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# Apple pectin for the reduction of niacin-induced flushing

**Patrick M. Moriarty, MD*, James Backes, PharmD, Julie-Ann Dutton, MS, RD, Jianghua He, PhD, Janelle F. Ruisinger, PharmD, Kristin Schmelzle, MS**

*Department of Medicine (Dr. Moriarty); Clinical Pharmacology (Dr. Moriarty); Atherosclerosis–LDL–Apheresis Center (Dr. Moriarty, Dr. Backes, Ms. Dutton, and Dr. Ruisinger); Department of Biostatistics (Dr. He and Ms. Schmelzle); and Schools of Pharmacy and Medicine (Dr. Moriarty, Dr. Backes, and Dr. Ruisinger), The University of Kansas Medical Center, 3901 Rainbow Blvd. Mailstop 3008, Kansas City, KS 66160, USA*

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**BACKGROUND:** Niacin, or vitamin B3, when used in high doses can significantly improve the levels of all major lipoproteins. Despite these benefits, the use of niacin is greatly limited secondary to benign yet bothersome cutaneous flushing primarily involving the face and upper extremities. Pretreatment with aspirin or other prostaglandin inhibitors has demonstrated significant reductions in niacin-induced flushing (NIF), but other treatment options are needed. Clinical and anecdotal evidence suggests the ingestion of pectin-containing fruits (eg, apple) mitigates NIF; however, clinical trials evaluating this are nonexistent.

**OBJECTIVE:** That pretreatment with encapsulated apple pectin would limit the incidence, severity, time of initiation, and duration of NIF.

**METHODS:** We enrolled 100 niacin-naïve subjects (n = 25 per group) and preteated them in a double-blind manner with apple pectin, apple pectin + aspirin, aspirin, or placebo, followed by a one-time 1000 mg dose of niacin extended-release (niacin ER). Subjects then assessed major flushing parameters hourly for the next 6 hours with a validated visual analog scale.

**RESULTS:** Apple pectin and aspirin each significantly lowered the duration of NIF and produced nonsignificant but positive improvements in all other major flushing parameters compared with placebo.

**CONCLUSION:** Apple pectin may potentially be an alternative to aspirin for the prevention of NIF. Larger trials are needed to further evaluate the benefit of pectin on NIF.


Coronary heart disease (CHD) continues to be the leading cause of morbidity and mortality in the United States, affecting an estimated 13 million individuals or approximately 7% of the total population.[1] Dyslipidemia is a major modifiable risk factor for CHD. The National Cholesterol Education Program Adult Treatment Panel's third report focuses on evidence from clinical trials demonstrating the importance of reducing low-density lipoprotein cholesterol to lessen the risk of CHD.[2] The Adult Treatment Panel's third report also emphasizes the excess CHD risk associated with elevated triglycerides levels and low levels of high-density lipoprotein cholesterol [(HDL-C); mixed dyslipidemia] and defined Lipoprotein a [Lp(a)] as an emerging CHD risk factor. Recent data further support this statement with findings demonstrating an unequivocal causal relationship with Lp(a) and CHD.[3]

Niacin, or vitamin $B_3$, when used at high doses (>500 mg daily), can safely and significantly modify all major

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* Corresponding author.
E-mail address: pmoriart@kumc.edu

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lipid parameters.[4] Niacin is especially effective at improving mixed dyslipidemia and is the primary agent for reducing Lp(a).[4] Findings from the Coronary Drug Project demonstrated that niacin reduced cardiovascular events,[5] whereas the recently published Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) study showed no reduction in the incidence of CHD when niacin was added to statin therapy.[6] A similar outcomes trial, Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE), has completed enrollment and should provide needed findings for the clinical use of niacin when used with a statin.[6]

The use of niacin is greatly limited due to adverse events, in particular cutaneous flushing primarily involving the face, torso, and upper extremities. Flushing is a self-limiting but common side effect that may be minimized by pretreating patients with aspirin, nonsteroidal anti-inflammatory agents (NSAIDs), or antihistamines.[7–9] Of these therapies, aspirin is considered the "gold standard" for preventing niacin-induced flushing (NIF). Even with these pretreatment measures, flushing still occurs in >50% of patients and is the major reason for discontinuation of therapy.[10] In addition, some patients are unable to use aspirin secondary to hypersensitivity or other contraindications. Thus, additional modalities to reduce flushing are essential.

Other potential options are being investigated. Maccubbin et al[11] recently reported that the selective prostaglandin $D_2$ receptor 1 antagonist laropiprant (LRPT), in combination with niacin extended-release (niacin ER), reduced the incidence, frequency, and intensity of NIF compared with niacin ER alone. However, a comprehensive safety profile still must be established to prove the safety of LRPT in human subjects before the Food and Drug Administration approves LRPT for clinical use in the United States. The HPS2-THRIVE study currently in progress is seeking to determine the safety profile of LRPT.

Clinical and anecdotal information suggests consuming fruits such as an apple or applesauce just prior to niacin dosing reduces the incidence and severity of flushing. The active ingredient in applesauce thought to minimize flushing is pectin,[12] which is composed of a complex set of polysaccharides found primarily in the cell walls of plants.[13] Certain fruits, primarily apples and citrus, are especially abundant in pectin and are often the sources used for pectin extraction. Commercially, modified citrus pectin can be obtained as a capsule or powder.

Pectin has always been a natural component of the human diet, and the joint Food and Agriculture Organization/World Health Organization committee consider it to be a safe additive with no limits on daily intake.[13] Pectin has numerous applications in the food, pharmaceutical, and other industries.[13] In food, pectin is commonly used as a jelling agent or stabilizer in jams, jellies, and juices. It is also available as a nutritional supplement and serves as a source of soluble fiber, providing modest reductions in blood cholesterol levels. Pectin has been a component in drug formulations for its stabilizing properties but also plays a role in drug delivery. For example, pectin has been used as an encapsulating agent to protect the gastrointestinal (GI) tract and drug while promoting the sustained release of medication. Ashford et al[14,15] evaluated pectin for colonic drug delivery and concluded it provided optimal protection of the drug during transit time while maximizing colon-specific delivery. Pectin has also demonstrated a prolongation of gastric-emptying,[16] potentially further promoting the slowed absorption of medication.[17] We hypothesized that pretreatment with encapsulated apple pectin would limit the incidence, time of initiation, duration, and severity of NIF compared with placebo.

## Methods

### Study design and protocol

This was a single-site, randomized, double-blind, placebo-controlled, 4-arm parallel design pilot study (Fig. 1). One-hundred healthy niacin-naïve subjects 18–70 years of age were randomized in a double-blind manner to receive apple pectin 2000 mg (n = 25), regular nonenteric coated aspirin 325 mg (N = 25), apple pectin 2000 mg + regular nonenteric-coated aspirin 325 mg (N = 25), or matching placebo (N = 25) 30 minutes prior to a one-time 1000 mg dose of niacin ER (Niaspan, North Chicago, IL). Prior to commencement, the study was approved by the institutional review board at the Kansas University Medical Center.

All treatments and matching placebo capsules were manufactured by a local specialty compounding pharmacy. The source of apple pectin was malus pumila, and the certificate of analysis indicated it contained no contaminants. The product was further analyzed and also found to be free of quercetin, another agent with potential effects on NIF.[18] All doses for each arm were packaged in identical bottles and labeled by a noninvestigator pharmacist according to a randomization table. The niacin ER 1000 mg tablets were provided by Abbott Laboratories (North Chicago, IL).

Initial screening occurred via the telephone. Subjects who met preliminary study criteria were scheduled for a screening visit. At the screening visit, a physical examination, comprehensive metabolic panel, and dietary counseling, including instruction on minimizing apple pectin consumption 7 days prior to the next visit, were performed. Upon successful screening, subjects were then asked to return for the dosing visit. For this visit, subjects were instructed to consume a low-pectin and moderate-fat breakfast approximately 1 hour before their appointment. Subjects also were counseled to avoid alcohol consumption within 12 hours of, and hot beverages immediately before the visit. Subjects were then randomized and administered either apple pectin, apple pectin + aspirin, aspirin, or placebo.

Thirty minutes after ingestion of the treatment or control, subjects were administered the niacin ER 1000 mg.