Mother Was Right: Eat Your Vegetables and Do Not Spit!

When Oral Nitrate Helps With High Blood Pressure

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Do not spit in the plate from which you eat.

*Italian proverb*

Higher incidence of hypertension, atherosclerosis, and diabetes is a price that the “industrialized” world pays for abrupt changes in lifestyle and habits. These diseases increase rapidly in fast growing economies, where changes in diet are a significant factor with higher intake in food rich in cholesterol, saturated fat, salt, and sugar. More abundant consumption of fruits and vegetables is often recommended to reduce the occurrence of these diseases. Yet, as stated by Lundberg et al, few studies have thoroughly addressed the relationship between the intake of fruits and vegetables and cardiovascular disease.1 Appel et al found that in subjects with borderline hypertension (BHT) the intake of vegetables decreased blood pressure almost to the same extent as with standard antihypertensive monotherapy suggesting that diet alone can improve cardiovascular health.2 Although the factors in green leafy vegetables that account for this protection remained largely unknown, bioconversion of inorganic nitrate to nitrite, NO, and other secondary reaction products (nitroso/nitrosyl compounds) may play a key role in decreasing hypertension.1

In the present issue of Hypertension, the study by Webb et al1 shows that ingestion of beet juice, which is high in dietary nitrite/nitrate, by healthy volunteers not only markedly reduced blood pressure (≈10 mm Hg), but also prevented endothelial dysfunction after ischemia-reperfusion (without altering preischemic artery dilation) and decreased ex vivo platelet aggregation. The ingestion of beet juice was coincident with a dramatic increase in plasma levels of nitrate and nitrite. The study further showed that bacterial mediated conversion of nitrate to nitrite on the tongue could significantly increase nitrite in the plasma leading to these cardiovascular effects, which were abated when microbes were eliminated by spitting (Figure). Thus, dietary nitrite may reduce cardiovascular risks through a low cost and natural procedure as opposed to the expensive and typically multidrug approach.

The use of nitrite/nitrate as a food preservative, or for their medicinal properties, can be found in the ancient societies of China and Rome. In 2003, the European Food Safety Authority established that adding nitrite or nitrate during the production of cured meats is essential to prevent development and production of toxins from *Clostridium Botulinum.*

Yet in the 1970s, there was a considerable change of view about dietary nitrate/nitrite as a consequence of studies that showed nitrosamines could be formed from nitrite via N2O3 (Eq. 1) under the acidic conditions of the stomach. In animal models, identification of nitrosamines associated with numerous tumors lead to intense concern about the risk of nitrite/nitrates in our diet.4 However, this is still an open issue as recent epidemiological studies suggest no correlation between nitrate/nitrite levels in drinking water and dietary intake with some forms of cancer. Although some studies indicate nitrate in meat products may increase cancer risk, more studies are needed.5

In the late 1980s, the discovery of NO as an endogenous mediator of several functions in the cardiovascular and immune system brought to light the evidence that nitrite and nitrate are endogenously generated. Until recently, it was generally accepted that the only source of the release of NO in vivo was the oxygen-dependent conversion of arginine to citrulline and NO via NOS. However, nitrite is reduced to NO in rat ischemic heart,6 and in human subjects nitrite-induced vasodilation is associated with reduction of nitrite to NO under hypoxia.7 These studies suggest that nitrate and nitrite are no longer just the “inert endproducts of NO.”8 Additional investigations have strengthened the view of nitrite as a potential pharmacological tool, particularly in cases of acute cardiovascular disease conditions. Indeed, nitrite can alleviate ischemia reperfusion injurya and protect against cerebral incidences such as vasospasms by selectively reducing nitrite to NO under hypoxic conditions. However, several relevant questions concerning nitrite anions and the circulatory system remain: (1) How long can the beneficial effects of nitrate/nitrite last? (2) Could dietary supplementation of nitrite and nitrate reduce the onset of cardiovascular diseases in the long-term? In the specific case of hypertension, could nitrite control systemic blood pressure over a sustained period of time?

The discovery of an active nitrite cycle in humans8 (Figure) provided new insight into how NO2− pharmacological actions might be prolonged over time, suggesting that the body operates to keep plasma nitrite concentration relatively high rather than totally excreting it. As shown in the Figure, nitrate is converted to nitrite in the saliva by bacteria, which then...
enter the gastric juices. Under acidic conditions, nitrite generates NO2, NO, and N2O3 via a proton driven mechanism.

\[
\text{(1) } 2\text{H}^+ + 2\text{NO}_2^- \rightarrow \text{N}_2\text{O}_3 + \text{H}_2\text{O} \rightarrow \text{NO}_2 + \text{NO}
\]

The presence of antioxidants, such as those found in vegetables (ascorbate), scavenges NO2 increasing NO in the gastric juices thus maintaining the integrity of the mucosa lining the stomach (eq. 1). The gastro-intestinal (GI) tract readily absorbs these nitrogen oxides as indicated by Webb et al observing a sudden rise in plasma levels of nitrite and nitrate (>16-fold) 30 min after the ingestion of beet juice.3 Nitrate has a half-life of about 5 h and is excreted mostly by the kidneys and to a lesser degree through the salivary glands and the skin. After ingestion of beet juice, nitrate levels peaked at 1.5 h and remained elevated even after 24 h as compared to that seen in subjects who ingested water only. The beneficial actions lasted for 3 h after ingestion, pointing to the oral and GI flora as a key component to increase nitrite levels and “perpetuate” its effects.3 The nitrite cycle resembles the “enterohepatic cycle” of the biliary salts. In this cycle, part of the bile is reabsorbed by the intestine and transported back to the liver, thereby conserving biliary salts for same and future meals. Is there an analogous mechanism with nitrate/nitrite? Could the efficiency of the “enterosalivary circle” differ among subjects, and why? Do changes in nitrite cycle contribute to the maintenance of the hypertensive state?

These questions arise from present evidence showing that nitrite and nitrate, derived from vegetables, may have a positive impact on human health, by directly countering high blood pressure and limiting platelet aggregation and endothelial dysfunction that set the ground for chronic vascular process such as atherosclerosis.

Importantly, Webb et al may provide insight into a number of questions and problems in public health.3 For example, the use of dietary nitrite may be helpful during the administration of nonsteroidal antiinflammatory drugs (NSAIDs) which is still a serious problem. These antiinflammatory drugs have been found to have beneficial effects in numerous chronic diseases, from cancer to arthritis. However, their chronic use increases cardiovascular risks and stomach ulceration, which has dampened the enthusiasm for long-term treatment with these drugs. Nitrite here provides again a potential pharmacological shelter in that nitrate levels in drinking water appears to strengthen the integrity of the gastric mucosa during diclofenac administration by generating NO in the stomach.10

The study by Webb et al brings up a number of other interesting questions, and some of them concern the correlation between oral health and cardiovascular diseases.3 The “spitting” population of this study clearly indicates an important causative link between the presence of oral bacteria and the conversion of nitrate to nitrite. However, studies have shown that tooth decay, periodontal (gum) diseases, attributable to insufficient oral care, may increase the risk for cardiovascular disease. So are there good and bad oral bacteria?

All in all, the findings of this and other studies support the notion that nitrite is not simply an “innocent by-stander” but
might play a pivotal role in maintaining our healthy status, particularly when hypoxia is a main actor on the scene. So our mothers were absolutely right: eat your vegetables and be polite don’t spit!

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References
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