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The magnitude of improvement in flow-mediated dilatation following exercise training is similar in postmenopausal women with and without type 2 diabetes

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A decline in endothelial function as measured by flow mediated dilatation (FMD) is an early independent predictor of cardiovascular disease (CVD) and has been seen in diabetes (1)and following the menopause in women (2). Whether exercise training can improve endothelial function to the same magnitude in postmenopausal women with type 2 diabetes compared to those without diabetes is unclear and the purpose of the present study. 38 apparently healthy postmenopausal women (ND) and 15 postmenopausal women with type 2 diabetes (T2) volunteered for this study. All participants completed a maximal exercise test for the assessment of peak oxygen uptake (VO2peak), and were assessed for waist circumference and percentage body fat via skinfold analysis, FMD via reactive hyperaemia and ultrasound, blood pressure via shygmomanometry and HOMA via fasting blood sampling. Participants were then randomised into body mass matched exercise training or control groups. The exercise training group trained under supervision twice per week (+one home session) at 55, rising to 75% VO2peak for six months. The control participants continued life as normal. Following the six month intervention all baseline assessments were repeated and the impact of exercise training upon FMD compared between ND and T2 groups via two way mixed mode ANOVA (time x group). The control data were assessed separately and confirmed no change in any variable over 6 months in either the ND or T2 women. At baseline there were no significant differences in VO2peak (ND: 24.4 ±3.6, T2: 21.2 ±5.6 ml.kg.min-1), percentage body fat (ND: 37.9 ±5.2, T2: 40.6 ±5.6 %), blood pressure (ND MAP: 91 ±10, T2:100±12 mmHg) or FMD (ND: 4.2±2.9, T2: 4.1 ±2.9 %) between the ND and T2 women ($P > 0.05$). HOMA was greater in the T2 women (ND: 1.7 ±0.1, T2: 4.7 ±2.0 $P < 0.05$). Following training VO2peak improved more so in the ND than the T2 women (to 29.82±5.6 and 24.50±6.7 ml.kg.min-1, respectively (interaction $P = 0.06$), whilst waist circumference decreased by a greater magnitude in the T2 participants (ND: -0.5, T2: - 3 cm: interaction $P < 0.05$). Blood pressure and HOMA were not significantly affected by training ($P > 0.05$). FMD improved to 7.0 ±2.9 and 7.1 ± 2.0 % in the ND and T2 women respectively, but importantly there was no difference between groups in the magnitude of improvement (interaction $P > 0.05$). The impact of exercise training upon endothelial function was biologically significant even in a milieu of low oestrogen concentration plus insulin resistance.

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Pressure-dependent myogenic tone in ischaemic vascular disease

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Advanced peripheral vascular disease, critical limb ischaemia (CLI) is associated with an inability to regulate blood volume within the capillary beds of the diseased part of the leg. Part of the sequelae accompanying CLI can be associated with dysfunction of resistance arterioles. Reactive oxygen species (ROS) were originally considered toxic metabolites. Increasing evidence suggests that they can play an important signalling role in essential physiological functions including pressure-dependent arteriolar myogenic tone (1). In addition to the well documented calcium/ calmodulin/ myosin light chain kinase dependency of myogenic contraction evidence suggests that G and F actin based structures contribute to myogenic tone (2). Here ROS and G/F actin mechanisms of arteriolar contractile responses in skeletal muscle arterioles isolated from the diseased part of the leg (DSM) vs. arterioles isolated form the healthy part of the leg (PSM, internal control) have been examined.

Methods: Resistance arterioles (lumen diameter ~80μM) were isolated from skeletal muscle biopsies taken from subjects with CLI. Pressure-dependent and pressure-independent mechanisms of vascular tone were studied (Danish MyoTech P110 pressure myograph).

Results: There was no difference in pressure-independent mechanisms of vascular tone (DSM vs. PSM). Pressure-dependent myogenic constriction was reduced (20.9 ± 2.3% vs. 4.2 ± 1.2% and 28.2 ± 3.1% vs. 6.8 ± 1.4%, PSM vs. DSM at 80mmHg and 120mmHg respectively; n=6 pairs). The antioxidant NAC, the inhibitor of NAD(P)H oxidase DPI and cytochalasin D, an inhibitor of actin polymerisation inhibited myogenic responses in PSM arterioles. NAC, DPI and cytochalasin D had no effect on pressure-dependent myogenic contraction measured in the DSM arterioles. NAC, DPI and cytochalasin D actions were selective to myogenic contraction as they had no effect on pressure-independent contraction.

Discussion: Based on these results we confirm that the myogenic response involves two discrete contractile components2. One pathway involves the conventional signalling pathway for vascular smooth muscle constriction. The other involves activation of NAD(P)H oxidase, elevation of ROS and actin polymerization. Since the NAD(P)H/ROS/actin polymerization-dependent response is absent in arterioles associated with CLI, we propose that deregulation of this second pathway negates the ability of these arterioles to resist pressure-dependent forced dilatation and generate a myogenic contraction and this dysfunction significantly contributes to the altered vascular function associated with CLI.

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