Health Effects of Increasing Muscle Activation While Sitting in Office Workers

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Overview of Study Design

The primary purpose of the proposed study is to examine if altering sitting behavior in office workers alters blood glucose regulation and cardiorespiratory fitness. The secondary aim is to examine how the intervention may influence blood pressure, body composition, and blood lipids. We will recruit physically inactive to recreationally active subjects that have a sedentary job in which they sit for at least 6 hours/day 5 days/week. Participants will be placed evenly into one of two groups. The first group will begin the intervention immediately following the baseline health testing. The second group will be a delayed intervention group. This group will undergo the initial baseline health testing and then make no changes to physical activity for the following 4 weeks after which they will repeat the health testing. Next this group will perform the intervention just like the first group.

The study will begin with a blood lipid (HDL, LDL, total cholesterol, and triglycerides) measurement, resting blood pressure measurement, VO_2max test to determine aerobic capacity and fitness level, and instructions regarding the nutritional requirements. These measurements will take place at the University of Colorado Boulder Clinical Translational Research Center (CTRC). The following meeting will be for a dual energy absorptiometry (DXA) scan which will take place in the UCB Exercise Physiology Laboratory located within the UCB Ramaley Biology building. For the following week, subjects will wear an activity monitor so that we can determine their baseline sitting levels. After wearing the activity monitor, subjects will undergo an oral glucose tolerance test (OGTT). The location for the OGTT will be a private room located within the UCB library or a private room associated with our lab (the Applied Exercise Science Laboratory). Subjects will then be evenly split into two groups. Subjects in the first group will be given a compact cycle ergometer (a DeskCycle) and instructed to use it for 15 minutes within every 60 minutes while at work for the next 4 weeks. In addition, subjects will be instructed to maintain their normal exercise/physical activity routine, which will be documented using physical activity logs and an activity monitor worn during the final week of the intervention. Immediately following the four-week intervention, subjects will repeat the procedures utilized during the pre-intervention testing (although the order of the sessions will be reversed). Subjects in the second group (delayed intervention group) will also do this same intervention, however, they will first have 4 weeks of no intervention and will repeat the health testing before being given a DeskCycle to use. We will then compare the results from the tests to determine how breaking up daily sitting levels can influence health markers.

Initial Screening Protocol

To study the impact of sitting on health markers in office workers, we will recruit physically inactive to recreationally active males and females (18-55 years old) from the University of Colorado Boulder libraries, general campus, and the surrounding Boulder area. Potential subjects will find out about the study by flyers placed around the university and Boulder area. In addition, flyers will be sent out through email newsletters (for example CU department newsletters). Interested individuals will then contact the researchers and complete a preliminary health questionnaire to determine if they meet the inclusion criteria. The researchers will determine if subjects can be included in the study based on their responses. The preliminary screening will be completed either 1) over the phone; 2) via a secure online website (Red Cap) or 3) by being sent and returned through the mail (USPS). The screening tool sent through the mail and via the secure online website will only include a unique code number and not any identifying information such as a name. The health questionnaire will be used to determine if subjects meet

inclusion/exclusion criteria. In addition, the screening questions will be limited to inclusion/exclusion criteria (i.e. daily sitting amounts) and demographic data will not be collected until after the informed consent document is signed. If a subject would prefer to perform the screening over the phone, the health questionnaire will be completed over the phone. Also included in the email (or over the phone), the contact person will provide the potential subject with more information about the study.

VO_2max Test Session

Those individuals who meet the inclusion criteria will proceed to the informed consent process, medical history and physical exam, blood lipid measurement, blood pressure measurement, perform a VO_2max test, and be instructed on the dietary requirements associated with the study. The session will last about 2 hours. Subjects will need to arrive at the CTRC following an overnight fast.

Informed consent will be obtained by a member of the research team. Informed consent will be obtained in a quiet and private room to ensure confidentiality. Consent will be obtained after the subject has thoroughly read the informed consent form. The subject will be asked if he/she has any questions or is confused on the purpose, methods, or any risks or benefits of the study. The participant will also be asked to describe the procedures back to the researcher in his/her own words to ensure comprehension.

After obtaining informed consent, subjects will undergo a medical history and physical exam by the CTRC clinical staff. Following this, a blood sample will be taken via a single venipuncture by a trained member of the CTRC staff. Approximately 5ml of blood will be taken from a vein in the arm or hand for determining a blood lipid profile (HDL, LDL, total cholesterol, and triglycerides). This blood sample will be sent to the University of Colorado Hospital (UCH) to be analyzed by direct assay.

Next, we will take a resting blood pressure measurement using a Datascope Accutorr V automatic blood pressure monitor. Subjects will sit quietly in a private room with feet flat on the floor. Blood pressure readings will be taken every 5 minutes until values change by ≤2mmHg.

Following this, subjects will perform a VO_2max test on a bicycle ergometer. In accordance with the UCB CTRC requirements, females >50 and males >40 years old will require a physician to be present and will perform a combined VO_2max test and graded exercise test (GXT). During the GXT, a physician will be present to monitor the output from a 12 lead ECG. The GXT portion of the test will be used to confirm the older subjects are able to participate in the study and the GXT portion will only be performed during this initial visit – the following VO_2max testing sessions will only involve VO_2 measurement. The initial stage of the test will be a workload of 0 Watts and the workload will increase every 2 minutes by 25 Watts (females) or 40 Watts (males). During the last 30 seconds of each stage, we will determine rating of perceived exertion (RPE) using the Borg scale. The test will end once the subject reaches volitional fatigue. During the test, metabolic variables (VO_2, VCO_2, and V_E) will be measured using indirect calorimetry. Heart rate will also be measured throughout the test.

After the VO_2max test, subjects will be instructed on the dietary requirements of the study by a member of the research team. Subjects will fill out a nutrition assessment form, including vitamin and supplement use. Subjects will receive instruction on how to follow a 150-gram carbohydrate diet for the 3 days prior to their OGTT sessions. Carbohydrate, caffeine, and alcohol ingestion during the days leading up to an OGTT can influence the results obtained during the OGTT. Thus, subjects will also be instructed to refrain from eating/drinking foods

with caffeine or alcohol for the 3 days prior to the OGTT. Lastly, subjects will be instructed to record their diet during the 3 days using myfitnesspal.com so that diet compliance can be verified. The website myfitnesspal.com is an easy to use electronic diet log. Subjects select foods they ate and portion sizes for those foods and the website provides summaries of macronutrient consumption (i.e. carbohydrate) along with a list of foods consumed. Dietary compliance will be verified by inspecting this electronic diet log of subjects to make sure they consumed 150g of carbohydrate and did not eat/drink foods with caffeine or alcohol. Subjects will log in to myfitnesspal.com and/or download their diet log so that a member of the research team can check it. Subjects will not be asked for their log in information and the diet logs will only be checked prior to the OGTTs.

DXA Testing Session

No more than a week after the first visit at the CTRC, subjects will undergo a dual energy x-ray absorptiometry (DXA) scan (GE Lunar DEXA system) at the UCB Exercise Physiology Laboratory performed by a trained member of the research staff. The DXA scan will be used to determine whole body muscle, fat, and bone masses. Females will be asked to take a urine pregnancy test prior to the DXA scan. Height and weight will also be measured to determine BMI. To better describe our subjects, we will collect anthropometric data. This anthropometric data will only be collected during this initial DXA session and will not be a variable for determining the effect of the workplace intervention. The waist to hip ratio will be measured with the waist circumference measured at the narrowest part of the torso (above the umbilicus and below the xyphoid process) and hip circumference at the hip or buttocks region, whichever is larger above the gutueal fold. Abdominal sagittal diameter will be measured at the level of the umbilicus. Waist circumference will be normalized to subject height.

These procedures will be performed at the UCB Exercise Physiology Laboratory located within the Ramaley Biology building. The use of the DXA machine for research purposes has been approved by UCB Environmental Health and Safety. To ensure the safety of research participants, the DXA machine undergoes preventative maintenance annually by the manufacturer. Additionally, the x-ray unit is inspected every 2 years by a qualified inspector for the State of Colorado.

Subjects will also be instructed to wear an activity monitor and record their daily training for the following week (Trost et al. 2005). Thus, at the end of the DXA session, subjects will be instructed on the use of the activity monitors and how to wear them. We will provide subjects with an activity monitor (Actigraph GT3x+, Actigraph, Pensacola, FL) that they will be instructed to wear on their hip in line with the right leg. Subjects will also be instructed on how to complete the exercise/training logs provided by the research team.

OGTT Session

After wearing the activity monitor for one week, subjects will undergo an OGTT. The location for the OGTT will be a private room within the UCB library or a private room associated with our lab (the Applied Exercise Science Laboratory. Prior to the OGTT, subjects will be instructed to fast overnight, minimize physical activity for that day (i.e. minimal walking and no other exercise) and consume at least 150g of carbohydrate during the 3 days prior. The OGTT session will last 2.5 hours.

The visit will begin with a member of the research team inquiring about hydration, restroom, and fasting status. The time of the subject's last meal will also be recorded. The subject will then be given time (10-15 min) to acclimate to the lab setting. During this time, we will download the data from the activity monitor and collect the completed physical activity and diet logs from the subjects. The procedure will be fully explained to the subject. If the subject is visibly agitated after 15 minutes, we will confirm that the subject would still like to proceed with the test. If the subject is experiencing extreme agitation, (e.g. crying, shaking) the test will be rescheduled and/or the participant will be excluded.

Subjects will then have a finger stick to collect 25 µL of blood that will be mixed with a "cocktail" containing 50 µL of a buffer, lysing (Triton XL-100), and anti-glycolytic (sodium fluoride) solution. The finger sticks will be performed by a trained member of the research staff who has completed the Blood Borne Pathogen biosafety training. Each sample will then be analyzed in duplicate using a YSI 2300 glucose analyzer (YSI, Yellow Springs, OH USA). As part of our safety measures, we will also measure blood glucose levels on the spot using a handheld glucometer (Precision Xtra glucometer). Before starting the OGTT, if blood glucose values are outside of the range of 60-120mg/dL, the session will be cancelled and rescheduled.

Next, subjects will have 2 minutes to consume a 300ml beverage with 75 grams of glucose. Once subjects have finished the glucose beverage, a timer will start. Over the next 2 hours, subjects will be allowed to read, type on the computer, watch TV, or continue their normal work routine as long as they are sitting. Some subjects (especially those not accustomed to sugar intake) may have an adverse reaction (nausea, light-headedness, fatigue) to the glucose drink. We will ensure there is an appropriate receptacle nearby (any nausea that leads to vomiting or lasts more than 30-60 minutes will lead to termination of the OGTT). During the test, if a subject is feeling lightheaded, faint, or nauseous, a member of the research team will provide the subject with the assistance they need (i.e. water, cool towel, lay them down with feet elevated, etc.). If the situation is life threatening, 911 will be called and the subject will be maintained until paramedics arrive.

Because the two-hour time point is commonly used as a marker for diabetes risk we will only measure glucose levels at this time point during the OGTT. Two hours after the subjects finished the glucose drink, a trained member of the research team will perform another finger stick and we will determine the 2-hour post glucose levels. Blood glucose levels will also be measured on the spot at this time as well. At the 2-h post OGTT time point, if blood glucose values are <60mg/dL, subjects will be required to eat a granola/energy bar or consume a sugary beverage (provided by the researchers) prior to leaving. A member of the research team will remain by the subject's side (or slightly behind them) as they stand from the chair in case of dizziness or vertigo.

Subjects will be informed about any clinically relevant abnormal finding during the session.

DeskCycle Intervention

Following the pre-intervention testing sessions, subjects will be evenly placed into one of two groups. The first group will be given a compact cycle ergometer (a DeskCycle) to use immediately following the pre-intervention testing sessions. The second group will be a delayed intervention group and as such, will make no changes for the 4 weeks after the pre-intervention testing sessions. Subjects in the delayed intervention group will repeat the testing sessions after this 4-week control and then begin the DeskCycle intervention like the first group.

Subjects will be instructed to use the DeskCycle for 15 minutes within every 60 minutes while they are at work. There are currently no well-defined studies regarding how often sitting bouts need to be broken up. However, a recent expert statement suggests "For those occupations which are desk based, workers should aim to initially progress towards accumulating 2h/day of standing and light activity" (Buckley et al. 2015). In addition, research suggests that breaking up sitting throughout the day is important for health (Healy et al. 2008). Subjects will be instructed to use the DeskCycle for 15 minutes within every 60 minutes throughout an 8-hour workday. Therefore, subjects will be required to cycle for 2 hours each workday but will be instructed that they can cycle more if they would like.

A variety of intensities can be performed when using the DeskCycle. For this protocol, we will instruct subjects to use settings "2" or "3" on the DeskCycle. Previous work by Dunstan et al. (2012) found that breaking up sitting bouts with light-intensity walking was just as beneficial as breaking up the sitting bouts with moderate-intensity walking. Preliminary work in our lab has found that settings "2" and "3" double energy expenditure compared to resting values, which is similar to light-intensity walking. To monitor adherence to the protocol, subjects will complete a log (Attachment 11) that includes when and how long they rode the DeskCycle every hour. The DeskCycle's built in computer will also be used to monitor adherence. Subjects will also be instructed to maintain their normal exercise routine and this will be monitored with the use of activity logs (Attachment 6).

Additionally, during the final week of the intervention, subjects will be given an activity monitor to wear so we can determine if there are any compensatory changes to physical activity when using the DeskCycle. Because Actigraph activity monitors do not accurately detect cycling, the activity monitors will be used to determine physical activity levels when subjects are not using the DeskCycle. Previous research has suggested that physical activity increases when performing the intervention but there is a compensatory change so that physical activity the remainder of the day is lower. We will use the activity monitors to measure physical activity levels when subjects are not cycling and thus determine if there are compensatory changes with a DeskCycle intervention.

Follow-up Physiological and Blood Parameter Testing Sessions:

We will repeat the physiological testing 4 weeks after starting the DeskCycle intervention. The post-intervention testing sessions will follow the same format as the pre-intervention testing sessions. Unlike the pre-intervention testing though, the OGTT session will be first. The order of the sessions will be reversed for the post testing because we do not want the VO_2max test to influence the more sensitive blood parameter measurements. For example, the high-intensity physical activity associated with the exercise test could influence blood glucose regulation within the following few days when the OGTT would take place. Prior to the OGTT session, subjects will be asked to eat at least 150g of carbohydrate to prepare for the OGTT and refrain from consuming caffeine or alcohol. In addition, we will ask subject to repeat their exercise routine that they performed during the 3 days before the preliminary OGTT session. Within 1 week, subjects will report back to the CTRC for the VO_2max testing session (which includes the exercise test, blood pressure measurement, and blood draw for a lipid profile) and to the UCB Exercise Physiology Lab for the DXA scan. In between the sessions, subjects will be able to continue to use the DeskCycle. We will then compare the pre- and post-intervention measures to determine how breaking up sitting bouts with a DeskCycle may influence markers associated with disease states like diabetes and cardiovascular disease.

Sample Size Justification

To determine the sample size for our primary aims (blood glucose and cardiorespiratory fitness), we calculated the required sample size for a power value of 80% ($\beta = 0.2$) and a 2.5% Type I error rate ($\alpha = .025$). We utilized the statistical software G*Power for determining sample size when comparing the difference between two dependent means with a two-tailed t-test. Based on previous research in our lab, the expected increase in cardiorespiratory fitness (VO_2max) is 0.18 L/min with a standard deviation of the difference being 0.16 L/min. A sample size of 11 would therefore be required. For blood glucose, using data from a different study in our lab, the expected decrease in 2-hour post OGTT glucose is 16.0 mg/dL with a standard deviation of the difference being 21.5 mg/dL. This results in a required sample size of 20. Because the glucose comparison requires the greatest number of subjects, we will have 20 subjects complete the protocol. Based on similar protocols in our lab, we expect a dropout rate of 20% so we will aim at recruiting approximately 25 subjects in order to attain the necessary complete data set for the desired 20-subject total. The secondary aims (blood pressure, body composition, and blood lipids (HDL, LDL, total cholesterol, and triglycerides)) of the study are exploratory in nature and therefore we will not power the study based on these other measures.

Analysis Plan

The primary outcomes will be 2-h OGTT blood glucose and cardiorespiratory fitness. For blood glucose regulation, we will compare the resting (pre OGTT) glucose levels and we will also compare the 2-hour post-load glucose levels. Secondary outcomes will be resting blood pressure, body fat, and blood lipid levels (HDL, LDL, total cholesterol, and triglycerides).

Comparisons of both primary and secondary outcomes will be made with paired two-tailed t-tests. To examine the effect of the control condition in the delayed intervention group, we will compare the pre- and post-control values. If there is a difference between these measures, we will keep the groups split up and calculate the difference scores between the pre- and post-intervention values. We will then compare these difference scores from each group. Previous research from our lab has found no difference in VO_2peak following a short control period. Thus, we expect there will be no difference following the control condition. If there is no difference in the control condition for the delayed intervention group, we will combine the two groups. We will then determine the effect of the intervention by comparing the pre- and post-intervention values (for the delayed intervention group, we will use the post-control/pre-intervention values). Statistical significance will be evaluated at the alpha = 0.025 level to accommodate the multiple outcomes being tested for this project.