The cardiovascular benefits of consuming flaxseed: Possible modes of action

Chantal M.C. Dupasquier and Grant N. Pierce
Institute of Cardiovascular Sciences, St Boniface Hospital Research Centre and the Department of Physiology, University of Manitoba, Winnipeg, Manitoba, Canada

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Introduction

Atherosclerotic coronary heart disease (CHD) is estimated to be the leading cause of cardiovascular morbidity and mortality worldwide [1]. However, it is becoming increasingly evident that this disease is largely attributable to factors that can be altered or prevented by lifestyle modification, including dietary choices [2]. Increasing the consumption of omega-3 (ω-3) fatty acids has been suggested as one dietary strategy to provide cardioprotection against ischemic heart disease and significantly reduce the incidence of myocardial infarcts and stroke [3, 4]. The most common way to consume ω-3 fatty acids has been in the form of marine oils like fish. However, dietary compliance for fish supplementation is often an issue due to concerns about environmental toxins, palatability and eructation [5]. Sadly, no matter how good a product is for you, if the general population will not ingest it, it will never provide the expected benefits. Finding an alternative source of ω-3 PUFAs, therefore, could be an important issue for cardiovascular health.

Flaxseed (linseed) is the richest plant source of the ω-3 PUFA α-linolenic acid (ALA; C18:3n-3) [5]. ALA has been identified in several epidemiological trials as having significant beneficial effects versus heart disease [6-9]. ALA can also be converted in the body to the cardioprotective ω-3 PUFAs found in fish oils, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [10, 11]. Dietary flaxseed also contains a rich source of soluble and insoluble fibres that may provide cardioprotective action and lignans like secoisolariciresinol diglucoside (SDG) which have demonstrated potent antioxidant and anti-atherogenic effects [12, 13].

The observation that flaxseed can inhibit atherosclerosis is an important one with implications for cardiovascular health. Our aim was to identify in a series of papers the processes by which dietary flaxseed can be cardioprotective. The hypotheses that were tested were that dietary flaxseed may retard atherosclerotic development, protect against vascular contractile abnormalities and inhibit arrhythmogenesis in models of diet-induced CHD. To also identify the exact mechanism(s) by which dietary flaxseed achieves the beneficial effects was also a goal of our work. Our long term objective is to determine if a dietary flaxseed intervention should be tested as a strategy to modify heart disease in human populations.

Summary of the Experimental Design

We have examined the effects of flaxseed supplementation on these parameters in two animal models, the hypercholesterolemic rabbit and more recently, the cholesterol

fed, low density lipoprotein receptor (LDLr-/-) deficient mouse. Male New Zealand White (NZW) rabbits were fed a diet containing flaxseed in the absence or presence of dietary cholesterol for a period of 6 - 16 weeks. Atherosclerosis, aortic vessel contractile function and arrhythmogenesis were measured in two separate studies [14, 15]. However, the cholesterol-fed rabbit model has been criticized as a model for atherosclerosis [16, 17]. Therefore, in other studies, the LDLr-/- mice were fed an atherogenic diet in the presence or absence of one of three doses of dietary flaxseed for 6 months at which time we measured plasma lipids and the extent of aortic atherosclerotic development [18].

Summary of the Results

1. The effect of flaxseed supplementation on plasma lipids and atherosclerosis

Dietary flaxseed significantly prevents atherosclerosis in both animal models but, not surprisingly, there are limits on its potency [14, 18]. Longer durations of dietary interventions with high cholesterol make it more difficult for flaxseed to exert a protective action and lower flaxseed doses result in limited or no protective action. It may be important to remember these limitations when enthusiasm grows to implement strategies for its use in human population studies. It is also important to note that the effects of flaxseed supplementation on plasma lipids remain unclear. Flaxseed prevented the rise in plasma triglyceride levels over the 16 week period in the rabbit model but it had no effect on triglyceride levels in the LDLr-/- mice. Conversely, dietary flaxseed had no effect on cholesterol levels in rabbits but even low doses of dietary flaxseed significantly reduced plasma cholesterol levels in the LDLr-/- mice. Because there was not a close correlation between the progression of atherosclerotic lesions and the cholesterol lowering effect of dietary flaxseed in either study, the hypolipidemic effect of flaxseed is at best likely to be only one of the contributing factors to its anti-atherogenic potential. Another mechanism, likely the cellular actions of flaxseed, may be responsible for this anti-atherogenic action [18]. In this regard, two options can be considered. First, the powerful anti-oxidative action of the lignans within flaxseed may contribute to its anti-atherogenic potential [12, 13, 19]. It is well known that antioxidants can reduce atherogenesis in animals [20-22]. It is not insignificant to note, however, that this action does not appear to be effective in human studies of CHD [23-27]. Therefore, the utility of lignans in human studies may be questionable at this point in time. However, secondly, the omega-3 fatty acid content of the flaxseed may provide an anti-inflammatory action that could inhibit atherogenesis [18]. Omega-3 fatty acids are known to have an anti-inflammatory action [28, 29] and it is now known that infectious disease and inflammation represents an important causative mechanism in atherosclerosis [18, 30]. Flaxseed effectively inhibited the expression of inflammatory markers like IL-6, mac-3, VCAM-1 and the proliferative marker PCNA in aortic atherosclerotic tissue from LDLr-/- mice [18]. These cellular changes could be a result from the increased incorporation of ω-3 fatty acids in aortic tissues in flaxseed fed animals. Dietary supplementation with ALA from flaxseed oil has been demonstrated to reduce circulating levels of several atherogenic and inflammatory markers including, C-reactive protein, serum amyloid A, IL-6, and sVCAM-1 in dyslipidaemic patients [31, 32]. This mechanism may play an important contributory role in the anti-atherogenic effects of flaxseed in our models [14, 18] and, more importantly, may have this action in humans as well.

2. The effects of flaxseed supplementation on vascular function

The benefits of consuming flaxseed may extend beyond its anti-atherogenic potential. The endothelial lining of arteries normally acts as a barrier and modulator of vascular contraction and relaxation. Under atherosclerotic conditions, the endothelium can become damaged and exhibit a dysfunctional contractile relaxation. Our study has demonstrated that flaxseed protects against the loss of endothelial-dependent vascular relaxation induced by cholesterol feeding [14]. Vessels from cholesterol fed animals exhibited normal vascular relaxation in response to acetylcholine, an endothelial-dependent vasorelaxant, as compared to vessels from cholesterol fed animals. Flaxseed had no effect on endothelial-independent routes of modulating vascular response. Thus, flaxseed may provide critical functional and structural benefits to vessel integrity and viability.

3. The effect of flaxseed supplementation on the incidence of arrhythmias following ischemia/reperfusion injury

Arrhythmias commonly precede a myocardial infarction and may ultimately cause death. In order to determine the potential of flaxseed to protect against arrhythmias, rabbit hearts from animals fed a diet +/- cholesterol and +/- flaxseed were subjected to a period of ischemia followed by reperfusion and the incidences of ventricular tachycardia and fibrillation were monitored [15]. Dietary flaxseed supplementation completely suppressed the incidence of ventricular fibrillation (VF) normally observed during ischemia, and significantly reduced the incidence of VF during reperfusion in hearts obtained from cholesterol-fed rabbits. Flaxseed appears to exert its protective effect by shortening the QT interval and action potential duration of heart beats [15]. QT prolongation is associated with arrhythmias [33, 34]. It was concluded that the ALA content of the diet was primarily responsible for the anti-arrhythmic effects.

Conclusions

Dietary flaxseed inhibits the atherogenic effects of a high cholesterol diet in two animal models. The anti-atherogenic effect was achieved through a capacity to lower circulating cholesterol levels and at a cellular level by inhibiting cell proliferation and inflammation. This reduction is associated with an improved vascular relaxation response. Dietary flaxseed also has the capacity to inhibit the incidence of ventricular fibrillation. Our data lends further support to the hypothesis that nutritional interventions that elevate omega-3 fatty acids have the capacity to alter cardiovascular disease. The data supports the possibility that not only the omega-3 fatty acids from fish, DHA and EPA, can be cardioprotective, but dietary ALA can now be considered to possess this important action as well. Finally, because the anti-atherogenic effects of flaxseed have now been shown in more than one animal model, and, because the LDLr-/- mouse is a close representation of the clinical condition of coronary heart disease in humans [35, 36], it would be our opinion that the body of research now effectively argues for the initiation of careful, randomized controlled trials of dietary flaxseed in a patient population with symptoms of atherosclerotic heart disease.

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