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Sedentary time and markers of inflammation in people with newly diagnosed type 2 diabetes

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Sedentary time; Type 2 diabetes; Breaks in sedentary time; Inflammation

Abstract Background and aims: We investigated whether objectively measured sedentary time was associated with markers of inflammation in adults with newly diagnosed type 2 diabetes. Methods and results: We studied 285 adults (184 men, 101 women, mean age 59.0 ± 9.7) who had been recruited to the Early ACTivity in Diabetes (Early ACTID) randomised controlled trial. C-reactive protein (CRP), adiponectin, soluble intracellular adhesion molecule-1 (sICAM-1), interleukin-6 (IL-6), and accelerometer-determined sedentary time and moderate-vigorous physical activity (MVPA) were measured at baseline and after six-months. Linear regression analysis was used to investigate the independent cross-sectional and longitudinal associations of sedentary time with markers of inflammation. At baseline, associations between sedentary time and IL-6 were observed in men and women, an association that was attenuated following adjustment for waist circumference. After 6 months of follow-up, sedentary time was reduced by 0.4 ± 1.2 h per day in women, with the change in sedentary time predicting CRP at follow-up. Every hour decrease in sedentary time between baseline and six-months was associated with 24% (1, 48) lower CRP. No changes in sedentary time between baseline and 6 months were seen in men. Conclusions: Higher sedentary time is associated with IL-6 in men and women with type 2 diabetes, and reducing sedentary time is associated with improved levels of CRP in women. Interventions to reduce sedentary time may help to reduce inflammation in women with type 2 diabetes.

Introduction

Type 2 diabetes is one of the most prevalent chronic diseases worldwide, contributing significantly to the global burden of disease [1]. Diabetes is an independent risk factor for cardiovascular disease (CVD) and in people with CVD, the presence of diabetes worsens prognosis [2]. Chronic inflammation is implicated in the pathogenesis of type 2 diabetes and in the development of CVD and other
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diabetic complications including diabetic retinopathy [3]. Inflammatory cytokines secreted by adipose tissue are involved in the regulation of glucose metabolism and insulin resistance, and also in other inflammatory processes linked to an increased CVD risk [4]. For example, high levels of C-reactive protein (CRP) are related to risk of future CVD in people with type 2 diabetes [5]. The inflammatory nature of type 2 diabetes is partly mediated through increased adiposity [6], with hepatic CRP secretion suggested to increase in response to an adiposity-related increase in another inflammatory cytokine, interleukin-6 (IL-6). Adiposity is also associated with reduced levels of adiponectin [7], an anti-inflammatory cytokine with anti-atherogenic properties. Other, non-adipose, markers of inflammation such as soluble intracellular adhesion molecule-1 (sICAM-1), are independently associated with risk of CVD and provide information on the inflammatory state of the vasculature [8].

Regular physical activity is a cornerstone in the prevention and treatment of type 2 diabetes due to its actions on glucose control, and blood pressure [9] and is also known to reduce inflammation in people with type 2 diabetes [10], therefore providing a potential avenue for intervention to reduce CVD risk. However, people with type 2 diabetes have low levels of physical activity with few meeting physical activity recommendations of 30 min moderate to vigorous physical activity (MVPA) on five days of the week [11]. There is increasing interest in the role that sedentary behaviours may play in adult health. Higher levels of time spent sedentary are associated with an increased risk of type 2 diabetes, cardiovascular disease, and cardiovascular and all-cause mortality [12,13], independently of levels of physical activity. In addition, detrimental cross-sectional associations between sedentary time objectively measured with accelerometers and waist circumference, HDL-cholesterol and insulin resistance have been shown in both healthy individuals [14] and those with type 2 diabetes [15]. In adults with newly diagnosed type 2 diabetes, MVPA accounts for 3.2% of the day in contrast to 61.5% of the day spent sedentary [15], and reducing sedentary time may thus provide an alternative approach to managing health status in such individuals.

There is evidence that prolonged sedentary time may impact upon inflammation [16,17]. However, the mechanism by which this occurs and how much of the effect is mediated through differences in MVPA and adiposity is not well understood. Studies in healthy individuals or those at risk of type 2 diabetes have demonstrated higher levels of objectively measured sedentary time to be associated with CRP, independently of MVPA [14,18,19], and one study reported evidence of a sex difference, with self-reported sitting time associated with inflammation in women, but not men [20]. However, all associations were attenuated when adjusted for BMI [20]. To date, no studies have investigated the independent associations of objectively measured sedentary time with inflammatory biomarkers in individuals with type 2 diabetes.

Therefore, the aim of the present study was to investigate the sex-specific associations of objectively measured sedentary time with selected inflammatory biomarkers in individuals with newly diagnosed type 2 diabetes. If such associations are present, they may indicate an alternative route to improve health in people with type 2 diabetes.

Methods

Participants

This paper presents a secondary data analysis from the Early ACTivity in Diabetes (Early ACTID) study, a randomised controlled trial of physical activity and diet in the management of type 2 diabetes. This study has been described in detail previously [21]. Briefly, participants with newly diagnosed type 2 diabetes were recruited through primary care in the South West of England. Eligible participants had a clinical diagnosis of type 2 diabetes in the previous 6 months and were aged 30–80 years at diagnosis. Participants were excluded on the basis of uncontrolled diabetes (HbA1c > 10% [85.8 mmol/mol]), blood pressure > 180/100 mmHg, LDL-cholesterol >4 mmol/l, and body mass index (BMI) < 25 kg/m² or body weight >180 kg. Telephone screening was performed on 1634 participants, of whom 712 were eligible for face-to-face screening and 593 were enrolled in the study. All participants provided written informed consent prior to participation and ethical approval was obtained from the Bath Hospital Research Ethics Committee (05/Q2001/5). This study is registered (number ISRCTN92162869).

Metabolic and anthropometric outcomes

Venous blood samples were obtained following an overnight fast and analysis was conducted by individuals blinded to the patient’s identity. Serum was analysed for IL-6, sICAM-1 and adiponectin using commercially available solid phase ELISAs (Quantikine, R and D Systems Inc., Abingdon; US). High sensitivity serum CRP was determined using an automated high sensitivity immunoturbidimetric assay and RX Daytona clinical chemistry analyser (Randox Laboratories Ltd., UK). Average intra- and inter-assay coefficient of variation (CV) was established from the repeated analysis of 20–60 samples at different concentrations. The intra-assay CV was 3%, 5%, 6% and 9% for CRP, adiponectin, sICAM-1 and IL-6, respectively. The inter-assay coefficient of variation was 6–7% for all assays except IL-6 which was 16%. Body weight and height were measured to the nearest 0.1 kg and 0.5 cm, respectively with participants wearing light, indoor clothing and without shoes. Waist circumference was measured at the midpoint between the lowest rib and anterior iliac. Social deprivation was measured using the Index of Multiple Deprivation (IMD) score, a measure of local area deprivation that takes into account income, employment, health and disability, education and training, housing and services, living environment and crime, based on re-
respondent’s postcode [22]. Information on current smoking status, ethnicity and medication were obtained by the research nurse.

**Physical activity and sedentary time**

Participants wore an uni-axial accelerometer (Actigraph GT1M; Actigraph LLC, Pensacola, FL, USA) set to record data every minute on a waist-worn belt for seven days during waking hours except when swimming or bathing. Accelerometer data were downloaded using Actilife software (version 10.52 Actigraph LLC) and data were processed using Kinesoft (version 3.3.62; Kinesoft, Saskatoon, SK, Canada) to generate outcome variables (mean daily physical activity, accelerometer counts per minute (cpm), and daily minutes of MVPA and sedentary time). For comparison with other studies, thresholds of $\geq 1952$ cpm for MVPA and $<100$ cpm for sedentary time were used to compute the average number of minutes spent in each behaviour [14,23]. Non-wear time was defined as a period of $\geq 20$ min with continuous zero values, and days with at least 10 h of measurement were considered valid. For inclusion in the analyses, participants were required to record at least three valid days of accelerometer data [15]. Medication was held constant between the baseline and 6 month assessments.

**Statistical analyses**

Since the Early ACTID intervention was not designed to influence sedentary behaviour, data were treated as a cohort and not analysed by trial arm. Descriptive characteristics are summarised as mean and SD, unless otherwise stated. Due to their skewed distribution, inflammatory marker variables were log transformed and are presented as geometric means. Sex differences in demographic, physical activity and inflammatory variables were explored using t-tests for continuous variables and the chi-squared test for differences for categorical data. Paired sample t-tests were used to describe differences in mean values of continuous variables between baseline and 6 months. Linear regression analyses were used to explore cross-sectional associations between sedentary time and inflammatory variables at baseline. Regressions were performed separately in males and females. Linear regression models were built with total sedentary time as the exposure and each inflammatory variable in turn as the outcome. Model 1 was adjusted for age, current smoking (yes/no), trial arm (diet, diet plus activity or usual care), deprivation score, lipid, blood pressure or diabetes-lowering medication (dichotomised as medication yes/no), accelerometer wear time, and MVPA. Model 2 was additionally adjusted for waist circumference. Linear regression was used to examine whether a change in sedentary time between baseline and 6 months predicted the inflammatory variables at follow-up. Models were adjusted as before, and also included baseline values of sedentary time, change in MVPA and the baseline inflammatory variable under investigation. Interaction terms were used to test differences in the effect of sedentary time by sex. CRP can be influenced by acute infection and therefore a sensitivity analysis was conducted to explore whether excluding high values ($>10$ mg/L) influenced the outcome. All analyses were conducted using STATA 12 (College Station, TX; StataCorp). The significance level was set as $p < 0.05$ for all analysis and $p < 0.1$ for interaction terms.

**Results**

A total of 593 patients were randomised to the Early-ACTID study. Of these, 285 (48%) fulfilled the accelerometer inclusion criteria, had complete inflammatory marker profiles at baseline and 6 months and were included in the present analyses. Participants who were included in the analysis tended to be younger than those who had incomplete data ($58.9 \pm 9.7$ years compared to $60.9 \pm 10.5$ years) but there were no other differences in terms of BMI, HbA1c, MVPA or sedentary time.

The baseline demographic, metabolic, inflammatory and physical activity characteristics of the participants are shown in Table 1 ($n = 285$), overall and for each sex separately. Men were more physically active than women. No sex-related differences in total sedentary time were observed. Females tended to be more obese and had higher levels of sICAM-1, CRP and adiponectin than males.

Table 2 shows the regression coefficients for the cross-sectional baseline associations between sedentary time with markers of inflammation, adjusting for medication status, trial arm, age, smoking, deprivation, accelerometer wear time and MVPA. An association was seen between IL-6 and sedentary time in both men and women. For every increased hour spent sedentary, IL-6 was lower by 8% (95% CI 0, 15) in men and 12% (95% CI 0, 24) in women. These associations were attenuated following adjustment for waist circumference. No other associations between sedentary time and inflammatory markers were seen. Removing MVPA from the models did not substantially change the coefficients and all models were unaffected by replacement of BMI for waist circumference. No associations between MVPA and markers of inflammation were observed following adjustment for confounders.

Changes in sedentary time and inflammatory markers between baseline and 6 months are shown in Table 1. Sedentary time was reduced in women only, decreasing by $0.4 \pm 1.2$ h per day between baseline and 6 months. In women, sICAM-1 had reduced by 7.9% (95% CI $-14.3$, $-1.1$) after 6 months and reductions of 42.0% (95% CI $-56.9$, $-22.1$) in CRP were also seen. In men, the only inflammatory cytokine to change was adiponectin increasing by 23.6% (95% CI 12.4, 36.0) after 6 months. Daily MVPA increased by $3.8 \pm 22.9$ min between baseline and follow-up in men, while no changes were seen in women.

Table 3 shows the longitudinal associations between sedentary time and inflammatory outcomes at follow-up. A change in sedentary time from baseline to 6 months
predicted CRP at follow-up in women, with a reduction of 1 h in sedentary time being associated with a 24% (95% CI 1.0, 48.0) reduction in CRP in women, with no associations seen in men.

Regression models containing appropriate interaction terms provided some evidence that any associations between sedentary time and CRP differed for men and women (Table 2). There was also evidence of an interaction by sex for the relationship between a change in sedentary time and CRP (Table 3). All results were unaffected if participants with a CRP >10 mg/L (n = 17) were excluded from the analysis, data not shown.

Discussion

This study investigated the cross-sectional and longitudinal associations between total sedentary time and markers of inflammation in a sample of adults with newly diagnosed type 2 diabetes enrolled in the Early ACTID diet and lifestyle randomised controlled trial. Independent cross-sectional associations between total sedentary time and IL-6 were seen in men and women; however, all associations were attenuated following adjustment for waist circumference. At 6 months follow-up, adiponectin had increased in men compared to baseline and sICAM-1 and

| Table 1 | Demographic, metabolic and inflammatory characteristics of participants at baseline and 6 months. |
|---------|------------------------------------------------------------------------------------------------------------------------------------|
| Characteristic | Men | Women | Total | P Value<sup>a</sup> |
| n | 184 | 101 | 285 |  |
| Age (years) | 59.8 ± 9.3 | 57.5 ± 10.3 | 59.0 ± 9.7 | 0.064 |
| BMI (kg/m²) | 30.6 ± 4.8 | 33.5 ± 7.0 | 31.6 ± 5.8 | <0.001 |
| Waist circumference (cm) | 107.6 ± 11.4 | 105.0 ± 14.9 | 106.7 ± 12.8 | 0.103 |
| Ethnicity (% white) | 97.8 | 96.0 | 97.2 | 0.382 |
| Family history diabetes (%) | 45.1 | 64.4 | 51.9 | 0.002 |
| Current smoker (%) | 5.0 | 8.2 | 7.0 | 0.311 |
| Deprivation index | 14.3 ± 10.0 | 16.9 ± 12.6 | 16.5 ± 15.2 | 0.052 |
| Time since diagnosis (days) | 147.0 ± 52.4 | 145.0 ± 49.4 | 146.3 ± 51.3 | 0.747 |
| HbA1c (%) | 6.6 | 6.8 ± 1.1 | 6.7 ± 1.0 | 0.086 |
| On BP medication (%) | 61.4 | 0.448 |
| On lipid medication (%) | 61.1 | 0.186 |
| On diabetes medication (%) | 36.5 | 0.014 |
| HbA1c (%) | 6.0 | 6.1 | 0.014 |
| IL-6 (pg/ml) | 7.1 (6.0, 8.2) | 7.6 (6.5, 8.7) | 7.3 (6.4, 8.2) | 0.215 |
| CRP (mg/L) | 2.0 (1.8, 2.2) | 2.0 (1.8, 2.2) | 2.0 (1.9, 2.2) | 0.658 |
| Adiponectin (µg/ml) | 5.4 (5.1, 5.9) | 5.2 (4.7, 5.8) | 5.4 (5.1, 5.7) | 0.577 |
| sICAM-1 (ng/ml) | 13.6 (12.3, 15.0) | 12.4 (11.1, 13.8) | 13.0 (12.2, 13.8) | 0.126 |

Results are presented as means ± SD, and number (column percentages).
<sup>a</sup> P value for differences between men and women. Significance level, p < 0.05.
<sup>b</sup> Inflammatory markers are displayed as geometric means ± SD with differences between baseline and 6 months are presented as ratios of the geometric means.
CRP were reduced in women. Lifestyle behaviours were also changed with men increasing MVPA and women reducing sedentary time. Longitudinal associations were demonstrated between a change in sedentary time and follow-up CRP in women. All associations were independent of MVPA. Our results build on accumulating evidence demonstrating between a change in sedentary time and reducing sedentary time. Longitudinal associations were also changed with men increasing MVPA and women decreasing MVPA. Our results build on accumulating evidence demonstrated between a change in sedentary time and reducing sedentary time. Longitudinal associations were also changed with men increasing MVPA and women decreasing MVPA.

This study has several strengths. The study included a relatively large number of adults with newly diagnosed type 2 diabetes. A range of outcome measures including metabolic health, lifestyle behaviours, inflammatory markers and potential confounders including medication status, smoking, and age were collected. Sedentary time was measured objectively using accelerometers. There are also limitations within this study. The observational nature of the analysis means causality cannot be inferred and there is a possibility of residual confounding by other factors, for example dietary intake while sedentary. The analysis was performed separately by sex to allow for differences in the sedentary behaviours as a result of the intervention. There was a suggestion of a possible sex-by-sedentary time interaction for CRP with women exhibiting a greater increase in CRP per unit increase in sedentary time. However, the large discrepancy in sample size between males and females makes meaningful comparisons between sexes difficult.

Although accelerometers offer increased accuracy compared to self-report, they have a number of limitations for the measurement of sedentary time. Whilst the thresholds used to define MVPA measured with the Actigraph accelerometer in adults are well defined, a range of thresholds have been used to define sedentary time [18,20,23]. In addition, the criteria used in data reduction procedures to discard continuous periods of zero values, generally interpreted as time when the accelerometer has been removed, commonly range between 20 and 60 min. Since sedentary time is defined as <100 cpm, and estimates therefore include zero as a ‘real’ value, these decisions may impact upon the measured volume of sedentary time. Such methodological differences limit the potential for comparisons across studies. The thresholds for sedentary time and handling of zero values used in the current study were selected to allow comparison with the AusDiab data [23]. A further limitation of waist-worn

| Table 2 | Cross-sectional linear regression analysis of the associations of sedentary time with inflammatory variables in the full baseline sample. |
|---------|----------------------------------------------------------------------------------------------------------------------------------|
| Sedentary time | Interaction terms |
|                     | Men (n = 184) | Women (n = 101) | B (95% CI) | P value |
| **Log sICAM-1 (ng/ml)** | | | | |
| Model 1 | 0.01 (−0.04, 0.02) | 0.642 | −0.01 (−0.05, 0.04) | 0.751 |
| Model 2 | −0.01 (−0.04, 0.02) | 0.336 | −0.02 (−0.07, 0.03) | 0.409 |
| **Log IL-6 (pg/ml)** | | | | |
| Model 1 | 0.08 (0.00, 0.15) | 0.049 | 0.12 (0.00, 0.24) | 0.043 |
| Model 2 | 0.07 (−0.01, 0.14) | 0.097 | 0.08 (−0.05, 0.20) | 0.228 |
| **Log CRP (mg/L)** | | | | |
| Model 1 | 0.05 (−0.09, 0.19) | 0.485 | 0.16 (−0.05, 0.36) | 0.129 |
| Model 2 | 0.02 (−0.11, 0.16) | 0.768 | 0.06 (−0.14, 0.27) | 0.537 |
| **Log adiponectin (µg/ml)** | | | | |
| Model 1 | 0.00 (−0.07, 0.06) | 0.937 | −0.08 (−0.17, 0.02) | 0.110 |
| Model 2 | 0.00 (−0.06, 0.07) | 0.979 | −0.05 (−0.15, 0.05) | 0.322 |

Regression results are presented as unstandardized coefficients (β) (95% CI). All models are adjusted for age, trial arm, smoking, deprivation score, lipid, glucose or blood pressure lowering medication, baseline sedentary time, change in accelerometer wear time, and change in MVPA. Interaction terms were performed on model 2.

| Table 3 | Longitudinal linear regression analysis of the association of sedentary time with inflammatory variables. |
|---------|----------------------------------------------------------------------------------------------------------------------------------|
| Variable | Δ SED between 0 and 6 months | Interaction terms |
| | Men B (95% CI) | P value | Women B (95% CI) | P value |
| sICAM-1 (ng/ml) | 0.02 (−0.01, 0.06) | 0.220 | 0.01 (−0.05, 0.01) | 0.723 | −0.01 (−0.06, 0.05) | 0.795 |
| IL-6 (pg/ml) | 0.07 (0.00, 0.16) | 0.081 | 0.08 (−0.03, 0.20) | 0.155 | −0.02 (−0.14, 0.11) | 0.801 |
| CRP (mg/L) | 0.05 (−0.11, 0.21) | 0.541 | 0.24 (0.01, 0.48) | 0.043 | −0.23 (−0.47, 0.00) | 0.054 |
| Adiponectin (µg/ml) | 0.03 (−0.04, 0.09) | 0.397 | 0.02 (−0.10, 0.13) | 0.740 | 0.01 (−0.10, 0.11) | 0.890 |

Regression results are presented as unstandardized coefficients (β) (95% CI). All models are adjusted for age, trial arm, smoking, deprivation score, lipid, glucose or blood pressure lowering medication, baseline sedentary time, change in accelerometer wear time, and change in MVPA.
accelerometers in the measurement of sedentary time is their inability to differentiate between postures, and potential for misclassifying standing time as sedentary, since sedentary behaviour is defined as “any waking behaviour characterised by an energy expenditure of less than or equal to 1.5 metabolic equivalents while in a sitting or reclining posture” [24]. To quantify the association between sedentary time and health outcomes precisely, more accurate measurement of sedentary time is required.

The inflammatory profiles of participants in the present study were indicative of low-grade inflammation [25]. Women had heightened inflammation, as indicated by elevated CRP, sICAM-1 and IL-6 compared to men. This is in agreement with previous studies who have also observed associations between sedentary time and adverse health outcomes in women only [20,26]. Previous studies have suggested that the physical activity patterns of men, who tend to do more MVPA than women, may offer protection against the detrimental health effects of sedentary time [20]. Poor dietary behaviours such as snacking are known to co-vary with time spent sedentary, and there are suggestions of a more consistent association in women [27]. More research is needed to understand the dietary implications of prolonged sedentary time, and how these might vary by sex.

The Early ACTID intervention did not specifically target sedentary behaviours. However, women in the cohort achieved an average reduction of sedentary time of 24 min/day after 6 months follow-up and furthermore the change in sedentary time was associated with CRP such that for every hour reduction in sedentary time, CRP was reduced by 24%. It has been suggested that improvements in IL-6 and CRP following lifestyle intervention are dependent upon increases in MVPA [28], or reductions in weight [29]. However, CRP was reduced at 6 months compared to baseline in women, despite no changes in MVPA and the addition of change in MVPA or weight into the regression model did not attenuate the observed associations. This finding further strengthens the cross-sectional associations between breaks in sedentary time and CRP observed in the NHANES cohort that were independent of time spent in MVPA [14]. The health benefits of MVPA are well documented and for people with type 2 diabetes include beneficial effects on lipid profiles, glucose control and inflammation [9]. However, people with type 2 diabetes commonly exhibit low levels of physical activity and interventions to increase MVPA often fail to achieve levels suggested to confer metabolic benefits [21]. In the current study, sedentary behaviour accounted for over 60% of the participants waking day [21], and plausible physiological mechanisms exist to explain the association between prolonged sedentary time and CRP [30]. The accumulating evidence of the detrimental health effects of prolonged sedentary time suggest targeting sedentary time may be an alternative strategy for improving the health of people with type 2 diabetes. These types of interventions may be particularly beneficial for women, who have a heightened state of inflammation and CVD risk and who may find increasing MVPA more difficult.

In conclusion, our data suggest that in women with newly diagnosed type 2 diabetes, sedentary behaviour can have a harmful effect on markers of inflammation which may be important for future risk of CVD. Inflammatory profiles were improved following 6 months of lifestyle intervention, with a change in sedentary time predictive of a change in CRP for the women only, a finding that warrants further investigation. These findings suggest that interventions to reduce sedentary time should be explored as potential ways to reduce chronic inflammation in women with type 2 diabetes. The incorporation of recommendations for reducing sedentary time into national guidelines would provide further impetus for the development of interventions to reduce sedentary time.

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Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

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