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Effects of 1 year combined flavan-3-ol and isoflavone intake, on biomarkers of vascular health in statin treated postmenopausal women with type 2 diabetes: a double-blind randomised controlled trial

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Type 2 diabetes (T2DM) increases cardiovascular disease (CVD) risk, adversely increasing common carotid artery intima-media thickness (CCA-IMT)[(1)] and endothelial dysfunction[(2)]. Previously, higher intakes of some flavonoid sub-classes (specifically flavan-3-ols) have been associated with reduced atherosclerosis progression[(3)], with animal and *in vitro* studies supporting benefits of this sub-class on Nitric Oxide (NO)[(4)] and NADPH oxidase activity[(5)] and of another sub-class, isoflavones, on vascular inflammation[(6)]. The ability to metabolise the isoflavone equol, from its precursor, daidzein, has also been associated with improved vascular function[(7)]. Despite these previous findings, the longer-term vascular effects of combined flavan-3-ol and isoflavone intakes remain under-studied and few studies have examined if these flavonoids augment standard therapies in controlling CVD risk in 'at-risk' populations, such as T2DM patients.

In a randomised double-blind, parallel-design, placebo controlled study which was conducted in accordance with the Declaration of Helsinki guidelines, postmenopausal women with T2DM consumed 27 g/d (split-dose) flavonoid-enriched chocolate (850 mg flavan-3-ols (90 mg epicatechin) + 100 mg isoflavones (aglycone equivalents)/d), or matched placebo for 1-year. CCA-IMT, vascular biomarkers and measures of arterial stiffness (pulse wave velocity (PWV), augmentation Index (AIx)) and blood pressure (BP) were assessed. Changes from baseline (0 M) to 1–year (12M) were assessed with univariate ANCOVA.

	Flavonoid (n = 47)				Placebo (n = 46)					
	0 M		0 to 12 M		0 M		0 to 12 M		Net effect 0 to 12M	p-value 0 to 12 M
	Mean	SE	Mean	SE	Mean	SE	Mean	SE		
CCA-IMT, *mm*	0.75	0.02	0.01	0.01	0.75	0.02	−0.01	0.01	+0.02	0.19
[1]PWV, *m/s*	8.9	0.4	−0.1	0.4	9.5	0.4	0.7	0.3	−0.8	0.01
AIx at 75HR, %	28.5	1.2	−0.6	1.2	29.5	1.4	−0.8	1.4	+0.2	0.89
AorticSBP, *mmHg*	119.6	1.9	−3.8	2.2	119.5	2.2	0.8	2.0	−4.6	0.07
AorticDBP, *mmHg*	74.4	1.3	−2.3	1.1	72.0	1.0	1.4	1.1	−3.7	0.06
AorticMAP, *mmHg*	93.4	1.4	−2.7	1.4	91.8	1.5	1.5	1.4	−5.2	0.06
SBP, *mmHg*	133.7	1.6	1.9	1.3	138.1	1.9	1.5	1.6	+0.4	0.37
DBP, *mmHg*	76.1	1.3	−0.2	0.8	76.6	1.1	−0.1	0.9	−0.1	0.83

SBP, systolic BP; DBP, diastolic BP; MAP, mean arterial pressure.[1], PWV data, n = 18 flavonoid, n = 17 placebo.

Overall, intervention did not significantly change CCA-IMT, AIx or BP. However, in a sub-group arterial stiffness (PWV) improved ($p = 0.01$) equating to a 10% CVD risk reduction. Although central aortic SBP, DBP and MAP were reduced, this did not reach statistical significance. Equol producer phenotype was associated with greater reductions in DBP, MAP and PWV (-2.24 ± 1.31 *mmHg*, -1.24 ± 1.30 *mmHg*, -0.68 ± 0.40 *m/s*; $p<0.01$.

Although 1-year intervention did not change CCA-IMT or BP, clinically relevant improvements in arterial stiffness were observed; the e*quol* producer phenotype was particularly responsive to vascular improvements. In postmenopausal T2DM patients receiving standard UK medication, the combined intake of several flavonoid sub-classes (flavan-3-ols and isoflavones) improved some measures of vascular health and these data may be of clinical relevance to support the care strategy of this 'at-risk' population group.

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