

Proposal: A Pre-Meal Beet Juice “Cocktail” for Prevention and Control of Type 2 Diabetes

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Abstract

Recent studies show that high-nitrate diets promote endogenous generation of nitric oxide (NO), especially in tissues that are relatively hypoxic; hence, such diets may promote vascular health and appropriate tissue perfusion, and have been shown to have clinical antihypertensive and platelet-stabilizing activity. Moreover, such diets tend to increase NO generation in skeletal muscle fibers, an effect associated with a more efficient utilization of ATP during muscle contraction. There is reason to suspect that increased generation of NO in muscle fibers might also promote increased insulin sensitivity by boosting GLUT4 expression while promoting mitochondrial biogenesis; this could rationalize epidemiology observing lower diabetes risk in those consuming diets rich in nitrate-rich green leafy vegetables. Beet juice is also a potent natural source of nitrates, and has been employed in clinical studies evaluating the impact of high-nitrate diets; it has the additional benefit of being exceptionally rich in potassium. A simple beet juice “cocktail”, made by adding apple cider vinegar, high-viscosity glucomannan powder, and a non-caloric sweetener to beet juice, is highly palatable, and may have especial utility for diabetes prevention and therapy if administered prior to meals, since both vinegar and glucomannan can slow the absorption of co-ingested carbohydrate, effectively lowering the glycemic index of meals. Hence, by slowing postprandial glucose absorption while concurrently promoting improved muscle insulin sensitivity, regular use of such a cocktail could alleviate the postprandial glucolipototoxicity thought to precipitate beta cell dysfunction in at-risk subjects. Vinegar may also promote insulin sensitivity and vascular health via systemic effects on AMP-activated kinase activity. Glucomannan has the potential to decrease LDL cholesterol and aid appetite control. This proposal aggregates the multiple health benefits of dietary nitrate, potassium, acetate, and soluble fiber.

High-Nitrate Diets May Improve Muscle Insulin Sensitivity

Recent studies reveal that dietary nitrate – derived primarily from green leafy vegetables – can be reduced sequentially to nitrite and nitric oxide (NO) *in vivo*; the amount of NO evolved from feasible dietary intakes of nitrate is physiologically meaningful, as it can evoke a hypotensive response that may be clinically useful in hypertensives, and decreases platelet aggregability *ex vivo*.¹⁻⁷ This finding is of particular interest in light of the fact that endogenous arginine-dependent production of NO is often compromised in vascular disorders, owing to uncoupling of NO synthase and/or increased ADMA levels.^{8,9} As is well known, physiological NO production helps to prevent atherogenesis, medial hypertrophy, and ventricular hypertrophy, while

stabilizing platelets and arterial plaque; hence, it plays a key role in the maintenance of vascular health.⁹⁻¹¹ There is also evidence that efficient cerebrovascular NO production may reduce risk for Alzheimer's disease,¹² and that NO mediates a portion of the protective impact of estrogen on bone density.¹³ Fortuitously, the vasodilatory potential of dietary nitrate may be greatest in vascular beds that are relatively underperfused, inasmuch as deoxyhemoglobin and other deoxygenated heme enzymes can efficiently reduce nitrite to NO.^{14, 15} For example, administration of nitrate-rich beet juice to elderly subjects has recently been shown to selectively boost blood flow to frontal lobe white matter regions of the brain that are prone to become ischemic in the elderly.¹⁶ Thus, nitrate-rich diets may have potential in the management of chronic or intermittent ischemic disorders, helping to match tissue perfusion to metabolic need.^{17, 18} These considerations may help to rationalize previous epidemiological studies linking increased intakes of green leafy vegetables to decreased risk for coronary disease or stroke.¹⁹⁻²³

However, epidemiology also suggests that risk for type 2 diabetes may be lower in those who consume increased amounts of green leafy vegetables.²⁴⁻²⁶ Of related interest is a report in which green vegetable consumption correlated inversely with insulin levels in Chinese women – suggesting that green vegetables might promote insulin sensitivity.²⁷ Whereas a link between increased NO production and protection from vascular disorders is readily rationalized,²⁸⁻³⁰ NO-mediated protection from diabetes is not so readily predictable.

I propose that a high dietary intake of nitrate may reduce diabetes risk and promote improved insulin sensitivity by boosting expression of GLUT4 and increasing mitochondrial biogenesis in skeletal muscle fibers. A recent study shows that physiological concentrations of NO increase the expression of both GLUT4 mRNA and protein in rat myotubes.³¹ This effect appears to be mediated by cGMP as well as by AMPK activation; the activating effect of NO on AMPK in muscle appears to be independent of cGMP, and may reflect increased activity of a kinase targeting this enzyme, and/or decreased activity of a phosphatase targeting it.³¹ Joint activation of guanylyl cyclase and AMPK likewise appears to mediate the a PGC-1alpha-dependent enhancement of mitochondrial biogenesis triggered by NO in muscle³²⁻³⁵ – an effect which presumably could complement the favorable impact of increased GLUT4 expression on insulin sensitivity.³⁶⁻³⁹ Conceivably, PGC-1alpha is also a mediator of the impact of NO on GLUT4 expression.⁴⁰

NO can be generated from nitrite within myofibrils by deoxymyoglobin-mediated reduction.⁴¹ A favorable impact of nitrite infusion on myocardial ischemia-reperfusion damage observed in mice was found to be absent in myoglobin knock-out mice.⁴² In light of the very short half-life of NO, the fact that nitrite can be reduced to NO within myofibrils is compatible with the possibility that physiological levels of nitrite can indeed influence muscle function via NO. Moreover, there are now several reports that nitrate-rich diets can reduce the O₂ cost of exercise, apparently by increasing the efficiency with which ATP promotes myofibril contraction; this evidently demonstrates that nitrate-rich diets can promote physiologically significant generation of NO within muscle fibers.^{7, 43, 44}

It should be noted that the chief mechanism whereby exercise training enhances insulin sensitivity (independent of its long-term impact on weight control) appears to be an increase in GLUT4 expression.^{45, 46} Thus, it is suggested that an adequate intake of dietary nitrate may mimic – and likely complement – the favorable impact of exercise on insulin sensitivity. Furthermore, if dietary nitrate does indeed promote muscle mitochondrial biogenesis, the favorable impact of this effect on capacity for fatty acid oxidation may have the potential to promote insulin sensitivity both acutely – by decreasing muscle fiber accumulation of ectopic fat metabolites that impair the efficiency of insulin signaling – and chronically, by improving the capacity of exercise training to promote leanness. Indeed, there is evidence that muscle mitochondrial density tends to be below average in patients with metabolic syndrome or type 2 diabetes, and that a genetic propensity for low muscle mitochondrial density may increase risk for these disorders.⁴⁷⁻⁵⁰

A further corollary is that nitrate-rich green vegetable juices and powders, as well as beet juice, may have some utility for improving glycemic control in type 2 diabetes – while lessening the elevated vascular risk associated with this disorder.

A Beet Juice Cocktail for Diabetes Prevention and Control

A recent survey of common vegetables concludes that celery, cress, lettuce, red beetroot, spinach and rucola tend to be rich with nitrate (>250 mg/100 g); the value measured for spinach was 741 mg/100 g.³⁰ This suggests that heavy consumption of spinach, spinach juice, and spinach powder might be a practical approach to achieving the physiological benefits of dietary nitrate. However, most clinical trials evaluating the physiological impacts of high dietary nitrate have employed beetroot juice (more commonly referred to as beet juice in the U.S.), which is said to provide nitrate in a range of 11-45 mM per liter. The daily intake of beet juice in most studies has been 500 ml, which corresponds to 340 mg -1.4 g nitrate daily.^{16, 43, 51} (Why this range is so large remains unexplained.) Beet juice has the ancillary advantage of being remarkably rich in potassium – about 93 mmol (3,600 mg) per liter;⁵¹ hence, if two one-cup (250 ml) servings of beet juice were added to the average American diet, while keeping total calorie intake constant, daily potassium intake would rise by about 50% in adult males, and 66% in adult females (based on data from the 2007-2008 NHANES survey). This would seem likely to notably amplify the cardiovascular protection afforded by the nitrate content of the juice – in part because modest increases in serum potassium provoke increased endothelial NO release, while also quelling endothelial oxidative stress and exerting a natriuretic effect.⁵²⁻⁵⁷

To amplify the potential of beet juice for prevention and control of diabetes – while improving its flavor – I propose a simple “beet juice cocktail”:

To a cup of (unsalted) beet juice, add about one tablespoon (15 ml) of apple cider vinegar, a packet of non-caloric sweetener (e.g. sucralose or stevia), and, optionally, a rounded half teaspoon (2.5-3 g) of high-viscosity glucomannan powder (e.g. Shimizu Propol A™). If using

glucomannan, stir intermittently for several minutes so that the glucomannan granules are well suspended. Ingest prior to the main meals of the day.

The vinegar and sweetener tend to make the beet juice more palatable, whereas the glucomannan is flavorless. However, the key purpose of the added vinegar and glucomannan is to decrease the effective glycemic index of the subsequent meal. Both vinegar and glucomannan have been shown to have this effect in previous clinical studies.⁵⁸⁻⁶⁴ Both tend to slow gastric emptying, and they also tend to slow the digestion and absorption of starch and oligosaccharides in the intestinal tract. The impact of glucomannan in this regard likely reflects the highly viscous fiber network it engenders, which could be expected to slow the interaction between amylase and starch granules. The retardant effect of vinegar (acetic acid) on polysaccharide absorption has not yet been adequately explained, although it has been shown that long-term exposure of intestinal epithelial cells to acetic acid *in vitro* reduces the disaccharidase activity of their luminal membranes;⁶⁵ if this effect can occur acutely *in vivo*, it may rationalize evidence that vinegar can slow the absorption of starch and disaccharides, but not of glucose.⁶²

By blunting and retarding the glycemic response to meals, a beet juice cocktail containing vinegar and glucomannan could be expected to alleviate the postprandial glucolipotoxicity that ultimately precipitates beta cell dysfunction and overt type 2 diabetes in subjects predisposed by poor muscle insulin sensitivity.⁶⁶ Indeed, the drug acarbose, which slows starch absorption by inhibiting alpha-glucosidase, has been shown to prevent or postpone the onset of diabetes in glucose-intolerant subjects,⁶⁷ and habitual ingestion of high-glycemic-index foods has been linked to increased diabetes risk.⁶⁸ But the beet juice cocktail proposed might be expected to potentiate this benefit by improving muscle insulin sensitivity via NO generation, aiding the efficient storage of absorbed carbohydrate postprandially. Moreover, avoidance of high postprandial glycemic excursions may itself benefit muscle insulin sensitivity, by avoiding rebound increases in fatty acid flux.⁶⁹ Evidently, these effects could be of benefit not only for diabetes prevention, but also for aiding glycemic control in patients who are already diabetic.

Complementary Benefits of Vinegar and Glucomannan

In addition to influencing carbohydrate absorption, vinegar may also have protective systemic effects, rooted in its ability to activate AMP-activated kinase (AMPK) via the AMP generated during acetate metabolism.^{70, 71} AMPK boosts the activity of eNOS via phosphorylation;⁷² Moreover, the therapeutic impact of metformin is believed to reflect AMPK activation,^{73, 74} and this drug, like acarbose, has been shown to reduce diabetes risk in high-risk subjects.⁷⁵ Ingestion of vinegar has been found to lower blood pressure in spontaneously hypertensive rats, improve glycemic control in diabetic mice, and to enhance flow-mediated vasodilation in postmenopausal women.^{70, 71, 76} Moreover, in a double-blind study, ingestion of 15-30 ml of apple cider vinegar daily was associated with significant loss of body fat and weight in overweight subjects.⁷⁷ The health benefits of moderate alcohol consumption may stem from the acetic acid generated by the catabolism of ethanol (albeit this catabolism can also generate oxidative stress

and the alkylating agent acetaldehyde, phenomena which outweigh the benefits of acetate when alcohol is consumed in excess).⁷⁸ There is a considerable “folklore” regarding the manifold health benefits of regular ingestion of apple cider vinegar; not unlikely, this arose from anecdotal observations of genuine favorable effects.⁷⁹

Ancillary benefits of supplemental glucomannan include reduction in LDL cholesterol – stemming from increased fecal excretion of bile acids – and a satiating effect that may be helpful for prevention of weight gain.⁸⁰⁻⁸⁵ In the modest dose proposed here, glucomannan would not be expected to induce malabsorption or flatulence; it may however diminish the efficiency of absorption of fat-soluble nutrients or drugs.⁸⁶ Glucomannan can of course be omitted from the proposed beet juice cocktail if it is difficult to obtain or concerns regarding drug absorption provide a contraindication.

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