Intervention With Citrus Flavonoids Reverses Existing Metabolic Disorders and Attenuates the Progression of Advanced Atherosclerosis in High Fat--Fed LDLr-/- Mice

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Previous studies demonstrated that addition of the citrus flavonoids naringenin or nobiletin to a high-fat diet prevented the development of many disorders linked to the metabolic syndrome. In the present study, we assessed the ability of intervention with nobiletin or naringenin to reverse pre-established obesity, insulin resistance, hepatic steatosis, dyslipidemia and attenuate atherogenesis. Ldlr-/- mice were fed chow or a high-fat, cholesterol-containing (HFHC) diet for 12 weeks. For an additional 12 weeks, the HFHC-fed mice: (1) continued on the HFHC diet or were transferred to (2) chow, (3) HFHC + 3% naringenin, or (4) HFHC + 0.3% nobiletin. Following rapid weight gain during HFHC-induction, intervention with naringenin or nobiletin stimulated weight loss, while maintaining caloric intake. Micro-CT imaging revealed flavonoid intervention reversed adipose tissue accumulation by 40-60% in both subcutaneous and visceral depots. At 12 weeks, the HFHC-fed mice were hyperinsulinemic (6-fold), which was accompanied by increased fasting plasma glucose. Intervention with either flavonoid normalized plasma insulin and glucose and corrected impaired insulin and glucose tolerance. The HFHC diet increased cholesterol within VLDL (10-fold) and LDL (6-fold), which was reduced (~50%) by either naringenin or nobiletin intervention. HFHC-induction significantly increased hepatic steatosis. Flavonoid intervention reduced hepatic cholesterol (>50%) and triglyceride (~20%) via increased expression of Pgc1a and Cpt1a and reduced expression of Srebp1c. HFHC-induction increased atherosclerotic lesion area (13-fold), which was increased a further 2.5-fold at 24 weeks. Flavonoid intervention modestly retarded lesion size progression (16-20%). As well, intervention with naringenin or nobiletin slowed the accumulation of aortic cholesterol (~30-45%) and reduced lesional necrotic area (~25%), suggesting improved lesion morphology. These studies demonstrate in mice with pre-existing metabolic dysregulation and atherosclerosis that intervention with naringenin or nobiletin reverses obesity, dyslipidemia, hepatic steatosis and insulin resistance, and modestly attenuates the progression of advanced atherosclerosis.