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Short Communication

Objectively-Measured Physical Activity, Inflammation, Insulin Resistance, and Diabetes-Induced Chronic Kidney Disease

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Abstract

Background: Examine whether white blood cells (WBC) mediates the relationship between physical activity (PA) and insulin resistance in the broader population (objective 1), as well as the relationship between PA and chronic kidney disease (CKD) among those with diabetes (objective 2).
Methods: Data from the 2003-2006 NHANES study was used, with 3,477 adults examined in objective 1 and 811 adults with diabetes examined in objective 2. Participants wore an ActiGraph 7164 accelerometer to measure PA; insulin resistance was assessed using the Homeostasis Model Assessment; and CKD was assessed from the Chronic Kidney Disease Epidemiology equation.
Results: Regarding objective 1, and after adjustments, there was an inverse association between light-intensity physical activity (LPA) and WBC (b = -0.001; 95% CI: -0.002 to -0.0006), with WBC, in turn, positively associated with insulin resistance (b = 0.02; 95% CI: 0.003 to 0.03). Regarding objective 2, LPA was inversely associated with WBC (b = -0.003; 95% CI: -0.005 to -0.0008), with WBC, in turn, associated with CKD (OR = 1.13; 95% CI: 1.01-1.27).
Conclusions: These findings suggest that PA may be associated with insulin resistance and diabetes-induced chronic kidney disease through modulation of inflammation.

INTRODUCTION

Previous research has demonstrated an inverse association between physical activity and insulin resistance [1,2]; however, the majority of these epidemiological studies used self-reported physical activity methodology, which is prone to considerable measurement error [3]. Although regular physical activity participation may prevent the development of insulin resistance, at this point, the underlying mechanisms to explain this relationship needs further attention. Physical activity may improve insulin sensitivity by increasing the number and translocation of GLUT4 transporters [4]. Given that inflammation is associated with both physical activity and insulin resistance [5,6], it is also plausible to suggest that inflammation may be mediating the relationship between physical activity and insulin resistance. Recent research also indicates that elevated inflammation among adults with diabetes may facilitate the progression of diabetes-induced end-organ failure [7-10]. Although the majority of research in these areas have focused on moderate-to-vigorous physical activity (MVPA), it is plausible to suggest that light-intensity physical activity (LPA) may also play a beneficial role in mitigating inflammation as emerging research is starting to show beneficial effects of LPA on health outcomes [11].

To address these gaps in the literature, the two objectives of this study are: 1) examine whether inflammation (as determined from white blood cell [WBC] levels) mediates the relationship between objectively-measured

physical activity (both MVPA and LPA) and insulin resistance in a U.S. national sample, and 2) examine whether inflammation mediates the relationship between physical activity (both MVPA and LPA) and diabetes-induced chronic kidney disease (CKD) among a U.S. national sample of adults with diabetes.

METHODS

Study Design

Data from the 2003-2006 National Health and Nutrition Examination Survey (NHANES) were used. NHANES is an ongoing survey conducted by the National Center for Health Statistics (NCHS), a major section of the Centers for Disease Control and Prevention. NHANES uses a representative sample of non-institutionalized U.S. civilians, selected by a complex, multistage probability design. The survey consists of two primary components, including participants being interviewed in their homes and subsequently examined in mobile examination centers (MEC) across the selected counties. All procedures for data collection were approved by the NCHS ethics review board, and all participants provided written informed consent prior to data collection. In the 2003-2006 NHANES, 20,470 participants enrolled. After excluding participants with missing WBC, kidney function or covariate data, 12,684 remained. After excluding those with insufficient accelerometery data (i.e., < 4 days of 10+ hrs/day), 7,943 remained. Among these, 811 had evidence of diabetes. Only a subsample of participants was eligible for the morning fasting session. After excluding participants with missing fasting insulin or glucose data (used to calculate insulin resistance), 3,477 participants remained.

Measurement of Physical Activity

At the mobile examination center, participants who were able to walk were asked to wear an ActiGraph 7164 accelerometer on their right hip for 7 days. Accelerometers were affixed to an elastic belt that was worn around the participant's waist near the iliac crest. Participants were asked to wear the accelerometer during all activities, except water-based activities and while sleeping. The accelerometer measured the frequency, intensity, and duration of physical activity by generating an activity count proportional to the measured acceleration [12]. Estimates for LPA and MVPA were summarized in 1-minute time intervals. Activity counts between 100 and 2019 counts per minute were classified as light-intensity physical activity, and activity counts greater than or equal to 2020 were classified as MVPA intensity [13]. To determine the amount of time the monitor was worn, nonwear was defined by a period of a minimum of 60 consecutive minutes of zero activity counts, with the allowance of 1-2 minutes of activity counts between 0 and 100 [13]. Accelerometry has been shown to be a valid measure of physical activity, with accelerometer-determined activity counts from walking being highly associated with indirect calorimetry (r = 0.77) [14].

Objective 1: Does Inflammation Mediate the Relationship Between PA and Insulin Resistance Among the Broader Population?

In the 2003-2006 NHANES cycle, and after excluding those with insufficient accelerometry data, missing fasting insulin and glucose data (used to assess insulin resistance), missing data on the covariates (i.e. age, gender, race-ethnicity, C-reactive protein (CRP), body mass index, cotinine, comorbidity index, A1C, and CKD [as measure by glomerular filtration rate]), 3,477 remained, which comprised the analytic sample.

Measurement of Insulin Resistance and Chronic Kidney Disease

The Homeostasis Model Assessment (HOMA) was used to evaluate insulin resistance using the following formula: fasting serum insulin (uU/mL) x fasting plasma glucose (mmol/L) / 22.5 [15]. Glomerular filtration rate, an assessment of kidney function, was assessed from the CKD Epidemiology equation based on specified race, sex, and creatinine level, with CKD including those with a glomerular filtration rate < 60 mL/min per $1.73m^2$ [16].

Inflammation as Assessed by White Blood Cells (WBC)

The method used to determine WBC was based on the Beckman Coulter method of counting, in combination with an automatic diluting and mixing device for sample processing.

Covariates

Information regarding potential covariates was gathered based on previous research demonstrating a link between these covariates and physical activity, insulin resistance, and/or inflammation. Information about age, gender, race-ethnicity, and the number of comorbidities (i.e., comorbidity index) [17] participants had, were obtained from a questionnaire. Comorbidities were based on self-report of the following chronic diseases/events: arthritis, coronary heart disease, stroke, congestive heart failure, cancer, heart attack, emphysema, chronic bronchitis, asthma, and hypertension. Diabetes was also included as a comorbidity, with diabetes defined as a self-report of a previous diagnosis of the disease (excluding gestation diabetes mellitus), taking insulin or diabetic pills to lower blood sugar, a blood glycohemoglobin (i.e., hemoglobin A1C) of 6.5% or greater, or a fasting glucose level of 126 mg/dL or higher. Other covariates included serum cotinine, hemoglobin A1C, high sensitivity CRP, and measured body mass index (BMI).

Data Analysis for Objective 1

Analyses were performed using Stata. Fasting sample weights were used for the analyses for objective 1. Linear regression was used to examine the association between physical activity (independent variable) and WBC (dependent variable). Two models were computed, one for LPA and one for MVPA. Then, a linear regression was used to examine the association between WBC (independent variable) and insulin resistance (dependent variable). Insulin resistance was log-transformed to improve normality. A Sobel test was used to test for mediation. Models controlled for age, gender, race-ethnicity, CRP, BMI, cotinine, comorbidity index, chronic kidney disease, and A1C. Statistical significance was established as $p < 0.05$.

Objective 2: Does Inflammation Mediate the Relationship Between PA and Chronic Kidney Disease among Adults with Diabetes?

For this objective, only adults with evidence of diabetes were included in the analysis. After excluding those without diabetes, insufficient accelerometry data, and missing data on the covariates (i.e., age, gender, race-ethnicity, C-reactive protein, body mass index, cotinine, comorbidity index, and A1C), 811 participants remained for analysis of Objective 2.

Analysis for Objective 2

MEC sample weights were used for these analyses. Among those with diabetes, linear regression was used to examine the association between physical activity (independent variable) and WBC (dependent variable). Two models were computed, one for LPA and one for MVPA. Then, a logistic regression was used to examine the association between WBC (independent variable) and CKD (dependent variable). Models controlled for age, gender, race-ethnicity, CRP, BMI, cotinine, comorbidity index, and A1C. Statistical significance was established as $p < 0.05$.

RESULTS

Mean (SE) accelerometer wear time, age, BMI, % female, and % non-Hispanic white, respectively, for the sample in Objective 1 was 14.2 hrs (0.02), 44.2 yrs (0.6), 28.3 kg/m^2 (0.2), 51.0 % (1.0), and 71.5% (2.5). For the sample in Objective 2, the results for these characteristics were 14.05 hrs (0.08), 58.9 yrs (0.7), 31.7 kg/m^2 (0.3), 49.5% (2.1), and 66.2% (59.4). Additionally, 20.1% of those with diabetes had chronic kidney disease.

Objective 1: Does Inflammation Mediate the Relationship Between PA and Insulin Resistance Among the Broader Population?

After adjustments, there was a direct inverse relationship between LPA and insulin resistance (b = -0.001, p < 0.001). MVPA was also directly inversely related to insulin resistance (b = -0.003, p < 0.001). Similarly, there was an inverse association between LPA and WBC (b = -0.001; 95% CI: -0.002 to -0.0006; p = 0.001); results were similar for MVPA (b = -0.007; 95% CI: -0.01 to -0.002; p = 0.003). After adjustments, WBC was positively associated with insulin resistance (b = 0.02; 95% CI: 0.003 to 0.03; p = 0.01). The Sobel (p < 0.01) mediational test was significant for both LPA and MVPA.

Insulin Resistance and Diabetes

A logistic regression analysis was then computed to examine the association between insulin resistance and presence of diabetes. After adjustments, for every 1-unit increase in log-transformed insulin resistance, participants were 2.1 (OR = 2.14; 95% CI: 1.47 – 3.11; p < 0.001) times more likely to have diabetes.

Objective 2: Does Inflammation Mediate the Relationship Between PA and Chronic Kidney Disease among Adults with Diabetes?

LPA (1-min increase) was directly inversely associated with CKD (OR = 0.99, p = 0.003). LPA was inversely associated with WBC (b = -0.003; 95% CI: -0.005 to -0.0008; p = 0.01) among adults with diabetes; however, MVPA was not associated with WBC (b = -0.007; 95% CI: -0.02 – 0.008; p = 0.34). WBC, in turn, was associated with CKD. For every 1-unit increase in WBC, participants were 13% (OR = 1.13; 95% CI: 1.01-1.27; p = 0.03) more likely to have chronic kidney disease.

DISCUSSION

The purpose of this brief report was to further the understanding of the potential underlying mechanisms to explain the relationship between physical activity and insulin resistance and diabetes-induced chronic kidney disease. Although the magnitude of the associations were relatively small, the findings suggest that inflammation may help to explain the beneficial effects of physical activity in reducing the onset of insulin resistance in the broader population and chronic kidney disease among those with diabetes. Specifically, the 3 major findings of the present study include: 1) participants with higher physical activity levels had lower WBC levels, and those with lower WBC levels were less insulin resistant; 2) those with a greater degree of insulin resistance were more likely to have diabetes (as expected); and 3) among those with diabetes, those engaging in more light-intensity physical activity had lower WBC levels, and those with lower WBC levels were less likely to have chronic kidney disease. Overall, these findings suggest that physical activity may reduce the development of

insulin resistance and diabetes among the broader population via mitigation of inflammation, and then among adults with diabetes, physical activity may attenuate the progression of diabetes-induced chronic kidney disease through modulation of inflammation.

Research demonstrates that physical activity is inversely associated with insulin resistance [1,2,18]. The present study adds to the literature by suggesting that this association may occur through physical activity-induced reduction in inflammation. Additionally, these findings also suggest that physical activity may attenuate the progression of diabetes-induced end-organ damage through modulation of inflammation. Major strengths of this study include examining these understudied questions, utilizing a national sample of U.S. adults, and employing an objective measure of physical activity. Although accelerometry does overcome many of the limitations associated with self-report, it is important to note that it is not without its own inherit limitations, including an underestimation of physical activity for certain modes of exercise. Further, given that individuals without valid accelerometry data differ than those with valid accelerometry [19], it is not possible to fully discount on bias this may have introduced. Future experimental work is needed as the cross-sectional nature of the present study precludes any ability to render cause-and-effect. Also, future work looking at WBC levels along with other biomarkers (e.g., IL-6) will provide more conclusive evidence of a potential role of inflammation in mediating the relationship between physical activity and insulin resistance/CKD.

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