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Short Communication

Sitting time is negatively related to microvascular endothelium-dependent function in rheumatoid arthritis

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ABSTRACT

Background: Sedentary behaviour is linked to increased cardiovascular disease risk in Rheumatoid Arthritis (RA), but the biological processes underlying this relationship are not understood.
Objectives: To investigate the cross-sectional associations of habitual sedentary behaviour, with endothelial function in RA.
Methods: Sixty-eight RA patients (Mage = 55 ± 12 years) underwent Laser Doppler Imaging with iontophoresis, to assess microvascular endothelium-dependent (acetylcholine, ACh) and endothelium-independent (sodium nitroprusside, SNP) function. Large-vessel endothelium-dependent and endothelium-independent functions were measured via flow-mediated dilation (FMD) and glyceryl trinitrate dilation (GTN), respectively. Habitual sedentary behaviour (hours/week sitting) was self-reported (International Physical Activity Questionnaire).
Results: Regressions revealed sitting time significantly negatively predicted microvascular endothelium-dependent function (ACh, $_{unstandardized}\beta = -3.25$, $p = .02$, 95% CI [−6.07, −.42], $R^2 = 0.06$), but did not associate with other endothelial function outcomes (SNP, FMD, GTN).
Conclusion: Habitual sedentary behaviour (sitting time) appears to be adversely linked to microvascular endothelium-dependent function among people living with RA.

1. Introduction

Cardiovascular disease (CVD)[1] is the leading cause of death among people living with Rheumatoid Arthritis (RA) (Kitas & Gabriel, 2011), with RA increasing CVD risk by ~50% compared to the general population (Agca et al., 2017). High levels of sedentary behaviour (*waking behaviour ≤1.5 metabolic equivalents, whilst sitting/lying*) are linked to increased CVD risk in RA, independently of the benefits of physical activity (Fenton et al., 2017). Whilst the biological mechanisms underlying this adverse relationship are not yet known, recent experimental work suggests endothelial dysfunction may play an important role (Holder, 2017).

The endothelium maintains vascular homeostasis by regulating vascular tone and anti-atherosclerotic processes via the release of vasodilator molecules, such as nitric oxide (NO), prostacyclin (PGI2) and endothelium derived hyperpolarizing factor (EDHF) (Sandoo et al., 2010). Several non-invasive assessments of NO-mediated vasodilation (i.e., endothelium–dependent function) can be conducted in the microvessels and large-vessels, and provide early indication of future CVD risk in the general population (Lerman & Zeiher, 2005). RA patients also have endothelial dysfunction which likely results from subtle interactions between inflammation and classical CVD risk factors (Sandoo et al., 2011), adversely affecting downstream endothelium-independent vasodilatory processes (i.e., smooth muscle cell integrity).(Sandoo et al., 2010) Indeed, RA patients exhibit poor microvascular perfusion in the coronary circulation, even when the larger epicardial arteries are clear, which suggests that different vascular beds are affected differently by RA-related factors (Toutouzas et al., 2013). However at present, it is not clear which factors affect the specific vascular outcomes in RA (i.e., endothelium-dependent vs. independent function in the small

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[1] CVD, cardiovascular disease; RA, Rheumatoid Arthritis; NO, Nitric Oxide; DAS, Disease Activity Score; ESR, Erythrocyte Sedimentation Rate; HAQ, Health Assessment Questionnaire; ACh, Acetylcholine; SNP, sodium nitroprusside; FMD, Flow Mediated Dilation; GTN, Glyceryl-trinitrate.

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vs. large-vessels), and identification of such factors (e.g., the role of sedentary behaviour) is necessary to inform effective CVD prevention in this high-risk population.

To date, the majority of research investigating the implications of sedentary behaviour for endothelial function, has employed experimental designs to examine the effects of prolonged sitting (i.e., 3–5 h uninterrupted sitting in a laboratory) on large-vessel endothelium-dependent function in healthy males (Trinity, 2017). Research investigating the impact of more habitual (daily) sedentariness on microvascular and large-vessel endothelial function is required to better evaluate its role in the development of CVD. This is important to investigate in RA specifically, as the mechanisms that drive vascular dysfunction may differ to those in healthy adults (Grace et al., 2017).

The aim of this study was therefore to examine the cross-sectional associations between habitual sedentary behaviour (sitting time), with microvascular and large-vessel endothelium-dependent, and endothelium-independent function, in patients with RA. The data presented herein represents secondary analysis of previously published data, reporting associations between CVD risk and endothelial function in this cohort (Sandoo et al., 2012).

2. Materials and methods

Ninety-eight RA patients were recruited from Rheumatology outpatient clinics at Russells Hall Hospital (Dudley Group NHS Foundation Trust). All patients recruited met the 1987 RA criteria of the American College of Rheumatology. Informed consent was obtained from all participants included in the study. Ethical approval was granted by the local National Health Service Research Ethics Committee (approval number:10/H1206/59).

Participants reported to a temperature-controlled vascular laboratory (22 °C) to complete assessments, in a fasted state (12-h), having refrained from exercise for 24 h.

2.1. RA characteristics

Disease activity was assessed using the Disease Activity Score in 28-joints (DAS28) and erythrocyte sedimentation rate (ESR). Disease severity was measured via the Stanford Health Assessment Questionnaire (HAQ). Use of vasoactive medication (i.e., anti-hypertensives, beta-blockers and/or calcium channel blockers) was self-reported and corroborated with medical notes.

2.2. Global (10-year) CVD risk

QRISK2 was used to indicate ten-year CVD risk. QRISK2 score was calculated using participants; age, gender, height, weight, blood pressure, cholesterol (total/HDL ratio), smoking status, diabetic status, presence of kidney disease and family history of heart disease (Sandoo et al., 2012).

2.3. Endothelial function

First, microvascular endothelial function was assessed non-invasively in the forearm, using Laser Doppler Imaging with iontophoresis of 1% Acetylcholine (ACh, endothelium-dependent function) and 1% sodium nitroprusside (SNP, endothelium-independent function), in 2.5 ml solution containing 0.5% saline, according to previously established guidelines (Sandoo & Kitas, 2015). Following this, large vessel endothelium-dependent (flow mediated dilatation, FMD) and endothelium-independent (sublingual glyceryl-trinitrate, GTN) function, were measured using high-resolution Doppler Ultrasonography of the brachial artery (Sandoo & Kitas, 2015). Assessments of microvascular endothelial function were conducted first, as both FMD and GTN may affect blood flow in the forearm, and therefore iontophoresis measurements. Large vessel endothelium-independent function was assessed last, as administration of GTN causes systemic vasodilation, which would affect all preceding vascular tests.

Endothelial function was expressed as the percentage increase in perfusion or diameter from baseline. A single observer conducted all vascular assessments (AS), reporting intra-observer coefficients of variation of 6.5% (ACh), 5.9% (SNP), 10.7% (FMD) and 11.8% for (GTN). Data for ACh/SNP and GTN were not collected from 3 participants due to technical problems with equipment.

2.4. Sitting time

Habitual sitting-time was self-reported using the International Physical Activity Questionnaire (IPAQ). Participants reported their average time spent sitting on; 1) weekdays, and 2) weekend days (i.e., at home, whilst studying, leisure time), over the previous 7-days. Total weekly sitting time (hours/week) was computed; (weekday sitting time × 5) + (weekend day sitting time × 2).

Of the initial 98 participants recruited, 30 were excluded on the basis of missing IPAQ data (n = 27), or as extreme outliers (ACh/SNP, n = 3). Following these exclusions, missing data were < 5% for; QRISK2 = 2, DAS28 = 2, HAQ = 1, ACh/SNP = 3, GTN = 2). Missing values were therefore imputed for these variables to maximise statistical power (expectation maximisation method), retaining a final sample of n = 68 for statistical analyses. Participants in this final sample were not significantly different to those excluded on the basis of missing IPAQ data/extreme outliers (n = 30) for all targeted variables (Table 1).

Cross-sectional associations between habitual sitting time and endothelial function outcomes were examined via multiple regression analyses, in conjunction with bootstrapping. Bootstrap-generated 95% bias-corrected confidence intervals were constructed for 5000 samples (Shrout & Bolger, 2002), and analyses were adjusted for global CVD risk, RA characteristics, and vasoactive medication. Bootstrapping is a non-parametric resampling procedure reported to be superior to alternative tests with respect to Type 1 error rates and power (Table 1). (Shrout & Bolger, 2002) Analysis was performed using SPSS (version 24.0).

3. Results

Descriptive statistics are reported in Table 1. The sample was largely female, with moderate disease activity and moderate-to-severe disability. Regression analysis (Table 2) revealed habitual sitting time was significantly negatively related to microvascular endothelium-dependent function (ACh, $_{\text{unstandardized}}\beta = -3.25$, $p = .02$), but not microvascular endothelium-independent function (SNP, $_{\text{unstandardized}}\beta = -1.94$, $p = .07$). Sitting time accounted for 6% of the variance in microvascular endothelium-dependent function, with the total model explaining 18% of the variance in this outcome. Habitual sitting time did not significantly predict large-vessel endothelium-dependent vasodilation (FMD, $_{\text{unstandardized}}\beta = .01$, $p = .84$) or endothelium-independent vasodilation (GTN, $_{\text{unstandardized}}\beta = -.06$, $p = .37$).

4. Discussion

This is the first study to reveal that higher self-reported sitting time is predictive of impaired microvascular endothelium-dependent function among people with RA. This cross-sectional association was observed after adjusting for global CVD risk, RA characteristics and vasoactive medication. Results provide new evidence to suggest “too much sitting” may be linked to poorer endothelial function, and contribute toward increased CVD risk in RA (Kitas & Gabriel, 2011; Fenton et al., 2017).

A recent experimental study in healthy males reported significantly reduced hyperaemic response in the microvessels, but not the large-vessels of the brachial artery, following 6-hours of uninterrupted sitting