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"BEET IT"

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Consumers are inundated with information and advertising for dietary supplements. In response, they have created a rapidly-growing market estimated in value at $133 billion in 2016. With projected annual growth of nearly 10%, this market is projected to reach $278 billion by 2024 (Grand View Research Inc., San Francisco CA). Supplements are touted to do many things; reduce free radicals and aging or enhance testosterone production or weight loss, etc. However, few of these supplements undergo rigorous placebo-controlled trials to assess their scientific merit. Indeed, a recent meta-analysis found no clinical benefit for patients taking multivitamins and mineral supplements on cardiovascular outcomes (1).

However, some supplements have been studied in depth and may have cardiovascular benefits. The dietary supplement beet root juice (BRJ) contains high quantities of nitrate (Figure 1). Once thought as an inert byproduct of nitric oxide (NO) metabolism, nitrate and nitrite are now thought to be circulating reservoirs of stored NO. Nitrate is rapidly absorbed in the gut and circulates in the plasma. Circulating nitrate is actively taken up by the salivary glands and secreted in saliva where it is converted to nitrite by oral facultative bacteria in the deep crypts of dorsal surface of the tongue. This nitrite-rich saliva is absorbed in the stomach where the low pH favors its conversion back to NO or absorbed into the circulation where it may be converted to NO via a variety of enzymatic processes that reduces nitrite to NO (2). Acute ingestion of BRJ or inorganic nitrate results in significant increases in plasma levels of nitrite that peaks within 3 hours (3) or as exhaled NO that can be measured within 60 mins of nitrate ingestion (4).

BRJ has been found to enhance athletic performance and endurance in a variety of activities such as cycling, rowing and running. Bailey et al. (5) first reported the use of BRJ as a nitrate donor in normotensive young adult men (26 ± 7 years) undergoing submaximal cycling exercise. There it was found to double plasma nitrite levels, reduce systolic BP, improve muscle oxygenation and result in a significant 20% reduction in the oxygen cost of cycling exercise suggesting an effect on cellular metabolism. Hobbs et al.(2) randomized healthy subjects to increasing doses of beetroot juice (0–500g) and observed dose-dependent

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decreases in systolic and diastolic BP that peaked 2–3 hours post-ingestion. Urinary NO_x concentrations that reflected systemic NO production increased in proportion to the decline in BP. Muggeridge et al. (6) administered a single dose of beetroot juice (70 ml = 5mmol nitrate) to cyclists prior to performing submaximal exercise and time trials at moderate simulated altitude (2500 m). BRJ increased plasma nitrite from 39.1 uM to 150.5 uM and decreased V_{O2} during steady state exercise (2542 vs. 2727 ml/min vs. placebo) while improving their time trial. Although not every study using BRJ has improved exercise performance, the majority of studies suggest that the resultant increase in plasma nitrite levels following BRJ ingestion may be of cardiovascular benefit (7).

Subjects with peripheral arterial disease (PAD) and claudication may be an ideal cohort to benefit from increasing nitrite levels with BRJ as the conversion of nitrite to NO is enhanced in the relatively ischemic environment that arises from hypoperfusion (8). Compared to normal controls, subjects with PAD experience a decline in plasma levels of nitrite following exercise (9) consistent with the findings that NO production is impaired as a result of endothelial dysfunction and / or that the conversion of nitrite to NO is enhanced in the setting of low oxygen tension. In the ischemic hind-limb mouse model (10), increasing doses of sodium nitrite administered daily increased vascular density and hind-limb blood flow over 3–7 days and increased endothelial cell proliferation which was abolished in the presence of a NO scavenger. Importantly, no effect on blood flow in the contralateral non-ischemic limb was observed.

However, the pathophysiology of claudication is more than just endothelial dysfunction and impaired tissue perfusion from arterial obstruction as cellular and mitochondrial energetics are also impaired independent of blood flow. Anderson J et al. (11), observed that the phosphocreatine recovery time constant in the calf muscle of claudicants failed to correlate with measurements of calf perfusion. Similarly, patients undergoing a 12-week exercise program experience significant improvements in exercise duration that was related to improved cellular metabolism (carnitine) but not to blood flow. Thus, by 12 weeks, subjects demonstrated an increase in peak VO_2 suggesting improved oxygen delivery and/or oxidative metabolism (12). Given NO's known effect on mitochondrial energetics this may represent an additional pathway for the benefit of nitrate/nitrite to act in addition to improving endothelial function and hypoxic vasodilation.

Having previously demonstrated that changes in plasma nitrite levels and endothelial function were the most important predictors of exercise performance in subjects with PAD, Kenjale et al (3) were the first to examine if dietary supplementation of nitrate with BRJ would improve exercise capacity in this cohort. They observed that 500 ml of BRJ resulted in a 6-fold increase in plasma nitrite levels in 3 hours after ingestion, increased claudication onset time (COT) by 18% and peak walking time by 17% during a maximal cardiopulmonary stress test. Skeletal muscle (Gastrocnemius) oxygen extraction was reduced during exercise by near infra-red spectroscopy suggesting improved mitochondrial usage of oxygen. This is supported by findings in normal subjects administered nitrate for 3 days where exercise results in a significant decline in oxygen consumption secondary to improved efficiency of oxidative phosphorylation in mitochondria isolated by skeletal muscle biopsy (13)

Supervised exercise represents an effective strategy to improve exercise capacity in subjects with PAD and was recently approved for reimbursement in the United States by the Centers for Medicaid and Medicare Services. The benefits of exercise are multifactorial and may include improved endothelial function and mitochondrial energetics as well as reducing inflammation and generation of reactive oxygen species. Allen et al. (9) demonstrated that subjects with PAD (ABI=0.66) who underwent supervised exercise program for 3 months experienced increase in COT (66%) and peak walking time (52%). These findings were not associated with a change in ABI, but with improved indices of endothelial function as measured by brachial artery flow-mediated dilation and a restoration of the nitrite flux, which appears highly correlated with a subjects exercise capacity.

In this issue of *Circulation Research*, Woessner et al.(14), present their findings of a small clinical trial of 24 patients with PAD and intermittent claudication that tested the hypothesis that beetroot juice (nitrate) in conjunction with a supervised exercise program (n=11) would improve exercise capacity and delay onset of pain compared to exercise alone (n=13). This is the first clinical trial to examine the effects of both interventions together in the same cohort of subjects and could provide further insight into the mechanisms of benefit of these interventions on exercise time and endothelial function. Enrolled subjects were required to have a reduced ABI (< 0.9) and claudication as a limiting factor of exercise capacity. Subjects randomized to BRJ ingested the equivalent of 4.2 mmol NO_3-, 3- hours prior to onset of exercise as part of a 36-session program over 12 weeks. At each session, subjects exercised for at least 30 mins excluding rest periods to allow for resolution of claudication. As anticipated, subjects in both groups experienced significant improvements in COT and 6MW after 12 weeks of exercise. However, those subjects randomized to BRJ had a 3-fold greater improvement in exercise duration compared to the Control exercise group. These improvements are even more striking given that there were significantly more diabetics in the EX + BRJ group (6 vs. 2) and the presence of diabetes is associated with reduced endothelial function and COT compared to subjects without diabetes and PAD (15).

Tissue oxygenation assessed with near infra-red spectroscopy was utilized to monitor gastrocnemius perfusion during the pre- and post-treatment exercise session. Parameters of tissue oxygenation increased in both groups over 12 weeks of training but the improvement was significantly greater in the subjects randomized to BRJ. Additionally, the BRJ group experienced a blunting of the initial hemoglobin desaturation rate with exercise over time which was not seen in the exercise only group. The EX + BRJ also demonstrated a greater increase in peak reactive hyperemia following 5-min thigh occlusion that did not occur in the EX + Placebo group although this may have been due to the small sample size (9). Additionally, ABIs were significantly improved at the end of 12 weeks in the EX + BRJ group suggesting that structural changes may have occurred in the vasculature such as enhanced collateralization as observed in the ischemic rat hind-limb model (10).

Although this well conducted study was underpowered, it suggests that nitrate supplementation with BRJ provides additional functional benefits to patients with PAD above which can be achieved with supervised exercise. This promising strategy needs to be confirmed in a much larger clinical trial along with studies to explore if the acute benefits of

nitrate supplementation can be maintained with chronic administration. If confirmed, the strategy of providing nitrate supplementation to our PAD patients will be tough to BEET!

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Figure 1–.
Commercially available super-concentrated beet juice powder