducted a randomized, double-blinded, placebo-controlled trial to test whether extended-release niacin (niacin-ER) increases apoA-I-containing HDL-C, and improves vascular function in SCD. Twenty-seven SCD patients with HDL-C <39 mg/dL or apoA-I <99 mg/dL were randomized to 12 weeks of niacin-ER, increased in 500mg increments to a maximum of 1500mg daily, or placebo. The primary outcome was the absolute change in HDL-C after 12 weeks, with endothelial function assessed before and at the end of treatment. Niacin-ER-treated patients trended to greater increase in HDL-C compared with placebo treatment at 12 weeks (5.1 ± 7.7 vs. 0.9 ± 3.8 mg/dL, one-tailed $p=0.07$), associated with significantly greater improvements in the ratios of low-density lipoprotein to HDL-C (1.24 vs. 1.95, $p=0.003$), and apolipoprotein B to apoA-I (0.46 vs. 0.58, $p=0.03$) compared with placebo-treated patients. No improvements were detected in three independent vascular physiology assays of endothelial function. Thus, the relatively small changes in HDL-C achieved by the dose of niacin-ER used in our study are not associated with improved vascular function in patients with SCD with initially low levels of apoA-I or HDL-C.

Keywords

Sickle cell; niacin; high-density lipoprotein; endothelial function

Introduction

Our laboratory has shown that patients with sickle cell disease (SCD) have significantly decreased HDL-C and apoA-I.^{1,2} We have also demonstrated that among SCD patients, those with lower apoA-I levels have impaired vasodilatory responses to acetylcholine during forearm blood flow strain gauge plethysmography (FBF), and they tend to have elevated estimated pulmonary artery systolic pressures, an echocardiographic marker of pulmonary hypertension.¹ In support of this finding, in pulmonary arterial hypertension patients without SCD, plasma HDL-C levels are low, and predict clinical worsening and death.³

Niacin-ER treatment promotes an increase in HDL-C containing apoA-I.⁴ In particular, niacin-ER inhibits the degradation and hepatic clearance of apoA-I-containing HDL-C, inhibits cholesterol ester transport to low density lipoprotein (LDL) cholesterol, and also inhibits the actions of hepatic lipase.⁵ Interestingly, a precursor of niacin, nicotinic acid was used in a case report in SCD with possible improvement in disease manifestations.⁶ We reasoned that niacin-ER administration would increase levels of HDL-C and apoA-I in SCD, and improve vascular function, and tested this hypothesis in a randomized, double-blinded, placebo-controlled trial. Our primary outcome was absolute change in HDL-C, and secondary outcomes included absolute change in apoA-I and physiologic assessments of improved vascular function.

Methods

This was a prospective, single-center, randomized, double-blinded trial comparing niacin-ER with placebo treatment. The National Heart, Lung, and Blood Institute's Institutional Review Board approved all protocols (ClinicalTrials.gov identifier NCT00508989). All subjects provided written informed consent.

Subjects enrolled met all of the inclusion criteria: males or females 18 – 65 years of age, electrophoresis or high performance liquid chromatography documentation of homozygous hemoglobin S only phenotype, HDL-C <39 mg/dL or apoA-I <99 mg/dL, hemoglobin >5.5 g/dL, or if hemoglobin <9.0 g/dL, absolute reticulocyte count >95,000/μL. Subjects met none of the exclusion criteria: acute pain crisis requiring intravenous analgesics within 2 weeks prior to enrollment, women who were pregnant, lactating, or not using birth control at the time of enrollment, hemoglobin SC disease or hemoglobin A >20%. In addition, subjects were excluded if they used aspirin or non-steroidal anti-inflammatory drugs within 1 week prior to vascular testing, or used caffeine the day of vascular testing. Pre-existing conditions that may independently affect endothelial function caused subjects to be excluded, including diabetes mellitus, cigarette smoking within one month prior to enrollment, renal failure, gout, and significant cardiovascular disease such as uncontrolled hypertension, peripheral artery disease, or severe hypotension. The use of medications including sildenafil, tadalafil, L-arginine, fibrates, inhaled nitric oxide, or any prostaglandins such as epoprostenol or

treprostinil within one week prior to evaluation, or any statin within 4 weeks prior to enrollment caused subjects to be excluded.

Simple randomization was used to assign subjects to either 12 weeks of placebo or niacin-ER. The medication was incrementally dosed in 500mg steps every 4 weeks as tolerated, to a maximum dose of 1500mg daily. Subjects were withdrawn if they developed: rhabdomyolysis (creatinine kinase > 5 times the upper limit of normal), clinically significant myositis, red cell lysis, or hepatocellular injury (alanine aminotransferase > 3 times the upper limit of normal, or >123 mg/dL), elevated prothrombin time or partial thromboplastin time (to >1.5 times control values), or intractable flushing unresponsive to ibuprofen therapy or dose reduction.

Our sample size calculation was based on a previous study of 11 subjects with coronary artery disease and initial HDL-C 36 mg/dL treated with niacin-ER (doses initiated at 375mg and titrated up to 1500mg) for 12 weeks.⁴ The mean HDL-C in this group increased from 30.1 to 40.5 mg/dL, with standard deviation of 4 mg/dL both before and after treatment.⁷ Therefore with $\alpha = 0.05$ and a 98% power, the sample size needed to detect a mean difference of 10 mg/dL with SD = 4 mg/dL was 13 in each treatment group [JMP version 8.0]. Our original protocol was designed to enroll 40 subjects with SCD who met eligibility criteria, 20 randomized to niacin-ER and 20 to placebo. An interim analysis was planned when 12 subjects in each group completed the study.

To measure vascular and/or endothelial function, forearm blood flow (FBF), flow-mediated dilation (FMD) of the brachial artery, and peripheral arterial tonometry were performed at baseline and after 12 weeks of treatment. FBF was measured similarly to Gladwin et al..⁸ In brief, brachial artery and antecubital vein catheters were placed in the arm, with the intra-arterial catheter connected to a pressure transducer and an infusion pump that delivered 5% dextrose-in-water at 0.5 mL/min.⁸ After 20 minutes of rest, acetylcholine was infused at 7.5, 15, and 30 μ g/min, sodium nitroprusside was infused at 0.8, 1.6, and 3.2 μ g/min, and N^G-monomethyl-L-arginine was infused at 4 μ g/min. Each of the infusions was followed by a 30-minute washout with 5% dextrose-in-water infusion at 0.5 mL/min and repeat of a baseline measurement.^{1,9} After 3 minutes of each infusion dose (or 5 minutes for N^G-monomethyl-L-arginine), FBF was measured.¹ Infusions were done with acetylcholine to test endothelium-dependent vasodilation, sodium nitroprusside to test endothelium-independent vasodilation, and N^G-monomethyl-L-arginine to measure basal nitric oxide production.⁸

FMD and peripheral arterial tonometry (measured byendoPATTM, Itamar Medical Ltd., Caesarea, Israel) both involved occlusion-reperfusion to create a reactive hyperemia response. Using methodology similar to Celermajer et al.,¹⁰ FMD involved use of an ultrasound probe to measure brachial artery diameter at baseline and during reperfusion after 5 minutes of occlusion by a sphygmomanometer inflated to suprasystolic pressures. FMD was calculated as the percent change in brachial artery diameter following release of the pressure in the sphygmomanometer, or (peak diameter – baseline diameter) / baseline diameter x 100%.^{7,10}

The endoPAT device involves a probe placed around a subject's distal fingertip of the second phalange.¹¹ As a sphygmomanometer is inflated around the subject's upper arm, plethysmography is recorded. The endoPAT software calculates a reactive hyperemia index from the pulse wave amplitude recorded at steady state and during reperfusion after 5 minutes of occlusion by a sphygmomanometer inflated to suprasystolic.¹² Reactive hyperemia index 1.67 is considered an indicator of endothelial dysfunction.¹¹

Laboratory evaluations were performed in the Clinical Center Department of Laboratory Medicine at the National Institutes of Health by standard clinical laboratory assays, including standard complete blood counts with hemoglobin F levels, iron-binding studies, serum chemistry, lipid panels, amino terminal brain natriuretic peptide, homocysteine, and C-reactive protein. Soluble vascular cell adhesion molecule, as well as nitrite (from plasma and whole blood) and nitrate levels were measured in our research laboratory.¹ Blood samples were drawn every 4 weeks (or every two weeks if there was elevated clinical concern for adverse effects and/or liver dysfunction). Pills were counted for compliance at each visit.

The pre-specified primary outcome was the absolute change in HDL-C after niacin-ER treatment, i.e. post-treatment (week 12) HDL-C minus pre-treatment (week 0) HDL-C. Changes in HDL-C were planned to be compared using a one-sided Wilcoxon rank-sum test because our primary hypothesis was that there would be a greater increase in HDL-C in the subjects taking niacin-ER. An interim analysis was planned after data were complete for 24 subjects, at a two-sided 0.002 significance level. The following results are from the interim analysis, after which time the study was stopped for futility. All p-values are reported for the testing of a two-tailed hypothesis, unless specified.

Results

A database of 305 patients was evaluated for eligibility: 27 adults with SCD were randomized to receive either placebo or niacin-ER daily for 12 weeks: 12 subjects received niacin-ER, and 15 received placebo (Figure 1). Three subjects were unable to complete the protocol: 2 in the niacin-ER treatment group and 1 in the placebo treatment group, due to reasons unrelated to study medication (Figure 1). The main side effect reported was flushing, with 4 (27%) placebo-treated and 10 (83%) niacin-ER-treated subjects reporting at least 1 episode of flushing, despite using a placebo completely void of any niacin. Three subjects did not reach the target dose of 1500mg due to dose-dependent symptoms of flushing; two subjects in the niacin-ER group achieved a maximal dose of 1000mg and one only tolerated a dose no greater than 500mg.

At baseline, subjects were similar on all variables except for a slight elevation in C reactive protein in the niacin-ER treatment group (placebo 0.2 [interquartile range 0.2-0.83] vs. niacin-ER 0.89 [0.61-1.39] mg/dL, $p = 0.048$; Table 1).

There were few differences between treatment groups in complete blood count or other lipid panel levels after 12 weeks treatment. The difference in hemoglobin S level is likely caused by differences in clinically indicated blood transfusion. Throughout 12 weeks, 4 placebo-

treated subjects required a total of 6 transfusions, while in the niacin-ER-treated group, no subjects required transfusion (Figure 1). This is an intriguing though preliminary finding. Compliance with study medication did not significantly differ between treatment groups.

After 12 weeks, all niacin-ER-treated subjects had an increase in HDL-C from baseline, although the increase was smaller than expected, and non-significant (mean change in HDL-C for placebo 0.9 ± 3.8 vs. niacin-ER 5.1 ± 7.7 mg/dL, one-tailed $p=0.07$; percent change in HDL-C for placebo 3.9 ± 14.0 % vs. niacin-ER 16.2 ± 21.8 %), resulting in a negative primary outcome (Figure 2). Four of the niacin-ER-treated subjects had substantial increases in HDL-C of 11-15 mg/dL (35 – 41% increase). The remaining 6 niacin-ER-treated subjects who completed the study had an increase in HDL-C less than 10 mg/dL.

In post-hoc analyses, small but significant lipoprotein changes were detected consistent with expected niacin effect. The low density lipoprotein to HDL-C ratio decreased by niacin-ER treatment (placebo 1.95 [1.70-2.10] vs. niacin-ER 1.24 [1.04-1.51], two-tailed $p = 0.003$, Figure 3A), despite the fact that neither absolute low density lipoprotein nor absolute HDL-C significantly changed in the niacin-ER-treatment group. Similarly, there was no significant change in apoA-I (mean *change* in apoA-I placebo 5.3 ± 15.4 vs. niacin-ER 5.5 ± 20.1 mg/dL, one-tailed $p=0.49$). However, the ratio of serum apolipoprotein B to apoA-I, a cardiovascular risk marker in the general population, decreased in the niacin-ER treatment group (placebo 0.58 [0.47-0.68] vs. niacin-ER 0.46 [0.40-0.49], two-tailed $p = 0.026$, Figure 3B).

To further assess the effect of complete-case statistical analysis, imputation was done using the mean value for each treatment group. With intention to treat analysis, the change in HDL-C trended closer to significance (placebo 0.9 ± 3.6 vs. niacin-ER 5.1 ± 6.9 , one-tailed $p = 0.037$). A futility analysis was done. Using 80% power, $\alpha = 0.05$, with a mean difference to detect of 6 mg/dL and a standard deviation of 12 (the greater of the two standard deviations in Table 1), 104 additional subjects would be required.

Endothelial function did not improve following niacin-ER treatment with any of the methodologies (Figure 4), including venous occlusion strain gauge plethysmography, flow mediated dilation, and peripheral arterial tonometry. Values were generally similar to results in the literature for adults with SCD).^{8,13-15}

Discussion

To date, 8 studies have assessed endothelial function following isolated niacin therapy, but none in subjects with SCD. In subjects with the metabolic syndrome, Vaccari et al., Westphal et al., and Thoenes et al. demonstrated a significant increases in HDL-C, but Westphal et al. failed to show corresponding improvements in flow mediated dilation, while Vaccari et al. and Thoenes et al. treated subjects with niacin for 52 weeks.¹⁶⁻¹⁸ In subjects with coronary artery disease already on statin therapy, Kuvin et al. showed a significant increase in HDL-C and corresponding improvement in FMD, while Andrews et al. were unable to show increased FMD despite increasing their subjects' HDL-C by >25%.^{7,19} Warnholtz et al. were only able to demonstrate improved FMD in the tertile of

subjects who began with HDL-C < 45.²⁰ Of two studies of healthy subjects with low HDL-C, only one demonstrated statistically significant increases in HDL-C after niacin treatment, and neither showed significant improvements in FMD.^{21,22} All of these authors used niacin dosing equivalent to or below our chosen 1500mg, but 3 chose to treat for longer than 12 weeks.^{16,18,19,23} Furthermore recently, a meta-analysis was published in JACC, which concluded that while niacin reduces cardiovascular disease events, this reduction was not directly related to patients' changes in HDL-C.^{24,25}

Our results might have been limited by the maximal dose of niacin-ER chosen in the study design. Clinically, doses of niacin used for subjects with cardiovascular complications are often increased to 2000 mg, the dose at which maximal benefit has been shown.⁴ Maximal efficacy of niacin has been shown at 1500 – 2000 mg, and that doses beyond 2000mg daily only saturate the pharmacokinetic system and increase the amount of niacin excreted.⁴ Other published studies in dyslipidemic patients without SCD suggested a beneficial effect of niacin 1500mg daily in both lipid levels and endothelial function.⁴ Alternatively, patients with SCD may be relatively resistant to HDL-C increases associated with niacin administration to other patient populations. Consistent with this possibility, a recently published metabolomics study of sickle erythrocytes found approximately 50% lower levels of the related metabolite niacinamide compared to control erythrocytes.²⁶

A change in liver function with mild elevation in liver enzymes is an established side effect of niacin therapy.⁴ One subject was withdrawn from the niacin-ER-treatment group because of such liver enzyme elevations, although it was unclear if this was caused by niacin-ER or the apparent vaso-occlusive crisis in this subject at the time of transaminase elevation. The hepatocellular injury side effects of niacin likely explain the slight increase in alanine and aspartate aminotransferases, as well as lactate dehydrogenase, in the niacin-ER treatment group, but these results did not otherwise reach abnormal levels. There was a greater level of hemoglobin S (%) in the niacin-ER-treated subjects than the placebo treatment group at the end of the study. However, there were 6 transfusions in the placebo treatment group throughout the course of the study and no transfusions in the niacin-ER treatment group, likely accounting for this difference. It is unlikely that niacin-ER in any way prevented the need for clinically indicated blood transfusions, although this possibility cannot be entirely excluded. Unexpectedly, soluble vascular cell adhesion molecule 1 was elevated in the niacin-ER-treated subjects compared to placebo (P=0.01). However, this finding is not significant after Bonferroni correction for multiple comparisons.

In blood flow physiology measurements, the expected changes in endothelial function were not detected, presumably because the small HDL-C/apoA-I response to niacin-ER was inadequate to improve endothelial function. Although FBF during the NOS inhibitor NG^G-monomethyl-L-arginine infusion was higher in the niacin-ER group, it was observed apparently only because blood flow did not return completely to the previous baseline level during the 30-minute washout period following sodium nitroprusside infusion. The physiological significance of this slow return to baseline blood flow in the niacin-ER subjects after a nitric oxide donor is uncertain.

Patients taking hydroxyurea, a drug known to reduce hospitalizations for vaso-occlusive crises, were not excluded from this study, but there was no indication that this design affected the outcome of the study. The distribution of hydroxyurea use was relatively balanced in the study arms (53% in the placebo group and 58% in the niacin-ER group) (Table 1). However, there were unexpectedly fewer hospitalizations for vaso-occlusive crises and fewer transfusions in the niacin-ER group than in the placebo group (0 vs. 4; Figure 1), but this was not statistically significant.

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References

1. Yuditskaya S, Tumblin A, Hoehn GT, Wang G, Drake SK, Xu X, Ying S, Chi AH, Remaley AT, Shen RF, Munson PJ, Suffredini AF, Kato GJ. Proteomic identification of altered apolipoprotein patterns in pulmonary hypertension and vasculopathy of sickle cell disease. *Blood*. 2009; 113:1122–1128. [PubMed: 19023114]
2. Zorca S, Freeman L, Hildesheim M, Allen D, Remaley AT, Taylor JGt, Kato GJ. Lipid levels in sickle-cell disease associated with haemolytic severity, vascular dysfunction and pulmonary hypertension. *Br J Haematol*. 2010; 149:436–445. [PubMed: 20230401]
3. Heresi GA, Aytakin M, Newman J, DiDonato J, Dweik RA. Plasma levels of high-density lipoprotein cholesterol and outcomes in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2010; 182:661–668. [PubMed: 20448092]
4. Al-Mohaissen MA, Pun SC, Frohlich JJ. Niacin: from mechanisms of action to therapeutic uses. *Mini Rev Med Chem*. 2010; 10:204–217. [PubMed: 20167004]
5. Kamanna VS, Kashyap ML. Mechanism of action of niacin. *Am J Cardiol*. 2008; 101:20B–26B. [PubMed: 18157959]
6. Grek IJ, Findlay M. Sickle cell anaemia; report of a case with a note on therapy. *S Afr Med J*. 1951; 25:780–784. [PubMed: 14892912]
7. Kuvin JT, Ramet ME, Patel AR, Pandian NG, Mendelsohn ME, Karas RH. A novel mechanism for the beneficial vascular effects of high-density lipoprotein cholesterol: enhanced vasorelaxation and increased endothelial nitric oxide synthase expression. *Am Heart J*. 2002; 144:165–172. [PubMed: 12094204]
8. Gladwin MT, Schechter AN, Ognibene FP, Coles WA, Reiter CD, Schenke WH, Csako G, Wacławski MA, Panza JA, Cannon RO 3rd. Divergent nitric oxide bioavailability in men and women with sickle cell disease. *Circulation*. 2003; 107:271–278. [PubMed: 12538427]
9. Gladwin MT, Vichinsky E. Pulmonary complications of sickle cell disease. *N Engl J Med*. 2008; 359:2254–2265. [PubMed: 19020327]
10. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK, Deanfield JE. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet*. 1992; 340:1111–1115. [PubMed: 1359209]
11. Faizi AK, Kornmo DW, Agewall S. Evaluation of endothelial function using finger plethysmography. *Clin Physiol Funct Imaging*. 2009; 29:372–375. [PubMed: 19552735]

12. Barringer TA, Hatcher L, Sasser HC. Potential benefits on impairment of endothelial function after a high-fat meal of 4 weeks of flavonoid supplementation. *Evid Based Complement Alternat Med*. 2011; 2011:796958. [PubMed: 18955351]
13. Belhassen L, Pelle G, Sediame S, Bachir D, Carville C, Bucherer C, Lacombe C, Galacteros F, Adnot S. Endothelial dysfunction in patients with sickle cell disease is related to selective impairment of shear stress-mediated vasodilation. *Blood*. 2001; 97:1584–1589. [PubMed: 11238095]
14. Eberhardt RT, McMahon L, Duffy SJ, Steinberg MH, Perrine SP, Loscalzo J, Coffman JD, Vita JA. Sickle cell anemia is associated with reduced nitric oxide bioactivity in peripheral conduit and resistance vessels. *Am J Hematol*. 2003; 74:104–111. [PubMed: 14508796]
15. Bereal-Williams C, Machado RF, McGowan V 2nd, Chi A, Hunter CJ, Kato GJ, Hunter L, Dalby CK, Hauser KP, Tailor A, Cannon RO 3rd. Atorvastatin reduces serum cholesterol and triglycerides with limited improvement in vascular function in adults with sickle cell anemia. *Haematologica*. 2012; 97:1768–1770. [PubMed: 22773602]
16. Vaccari CS, Nagamia S, Thoenes M, Oguchi A, Hammoud R, Khan BV. Efficacy of controlled-release niacin in treatment of metabolic syndrome: Correlation to surrogate markers of atherosclerosis, vascular reactivity, and inflammation. *J Clin Lipidol*. 2007; 1:605–613. [PubMed: 21291702]
17. Westphal S, Borucki K, Taneva E, Makarova R, Luley C. Extended-release niacin raises adiponectin and leptin. *Atherosclerosis*. 2007; 193:361–365. [PubMed: 16887123]
18. Thoenes M, Oguchi A, Nagamia S, Vaccari CS, Hammoud R, Umpierrez GE, Khan BV. The effects of extended-release niacin on carotid intimal media thickness, endothelial function and inflammatory markers in patients with the metabolic syndrome. *Int J Clin Pract*. 2007; 61:1942–1948. [PubMed: 17935553]
19. Andrews TC, Whitney EJ, Green G, Kalenian R, Personius BE. Effect of gemfibrozil +/- niacin +/- cholestyramine on endothelial function in patients with serum low-density lipoprotein cholesterol levels <160 mg/dl and high-density lipoprotein cholesterol levels <40 mg/dl. *Am J Cardiol*. 1997; 80:831–835. [PubMed: 9381993]
20. Warnholtz A, Wild P, Ostad MA, Elsner V, Stieber F, Schinzel R, Walter U, Peetz D, Lackner K, Blankenberg S, Munzel T. Effects of oral niacin on endothelial dysfunction in patients with coronary artery disease: results of the randomized, double-blind, placebo-controlled INEF study. *Atherosclerosis*. 2009; 204:216–221. [PubMed: 18822413]
21. Benjo AM, Maranhao RC, Coimbra SR, Andrade AC, Favarato D, Molina MS, Brandizzi LI, da Luz PL. Accumulation of chylomicron remnants and impaired vascular reactivity occur in subjects with isolated low HDL cholesterol: effects of niacin treatment. *Atherosclerosis*. 2006; 187:116–122. [PubMed: 16458316]
22. Kelly JJ, Lawson JA, Campbell LV, Storlien LH, Jenkins AB, Whitworth JA, O'Sullivan AJ. Effects of nicotinic acid on insulin sensitivity and blood pressure in healthy subjects. *J Hum Hypertens*. 2000; 14:567–572. [PubMed: 10980588]
23. Hamilton SJ, Chew GT, Davis TM, Watts GF. Niacin improves small artery vasodilatory function and compliance in statin-treated type 2 diabetic patients. *Diab Vasc Dis Res*. 2010; 7:296–299. [PubMed: 20667937]
24. Lavigne PM, Karas RH. The current state of niacin in cardiovascular disease prevention: a systematic review and meta-regression. *J Am Coll Cardiol*. 2013; 61:440–446. [PubMed: 23265337]
25. Lavie CJ, Dinicolantonio JJ, Milani RV, O'Keefe JH. Niacin therapy lives for another day-maybe? *J Am Coll Cardiol*. 2013; 61:2197–2198. [PubMed: 23541967]
26. Darghouth D, Koehl B, Madalinski G, Heilier JF, Bovee P, Xu Y, Olivier MF, Bartolucci P, Benkerrou M, Pissard S, Colin Y, Galacteros F, Bosman G, Junot C, Romeo PH. Pathophysiology of sickle cell disease is mirrored by the red blood cell metabolome. *Blood*. 2011; 117:e57–66. [PubMed: 21135259]

Figure 1. Study assignments and outcomes

27 subjects were randomized to niacin-ER or placebo treatment. 14 placebo-treated and 10 niacin-ER-treated subjects completed the study; the subsequent analyses are based on these 24 completed cases. PE, pulmonary embolism; VOC, vaso-occlusive crisis; ALT, alanine aminotransferase.

Figure 2. HDL-C changes during treatment

Circles represent placebo-treated subjects; triangles represent niacin-ER-treated subjects.

Changes are not statistically significant.

figure 3. Changes in apolipoprotein particles during treatment

Significant improvements were observed during treatment with niacin-ER compared to placebo in **(A)** the ratio of LDL-C to HDL-C, consistent with a parallel improvement in **(B)** the ratio of apolipoproteins B to A-I (apoB/apoA-I). Significance was calculated by Mann-Whitney test, graphs represent median values and error bars indicate interquartile ranges.

Figure 4. Changes in physiological measurements of vascular function at the beginning and end of treatment

Multiple methods were used to assess vascular function, and none showed improvements following niacin-ER treatment. Forearm blood flow was assessed by venous occlusion strain gauge plethysmography during brachial artery infusion of (A) endothelial-dependent vasodilator acetylcholine (ACh), (B) endothelial-independent vasodilator sodium nitroprusside (SNP), and (C) nitric oxide synthase inhibitor N^G-monomethyl-L-arginine (L-NMMA). Post-occlusion reactive hyperemia index (RHI) was measured by (D) flow-mediated dilation (FMD) and (E) peripheral arterial tonometry (EndoPAT). Squares indicate patients on niacin and circles indicate patients on placebo treatment, mean values and error bars show standard error of the mean; significance was calculated by two-way analysis of variance with repeated measures.

Table 1

Laboratory values after 12 weeks treatment.

Variable	Placebo n=14 Mean ± SD Median IQR		Niacin-ER n=10 Mean ± SD Median IQR		p-value
Compliance (pill counts)	92%	85-100%	87%	82-92%	0.34
Tricuspid Regurgitant Velocity (TRV, m/s)	2.2	0.7	2.3	0.2	0.95
Alkaline Phosphatase (U/L)	65	50-79	93	69-110	0.11
ALT (U/L)	21	16-27	31	24-36	0.01
AST (U/L)	24	18-33	37	30-54	0.02
C-Reactive Protein (mg/dL)	0.5	0.2-3.1	1.2	0.5-4.6	0.36
Lactate Dehydrogenase (U/L)	267	209-302	323	269-373	0.04
sVCAM-1 (ng/mL)	648	242	1024	383	0.01
Hemoglobin (g/dL)	8.8	1.2	9.2	1.6	0.47
Hemoglobin S (%)	73.6	14.6	84.4	5.8	0.02
Reticulocyte Count (K/μL)	200	101	199	84	0.98
White Blood Cell Count (K/μL)	7.9	2.8	7.9	1.7	0.99
Systolic Blood Pressure (mmHg)	107	103-117	117	112-125	0.03
Diastolic Blood Pressure (mmHg)	63	56-73	68	63-75	0.24
HDL-C (mg/dL)	31	3.6	37	12	0.11
LDL-C (mg/dL)	57	52-66	51	33-62	0.21
LDL-C / HDL-C ratio	1.95	1.70-2.10	1.24	1.04-1.51	0.003
apoA-I (mg/dL)	96	80-108	104	87-110	0.62
apoB (mg/dL)	54	48-65	48	44-50	0.07
apoB / apoA-I ratio	0.58	0.47-0.68	0.46	0.4-0.49	0.03
Cholesterol (mg/dL)	109	98-119	104	77-129	0.75
Triglycerides (mg/dL)	89	48	78	36	0.55

Results indicate mean ± standard deviation (SD), or median [interquartile range, IQR] if nonparametric. Calculations based on 14 placebo- and 10 niacin-ER-treated subjects.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; apoA-I, apolipoprotein A-I; apoB, apolipoprotein B; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; sVCAM-1, soluble vascular cell adhesion molecule 1.