



Women's Health Update

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Two Important Interventions for Women and Cardiovascular Disease

Dyslipidemia of Diabetes, Metabolic Syndrome, and Elevated Fasting Glucose: How to Make the Most of Niacin by Tim Polacek, guest author;
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Type 2 diabetes, already an epidemic in the US, continues to increase. Additionally, untold numbers of the US population exhibit prediabetic conditions such as metabolic syndrome or elevated fasting glucose. As up to 80% of patients with diabetes will die of cardiovascular disease, this column will focus on typical atherogenic dyslipidemias associated with these conditions.¹

In the majority of patients with elevated lipoproteins, targeting LDL and total cholesterol reduction is the primary goal identified in the National Cholesterol Education Program (NCEP) Adult Treatment Panel III guidelines. The use of a synthetic or naturally occurring statin as a single agent effectively achieves these reductions in about 40% of patients.² However, treating LDL targets alone leaves significant residual risk, as roughly two-thirds to three-fourths of individuals will still go on to have a cardiovascular event, one example of which is the Heart Protection Study.^{3,4} In this study of simvastatin in 20,536 high-risk individuals over 5 years, the major vascular event rate for control and treatment groups was 25% and 20% respectively.

In diabetes and metabolic syndrome, LDL-targeted therapy alone may leave patients at even greater risk. This is because the typical dyslipidemia of these conditions is mixed, and includes elevated triglycerides, low HDL, and small, very dense LDL.⁵ Niacin favorably affects all of these lipid parameters, not only lowering LDL by 10% to 25%, but shifting them from the smaller, dense particles to larger, buoyant, less atherogenic particles. Triglycerides are reduced by 20% to 50%.⁵ With respect to HDL, niacin is widely regarded as the best single agent for increasing this subfraction from 15% to 35%.⁵ Finally, niacin is the only therapeutic agent known to lower Lp(a), a unique lipoprotein with atherogenic, thrombotic, and inflammatory properties.^{6,7}

When comparing this therapeutic profile with other agents, niacin appears in theory to be ideally suited to correct the mixed dyslipidemia of diabetes mellitus and metabolic syndrome. Historically, however, there have been significant reservations about the use of niacin in these patients. Since its use for cholesterol in the 1950s, niacin has been observed to increase fasting glucose in some patients.⁸ For many years, concerns of glycemic stability and even new onset diabetes led to these patients' being excluded from clinical studies. Gradually, with the increasing need for lipid treatment in these patients, clinical studies have more closely examined the effects of niacin on fasting glucose and insulin sensitivity. Two trials in particular, ADMIT and ADVENT, demonstrated favorable results in lipid parameters in individuals with DM, with few to no changes in glycemic status.^{9,10} ADMIT used immediate-release (IR) niacin in doses up to 1500 mg twice daily, and had modest effects on fasting glucose. These effects appeared temporary, as fasting glucose returned to baseline by week 16 of the trial. ADVENT used once-daily extended-release (ER) niacin and had no effects on fasting glucose, a very modest increase in HbA1c at the higher 1500 mg dose, and no changes in oral hypoglycemic agents. Another smaller study recently conducted in patients with MS is notable for using nonprescription, ER niacin 1000 mg once daily to demonstrate significant improvements in all lipid fractions, no changes in glycemic status, and a significant and sustained increase in adiponectin levels over 12 months.¹¹ The authors note that adiponectin has emerged as an important marker of insulin resistance and endothelial dysfunction, and low levels are strongly associated with MS and coronary heart disease.

While these placebo-controlled studies were reassuring with regard to glycemic status, they were not designed to demonstrate the effect of niacin on clinical outcome. This is where the Coronary Drug Project (CDP) comes in. Originally a six-year, multiarmed, placebo-controlled secondary



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prevention study, the niacin arm targeted an IR niacin dose of 1000 mg three times daily.¹² Due to tolerability issues, the average compliance-corrected dose reached was about 2000 mg daily. These patients demonstrated reductions in recurrent myocardial infarction (MI), nonfatal MI, coronary heart disease death, stroke, transient ischemic attack, new definite angina, and coronary surgery. A 15-year follow-up analysis (average 9 years after last study dose) demonstrated an 11% relative risk reduction in all-cause mortality.¹³ This total mortality reduction was similar, if not greater, in patients with a baseline fasting plasma glucose >100 mg/dl (5.5 mmol/dl). In 2001, an analysis of patients from the CDP with hyperglycemia or diabetes was reported. Grouped by baseline fasting plasma glucose, these six-year results demonstrated a trend for an increasing benefit in MI among those with the highest baseline glucose levels (see Table 1).¹⁴

Table 1:
Six-Year Results on Recurrent Nonfatal MI in CDP by Baseline Fasting Glucose

	Fasting Plasma Glucose*			
	<5.3 mmol/L	5.3–5.8 mmol/L	5.8–6.9 mmol/L	≥7.0 mmol/L
*Niacin %	11.1	9.8	10.6	7.1
†Placebo %	15.4	12.9	14.3	15.5
Odds ratio	0.68	0.73	0.71	0.42

*To convert to mg/dL, multiply by 18; †percent with MI

These analyses suggest that the long-term cardiovascular benefits of niacin therapy in the CDP outweighed any potentially adverse effects of niacin on glycemic regulation.

Consensus panels and guidelines have recently reflected this shift. Position statements from the NCEP, the American Diabetes Association, the American Heart Association, and the National Lipid Association share the opinion that glucose increases, if they occur, are clinically modest, and amenable to adjustments in oral diabetic therapy.¹⁵ DM patients should be monitored closely for glucose control during the titration phase of therapy.

So what form of niacin should one use and how should it be dosed? This is where the guidelines seem to fall short. Most practitioners are aware that IR forms cause more flushing, long-acting forms should not be used due to the risk of hepatotoxicity, and ER forms are somewhere in the middle. Inositol hexanicotinate (no-flush niacin) releases only trace amounts of nicotinic acid into plasma, and therefore has no effect on lipids.¹⁶ There is also consensus in that only niacin preparations with sufficient clinical data to define dissolution, bioavailability, safety, and efficacy should be recommended. Niaspan, having

*Nonprescription forms of niacin are sold as supplements and, as such, have not been evaluated by the FDA for therapeutic claims.

been approved by the FDA, has demonstrated safety and efficacy in numerous clinical trials, and is widely used by the medical community.¹⁶ According to Meyers et al. and Ito, nonprescription* extended-release formulations that should be recommended are Slo-Niacin (Upsher Smith) and Endur-Acin (Endurance Products Co.).^{17,18} A 2005 dissolution study of Niaspan and selected nonprescription ER niacin products demonstrated comparable dissolution times for Niaspan and Endur-Acin, with Slo-Niacin releasing somewhat faster (see Table 2).¹⁹

Table 2: Estimated Dissolution Rate of Extended-Release Formulations

Products	Mean ± S.D. % Niacin Released by 240 min	Estimated Mean ± S.D. Dissolution Rate ^a (mg/hr)
Niaspan	41.7±1.9	90.3±3.4
SLO Niacin	56.3±5.3	116.7±9.1 ^b
Endur-Acin	47.0±0.9	93.6±2.5

^aCalculations were normalized to a 1000-mg niacin preparation (n=3)

^bStatistically higher compared with the reference formulation, Niaspan, p <0.05

These data demonstrate an “extended release” profile for these preparations as differentiated in much of the medical literature, by “being absorbed over 8-12 hours, intermediate between IR and Long-Acting niacin.”²⁰ Niaspan and Slo-Niacin each use hydroxypropyl methylcellulose, a “polygel” formulation that is highly aquaphilic and has been noted to have some variability in dissolution and release according to changes in peristaltic activity.²² Endur-Acin utilizes a vegetable wax-matrix to produce a consistent, metered release, and has demonstrated excellent GI tolerability in clinical studies.²²

Sufficient clinical studies of these products and prescription Niaspan have been done to ensure safe and effective dosing with once- and twice-daily regimens. What is less well understood are the pharmacodynamic differences of different formulations *and regimens*. While IR forms are the best at raising HDL and have been used at doses up to 6 g, ER forms (dosed twice or three times daily) gain significant LDL effects at the expense of HDL and are generally limited to doses of 2 g. Dosing an extended-release form once daily more closely mirrors the kinetics and dynamics of IR niacin – that is, a total daily dose all at once results in a high serum peak that causes flushing, retaining the HDL improvements of IR, and equivalent LDL improvements on a mg/mg basis.²¹ This was demonstrated in a study of Niaspan 1500 mg at night compared with plain niacin 1500 mg in divided doses. LDL, TG, and HDL changes were all identical. Studies of nonprescription ER niacin brands in divided doses have consistently demonstrated two to three times the potency of IR on LDL and are generally limited to not more than 2000 mg before liver enzyme elevation occurs.²² This is also why once-daily ER can be pushed to higher doses (provided the patient tolerates the flush); higher doses increase the LDL response while still allowing a significant trough with no exposure to the liver.

With these differences in mind, one should decide on the primary goal of niacin therapy in order to determine how to dose niacin. If HDL elevation and TG reduction are the primary goal, then either multiple-dosed IR or a once-daily ER should be chosen. This would be the reasonable choice when adding niacin to an existing LDL therapy, or using niacin in a patient with normal LDL but low HDL. When tolerance due to flushing becomes an issue, or when LDL targeting is the primary goal, a twice-daily ER preparation can be used safely with careful titration at doses up to 2000 mg.²³ Regardless of the form of niacin or dosing regimen you choose, patients must have LFTs and uric acid monitored frequently during the titration phase, and periodically thereafter.

D-Ribose in Cardiac Function

Adenosine triphosphate (ATP) is central to the function of every cell in the body, and we rely on it as our energy currency. Without ATP, energy to sustain life would cease, and ribose is the fundamental building block of ATP. While clinicians may be more familiar with the use of ribose supplementation in chronic fatigue syndrome and fibromyalgia, this column explores its use in cardiovascular disease.

Cardiovascular disease is the most prevalent adult health problem in the US and the number one cause of death. In addition, 20% of men and women over age 40 are at risk for developing congestive heart failure (CHF) during their lifetimes.²⁴ Diastolic dysfunction has been identified as a major predictor of CHF risk, and ribose directly maintains adenine nucleotide pools that are necessary to maintain cardiac diastolic function and increase the energy reserve of the heart.^{25,26} Studies analyzing the effect of ischemia on myocardial function and metabolism have reported a reduction in ATP levels along with suppression of diastolic function after an ischemic episode.²⁷ Other investigations have hypothesized that an ATP insufficiency may be involved in ischemic CHF. Many CHF patients have abnormal diastolic function, and based on animal studies of ribose supplementation, demonstrating a shortened time to regenerate myocardial ATP levels following ischemic episodes, researchers asked whether ribose supplementation may improve diastolic function and quality of life in individuals with CHF.^{28,29}

A prospective, double-blind, randomized, crossover study was conducted to assess the effect of D-ribose supplementation on cardiac function and quality of life in 15 individuals with coronary artery disease and CHF.³⁰ D-ribose or placebo was administered as a powder 5 g three times a day, for 3 weeks; and after a 1-week washout, patients took the alternative regimen for a second 3 weeks. Myocardial function was assessed with echocardiography, quality-of-life questionnaire, and cycle ergometer testing. Neither D-ribose nor placebo significantly affected left-ventricular volume, stroke volume, or left-ventricular ejection fraction. However, D-ribose resulted in a higher atrial contribution to left-ventricular filling, a smaller left-

atrial dimension, and a shortened E wave deceleration compared with placebo. Peak work capacity was not altered by either D-ribose or placebo, but patients receiving D-ribose did have a significant improvement in their overall quality-of-life index score and improved physical function and improved exercise tolerance.

During the diastolic phase of the heartbeat, the heart's ability to relax depends on calcium ions' being pumped out of the cell. In order for the ventricle to fill completely, complete relaxation is necessary so that adequate filling of the ventricle can occur; and to achieve this ventricular relaxation, a fully charged ATP pool is required. Ribose is directly related to ATP concentration and recovery and diastolic cardiac function. Animal studies show that when ribose is given to hearts after a period of ischemia, cardiac ATP levels increase and diastolic function increases.³¹ There are numerous clinical and laboratory studies showing that supplementing with ribose will enhance the recovery of adenine nucleotide pools as well as enhancing diastolic function in heart pathology.³²⁻³⁵

Ribose has also been shown to increase tolerance to myocardial ischemia in individuals with coronary artery disease (CAD).³⁶ Twenty men with severe CAD underwent treadmill stress testing. Patients were randomly assigned to 3 days of placebo or 60 g daily of ribose supplementation. Exercise testing was repeated on day 5. ST-segment depression was significantly greater in the ribose group than in the placebo group. The ribose-treated group also had significant changes in both time to ST depression and time to moderate angina, whereas these were not significant in the placebo group. In essence, these individuals with CAD who received ribose for 3 days had an improved tolerance to ischemia.

As a result of this research, clinicians are learning to use ribose supplementation to improve cardiac function, exercise tolerance, and quality of life in patients with CHF in particular, but also in ischemic heart disease, angina pectoris, and cardiomyopathy. Additional research demonstrates the cardioprotective benefit of ribose supplementation in those with healthy hearts, to improve anaerobic energy reserves, and in raising the cardiac tissue hypoxic threshold such that during periods of intense exercise and endurance sports, cardiac stress is reduced because of greater cardiac muscle energy stores.³⁷⁻³⁹ While the cardiac research on ribose supplementation is small and preliminary, it suggests that cardiac patients, especially those with CHF and ischemic heart disease, could benefit from the cardioprotective benefits of ribose supplementation. Future research will clarify the benefits of D-ribose supplementation to cardiac patients and hopefully confirm these small studies.

Disclosure

Tim Pollack is the medical liaison for Endurance Products Inc.



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Tori Hudson, ND, is the co-owner and director of Education and Research for Vitanica, as well as on the scientific advisory board of Biogenesis, Nordic Naturals, Natural Health International, and Integrative Therapeutics.

Notes

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