Syrian Hamster model of postmenopausal hypercholesterolemia atherosclerosis and the development of plaques as imaged by high field MRI

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Introduction: The development of arterial plaques, known clinically as atherosclerosis, is at the root of a significant number of deaths related to heart attack and stroke. The risk for cardiovascular disease (CVD) drastically increases for women when they reach the age of menopause. Menopause is characterized by a cessation of ovarian function leading to a deficiency in circulating estrogens. One outcome of this estrogen deficiency is the unfavorable alteration in lipid profiles, which increases risks for atherosclerosis and CVD. This study builds upon an ongoing study to examine the anti-atherogenic effects of flaxseed in a hamster model of postmenopausal atherosclerosis. The focus is to examine *in vivo* identification of plaques in cerebral arteries and aortas of overiectomized (ovx) hamsters with endogenous contrast using high field, high resolution *in vivo* imaging. Furthermore, the impacts of functional foods, such as flaxseed, on plaque development are investigated.

Background: Stroke and CVD following atherosclerosis is one of the most common causes of deaths in America. It is estimated that atherosclerosis is the cause of about 50% of all deaths in the western world. Atherosclerosis is a subclinical disease with chronic inflammatory conditions that can be converted into life threatening CVD [1]. Flaxseed, known to reduce serum cholesterol, prevents atherosclerotic lesion formation by decreasing fatty streak area and severity of atheromatous. Recent findings indicate that postmenopausal women benefit from consuming flaxseed, an excellent source of numerous nutrients such as linolenic acid, soluble fiber mucilage and phytoestrogens, e.g., lignans [2]. Clinical studies have shown that flaxseed significantly lowered non-high density lipoprotein (HDL) cholesterol and apolipoprotein B concentrations without altering HDL-cholesterol in postmenopausal women. The hypocholesterolemic effects of flaxseed in ovx hamsters, a suitable animal to model lipid changes that occur in women after menopause, also have been demonstrated [3].

Methods: Plaque formations in cerebral arteries and the aorta were investigated *in* and *ex vivo* by comparing control (sham), ovx and ovx with different concentrations of flaxseed diet during three timelines: baseline, 4 months after ovx and 8 months. Hamsters were put on flaxseed diet for 4 months at the 2nd time point. At each time point, hamsters were imaged on a 21.1-T, 105-mm ultra-widebore magnet equipped with a Bruker Avance console and Mini0.7 gradients. Fast spin echo (FSE) images were acquired in two orientations: axial, covering the carotid and cerebral arteries to achieve a 133x133x500 μm resolution with TE/TR = 6.5/3000 ms, and coronal at 195x125x1000 μm resolution with TE/TR = 6.5/2500 ms. The diameter of the aorta was imaged at three places, rostral, dorsal and in between. Left and right vertebra aorta was measured dorsal to bifurcation, and the left and right carotid were measured in line with the 3rd cervical vertebra.
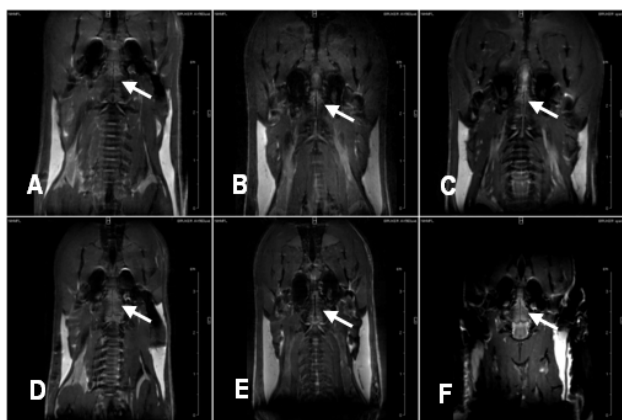
Results: Measurements of the basilar aorta and left and right vertebral aorta revealed no diameter change with time or between different groups. Images A-C are from the three time points (baseline, 4 months and 8 months, respectively) of the sham group; no plaque formation was expected or measured. Images D-F show the same time points for an ovx animal that did not receive flaxseed. White arrows indicate the basilar artery. The group with highest projected plaque formation, ovx with no flaxseed treatment, showed no difference in basilar artery diameter, and there was no hyperintense signal associated with fat accumulation in these arteries in either sham, ovx or flaxseed-treated animals. This trend also is seen in the left and right vertebral aorta. However, cardiac imaging performed at 8 months demonstrated different aortic diameters among the treatment groups. Histological data as well as high res images of *ex vivo* tissue are underway to confirm *in vivo* results.

Discussion and Conclusion: Cerebral images of high field, high resolution in vivo images reveal no apparent, measurable occlusion in the basilar and vertebral aorta. This result agrees with results from Langheinrich *et al* 2007 [4], where Apo^{-/-}/LDL^{-/-} double knockout mice showed no atherosclerotic lesions of the cerebral arteries. Although this high field study demonstrated no apparent plaque formation in the basilar artery, alterations of the aorta and other systemic vascular are expected. In fact, the hypocholesterolemic effects of flaxseed did impact the deposition of atherosclerotic plaques in the aorta, as well as the overall body weight and general health of the ovx hamster, as demonstrated previously [2]. In summary, this application marks the first attempt to utilize high field (21.1 T) MRI to image vascular events in both the cerebral and cardiac systems of a rodent model *in vivo* without the use of exogenous contrast enhancement.