Dietary Flaxseed Decreases Central Blood Pressure and the Concentrations of Plasma Oxylipins Associated with Hypertension in Patients with Peripheral Arterial Disease

Authors: Stephanie PB Caligiuri, Harold M Aukema, Delfin Rodriguez-Leyva, Amir Ravandi, Randy Guzman, Grant N. Pierce Abstract: Background: Hypertension leads to cardiac and cerebral events and therefore is the leading risk factor attributed to death in the world. Oxylipins may be mediators in these events as they can regulate vascular tone and inflammation. Oxylipins are derived from fatty acids. Dietary flaxseed is rich in the n3 fatty acid, alpha-linolenic acid, and, therefore, may have the ability to change the substrate profile of oxylipins. As a result, this could alter blood pressure. Methods: A randomized, doubleblinded, controlled clinical trial, the Flax-PAD trial, was used to assess the impact of dietary flaxseed on blood pressure (BP), and to also assess the relationship of plasma oxylipins to BP in 81 patients with peripheral arterial disease (PAD). Patients with PAD were chosen for the clinical trial as they are at an increased risk for hypertension and cardiac and cerebral events. Thirty grams of ground flaxseed were added to food products to consume on a daily basis for 6 months. The control food products contained wheat germ, wheat bran, and mixed dietary oils instead of flaxseed. Central BP, which is more significantly associated to organ damage, cardiac, and cerebral events versus brachial BP, was measured by pulse wave analysis at baseline and 6 months. A plasma profile of 43 oxylipins was generated using solid phase extraction, HPLC-MS/MS, and stable isotope dilution quantitation. Results: At baseline, the central BP (systolic/diastolic) in the placebo and flaxseed group were, 131/73 ± 2.5/1.4 mmHg and 128/71 ± 2.6/1.4 mmHg, respectively. After 6 months of intervention, the flaxseed group exhibited a decrease in blood pressure of 4.0/1.0 mmHq. The 6 month central BP in the placebo and flaxseed groups were, $132/74 \pm$ 2.9/1.8 mmHg and $124/70 \pm 2.6/1.6$ mmHg (P<0.05). Correlation and logistic regression analyses between central blood pressure and oxylipins were performed. Significant associations were observed between central blood pressure and 17 oxylipins, primarily produced from arachidonic acid. Every 1 nM increase in 16-hydroxyeicosatetraenoic acid (HETE) increased the odds of having high central systolic BP by 15-fold, of having high central diastolic BP by 6-fold and of having high central mean arterial pressure by 15-fold. In addition, every 1 nM increase in 5,6-dihydroxyeicosatrienoic acid (DHET) and 11,12-DHET increased the odds of having high central mean arterial pressure by 45- and 18-fold, respectively. Flaxseed induced a significant decrease in these as well as 4 other vasoconstrictive oxylipins. Conclusion: Dietary flaxseed significantly lowered blood pressure in patients with PAD and hypertension. Plasma oxylipins were strongly associated with central blood pressure and may have mediated the flaxseed-induced decrease in blood pressure.

Keywords: hypertension, flaxseed, oxylipins, peripheral arterial disease

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