Acute Effects of a Sit-stand Workstation on Blood Glucose Regulation in Working Women with Impaired Fasting Glucose

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Dedication

This dissertation is dedicated to my husband, Greg Bonikowske, and our beautiful baby girl, Sadie!

Abstract

Our society has become increasingly sedentary, which has resulted in numerous health complications. For example, there has been an increase in blood sugar regulation abnormalities, which can lead to pre-diabetes and eventually type 2 diabetes. This dissertation focuses on working women whom, upon initial screening, demonstrated a fasting blood sugar greater than 100 mg/dl. The participants completed two separate trials; 1) sitting and standing while completing an oral glucose tolerance test at work; and 2) sitting for one week followed by standing for one week at work while wearing a continuous glucose monitor and an accelerometer. The first Manuscript (Chapter 4) summarizes a randomized, cross-over pilot study evaluating the acute effect of standing at work on postprandial glucose. Results indicated elevated postprandial glucose while standing (Glucose iAUC = -124.9 ± 481.7, 95% CI [-386.7, 137]) relative to sitting. Manuscript II (Chapter 5) summarized a repeated measures pilot study examining the effect of standing in the workplace on blood glucose regulation over a one week period among women with impaired fasting glucose. Sedentary time significantly predicted blood glucose independent of physical acitivity (p = .015). Manuscript III (Chapter 6), also a repeated measures study, is a brief report examining the effect of a sit-stand desk on sedentary time during the work day among pre-diabetic adults. A nonsignificant reduction in sedentary time was found in the life, health, and combined life and health zones in the sit-stand condition relative to the sitting condition (life: 1.37 ± 2.77; 95% CI [-0.35, 3.08]; health: 0.55 ± 1.56; [-0.42, 1.52]; life and health: 1.92 ± 3.44; [-0.21, 4.05]; zone intensities are life < 2 mph, health 2-4.5 mph, and sport > 4.5 mph). Additional research should recruit larger sample sizes and examine the long-term effect of reducing sedentary time on blood glucose among working adults with impaired fasting glucose.

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Introduction

1.1 Background

Traditional physical activity interventions produce beneficial effects on glucose regulation and diabetes management (Andrews et al, 2011; The Look AHEAD Research Group, 2010). These interventions also significantly increase physical activity levels, which contributes to health improvements among individuals with impaired glucose regulation. In addition to traditional physical activity interventions, studies suggests that reducing sedentary time, time spent sitting, and increasing light activity (i.e. non-exercise activity thermogenesis; NEAT) can improve blood sugar regulation and produce beneficial changes in weight (Levine & Miller, 2006; Healy et al., 2008). The detrimental effects of sitting can occur independent of physical activity level (van der Ploeg, Chey, Korda, Banks, & Bauman, 2012). While increasing physical activity is an effective method for reducing disease risk, the problem with previous lifestyle intervention studies is that they have several components, are expensive, and may not translate well to the real world.

1.2 Rationale

This dissertation will address the following gaps in the literature regarding the effect of sitting on health outcomes:

1. Minimal published literature analyzes the acute effect of reducing sedentary time on blood sugar among pre-diabetic adults. Studies examining employee wellness programs have targeted healthy adults or those with chronic disease but not pre-diabetic adults specifically. Additional studies have examined variations of sit-stand desks in the workplace but again, a pre-diabetic population has not been studied utilizing this approach.
2. The literature contains limited studies evaluating the acute effect of light activity (i.e., standing) on blood sugar regulation in pre-diabetic women. There are no published studies evaluating postprandial glucose responses to standing vs. sitting among pre-

diabetic women. Research suggests that reducing sedentary time and incorporating frequent breaks could produce beneficial health outcomes including improved blood glucose regulation, reduced CVD risk, and reduced inflammatory biomarkers (Owen, Healy, Matthews, & Dunstan, 2010).

3. Finally, continuous glucose monitoring technology has not been utilized in the pre-diabetic population and therefore, the current studies will inform future research that aims to prevent the progression of pre-diabetes to type 2 diabetes. Thus, the manuscripts will add to the growing literature examining the effect of sit-stand desks on reducing sedentary time in the workplace, but specifically among pre-diabetic adults.

The purpose of this dissertation was to examine the effect of a sit-stand desk on blood glucose and sedentary time among prediabetic women. The sit-stand desk was the primary intervention tool, which was installed or was already at the participant's workplace for the intervention period. The purpose of the sit-stand desk was to increase light intensity activity, reduce sitting time, and reduce sedentary time at work. The desk is designed for working in a seated or standing position and is ergonomically correct in both positions. The workplace was a logical target for reducing sedentary time considering that many full-time employees spend three to five hours of their day sitting (Jans, Proper, & Hildebrandt, 2007; Brown, Miller, & Miller, 2003). A brief intervention that promotes reductions in sedentary time and increases in NEAT (i.e., light activity) has the potential to increase energy expenditure and improve blood glucose regulation.

The manuscripts within this dissertation are the first, to my knowledge, to examine the acute effects of a sit-stand desk intervention to reduce blood glucose and sedentary time among pre-diabetics in the workplace. The first manuscript evaluates the effect of a sit-stand desk on postprandial glucose during an oral glucose tolerance test (Specific Aim 1; Chapter 4). The data was collected from adults who spent the majority of their day sitting at their job. The participants

were recruited from Fairview Health Services and from the Minnesota Department of Human Services. The second manuscript investigates the effect of using a sit-stand desk for an entire working week on blood sugar regulation in pre-diabetic adults (Specific Aim 2; Chapter 5). The data for the second manuscript was collected from the same pre-diabetic adults that participated in the oral glucose tolerance test. The third manuscript examines the effect of a sit-stand desk on sedentary time at work relative to a traditional desk (Specific Aim 3; Chapter 6). The data for the final manuscript was collected concurrently from the participants who provided data in the second manuscript. The specific aims and hypotheses for the manuscripts are summarized below.

1.3 Specific Aims and Hypotheses

Specific Aim 1: To examine the acute effect of using a sit-stand desk at work on postprandial glucose among pre-diabetic adults.

Related hypothesis. Participants will exhibit lower postprandial glucose levels when using a sit-stand desk when compared to a traditional desk.

Specific Aim 2: To examine the effect of using a sit-stand desk at work on blood glucose control among pre-diabetic adults.

Related Hypothesis. Participants will exhibit improved blood glucose regulation when using a sit-stand desk when compared to a traditional desk.

Specific Aim 3: To examine the effect of using a sit-stand desk at work on sedentary time among pre-diabetic adults.

Related Hypothesis. Participants will engage in less sedentary time when using a sit-stand desk when compared to a traditional desk.

2

Literature Review

2.1 Introduction

2.1.1 Prevalence of Blood Sugar Regulation Dysfunction

Diabetes has reached epidemic proportions in the United States and worldwide. The World Health Organization (WHO) reports 346 million people worldwide have diabetes (WHO, 2011). Type 2 diabetes accounts for 90% of these individuals. In the United States alone, the number of people with diabetes has recently risen to 25.8 million along with an estimated 79 million afflicted with pre-diabetes (defined as blood sugar levels above normal but not at the diagnostic criteria; Centers for Disease Control and Prevention [CDC], 2011). In 2010, 1.9 million individuals were newly diagnosed with diabetes (CDC, 2011). Diabetes is the seventh leading cause of death and a chief cause of heart disease and stroke, kidney failure, lower limb amputations and new cases of adult blindness (CDC, 2011). Diabetes also leads to conditions such as retinopathy, neuropathy, hypertension, dental disease, pregnancy complications, depression, decreased quality of life, and susceptibility to other illnesses (CDC, 2011). The overall risk of death among diabetics is two times greater than their non-diabetic counterparts (CDC, 2011). A low level of physical activity and obesity are two of the primary risk factors and predictors for the development of diabetes (USDHHS, 2008). The literature review will outline the current knowledge related to the following: (1) Physical inactivity and blood sugar regulation (Part 1); (2) sedentary behavior and physical inactivity physiology (Part 2); and (3) continuous glucose monitoring (Part 3).

Part 1: Physical Inactivity and Blood Sugar Regulation

2.2 Prevalence of Physical Inactivity

The recent data on leisure-time physical activity levels in the United States indicate that in many parts of the nation more, than 30% of adults do not participate in any leisure-time physical activity (CDC, 2009). The current data demonstrates age-adjusted rates for leisure-time physical inactivity range from 10% to 43% in US counties (CDC, 2008). High levels of

diagnosed diabetes and obesity are also prevalent in the counties representing the high end of the spectrum. According to the World Health Organization (WHO), 50% of women and 40% of men are not achieving the recommended levels of physical activity (WHO, 2008). Additionally, a study examining physical activity using an objective measure (i.e., the ActiGraph) found that less than 5% of adults participated in the recommended 30 minutes of moderate-intensity physical activity on five or more days a week (Troiano et al., 2007). The results of this study suggest that the self-reported activity levels from the CDC and WHO are underestimating physical inactivity levels.

Physical inactivity is one of the primary risk factors for the development of type 2 diabetes (American Diabetes Association [ADA], 2011). Studies have shown that regular physical activity can prevent or delay the onset of type 2 diabetes among pre-diabetic individuals (CDC, 2011). Similarly, physical activity is effective in the management and control of blood glucose regulation among type 2 diabetics (Boule, Haddad, Kenny, Wells, & Sigal, 2003). Physical activity is beneficial to overall health and reduces the risk of numerous adverse co-morbid health conditions in type 2 diabetics. Reductions in the risk of premature death, heart disease, stroke, hypertension, high cholesterol, metabolic syndrome, breast and colon cancer, and weight gain are benefits derived from regular physical activity (USDHHS, 2008). Physical activity has both acute and chronic effects on blood glucose regulation.

2.2.1 Acute and Sustained Effect of Physical Activity on Blood Sugar Regulation

The primary acute effect of physical activity on blood glucose regulation is induced by muscle contraction and the glucose transporter GLUT-4. The up-regulation of GLUT-4 translocation during muscle contraction and subsequent insulin-independent glucose uptake is the primary adaptive response to acute activity (Dela et al., 1994). Although acute activity has beneficial effects on blood glucose control, a study noted that a single acute bout of exercise will not improve glucose tolerance in insulin-resistant diabetics (Rogers et al., 1988). As few as seven

consecutive days of vigorous exercise was shown to be effective in reducing insulin resistance and improving glucose tolerance (Rogers et al, 1988). The beneficial effects of an acute bout of activity in type 2 diabetics have been shown to persist into the post-exercise period (Minuk, Vranic, Marliss, & Hanna, 1981). An acute bout of activity leads to heightened insulin sensitivity immediately after activity and up to 20 hours after activity (Minuk et al., 1981; Devlin, Hirshman, Horton, & Horton, 1987

The acute benefits of physical activity are clear but it is less clear whether or not these acute effects translate into lifelong benefits. Specifically, the improvements in blood glucose control decline within 72 hours of the last activity session underscoring the necessity for chronic physical activity to prevent and control type 2 diabetes (Schnieder, Amorosa, Khachadurian, & Ruderman, 1984). Sustained physical activity is important due to the inverse relationship between fitness levels and mortality across levels of glycemic control (Kohl, Gordon, Villegas, & Blair, 1992). Sustained physical activity leads to a decreased hormonal response to submaximal exercises, which results in glucoregulatory hormones such as glucagon and catecholamines being released in smaller amounts. In addition, insulin levels do not fall as far at the onset of activity, which leads to an improved blood glucose level in a trained individual during activity (Brooks et al., 2005). Sustained physical activity also leads to improved utilization of free fatty acids (FFA) and gluconeogenesis, which results in enhanced blood glucose regulation. Moreover, research indicates that slow-twitch muscles have more GLUT-4 glucose uptake capacity making this oxidative muscle more efficient at utilizing glucose during physical activity even in the face of declining insulin (Kern et al., 1990). In addition to the acute effects of exercise on diabetes, it is important to examine the effect of exercising over time on type 2 diabetes. Below summarizes the observational and experimental studies examining this research question.

2.3 Observational Studies

Observational studies have investigated the association between physical activity and the risk of developing diabetes. For example, an early study conducted by Helmrich et al. (1991) assessed self-reported physical activity among 5,990 initially non-diabetic men. The participants were followed for incidence of diabetes from 1962 to 1976. Among these men, 202 developed diabetes during this period. The results suggested that vigorous activity was most effective for decreasing the risk of diabetes; however, moderate intensity activity was also effective. Specifically, the results indicated a 6% reduction in the risk of diabetes for each 500 kilocalories (kcals) of self-reported leisure-time physical activity reported per week (Helmrich et al., 1991). The results also demonstrated a relationship between the amount of physical activity and age-adjusted incidence of diabetes. There was an inverse relationship between diabetes incidence and the amount of vigorous sports activity and moderate intensity physical activity. This inverse relationship was slightly stronger for the vigorous intensity activity (Helmrich et al., 1991). The protective effect of physical activity was more pronounced in men at higher risk than the men at lower risk for developing diabetes suggesting the importance of targeting high risk groups for prevention. The beneficial effects of physical activity were independent of age, familial history of diabetes, obesity, and hypertension (Helmrich et al., 1991).

Additional observational prospective cohort studies were conducted by Manson and colleagues (Manson et al., 1991; Manson et al., 1992). The first study included non-diabetic, female registered nurses (n=87,253) followed for eight years. The women were asked about their physical activity participation and then followed to measure incidence of diabetes. After eight years of follow-up, the women who participated in vigorous physical activity at least one time per week had a 33% reduction in their age-adjusted risk of developing diabetes ($p<0.0001$; Manson et al., 1991). The second study was a prospective cohort study of United States male physicians (n=21,271) from the Physician's Health Study (Manson et al., 1992). The participants responded

to questionnaires assessing the frequency of participation in vigorous physical activity and other health-related variables. After five years of follow-up, the results indicated an inverse relationship between physical activity and diabetes risk. Specifically, compared to sedentary men, the age-adjusted relative risk among men who exercised vigorously at least once a week was 0.64 ($p=0.0003$; Manson et al., 1992). The study also reported that, "A dose-response gradient of increased exercise with decreased risk of NIDDM was observed (Manson et al., 1992)." Among those who exercised five times or more per week, there was a 42% reduction in the age-adjusted risk of diabetes compared to participants who exercised less than once a week (Manson et al., 1992). The findings from these two studies are consistent with the findings of Helmrich et al. (1991). Taken together, there is fairly strong evidence based on observational data of an inverse relationship between physical activity and the incidence of diabetes.

2.4 Intervention Studies

Given the effect of physical activity on both the prevention and treatment of Type 2 diabetes, several studies have examined the efficacy of lifestyle interventions for Type 2 pre-diabetics and diabetics. A majority of the studies have examined both physical activity and diet and therefore, studies including diet in addition to physical activity will be reviewed. One of the largest lifestyle intervention trials was the Look AHEAD trial, which targeted type 2 diabetics (The Look AHEAD Research Group, 2010). Specifically, 5,145 overweight and obese type 2 diabetic participants from multiple centers were recruited for the study. The primary aim of the study was to evaluate the long-term effects of an intensive lifestyle intervention. The trial included an intensive lifestyle intervention group (ILI) and a diabetes support and education (DSE) group. The ILI group intervention included a diet reformation which involved a reduction in daily caloric intake, liquid meal replacements, and a portion-controlled diet (The Look AHEAD Research Group, 2010). Participants were instructed to engage in at least 175 minutes of physical activity per week. Their goal was to lose 7% of their body weight by the first year

and to maintain this during the following years. The ILI group also contained a behavioral component that emphasized self-monitoring, goal setting, and problem solving for diet and physical activity. In contrast, the control DSE group was offered three group sessions each year. Standardized information was presented at these group sessions including diet, physical activity, and social support; however, no information regarding behavioral strategies was presented.

The ILI group exhibited greater improvements in fitness, weight, blood pressure, glycemic control, and HDL and TG levels than the DSE group (The Look AHEAD Research Group, 2010). The greatest changes from baseline were seen at year one follow-up; however, the ILI group continued to maintain greater changes compared to baseline than the DSE group at one year. The ILI group also had a greater percentage of participants who met the ADA goal for HbA1c levels when compared to the DSE group. Fitness levels increased among the ILI group and were maintained at a higher level compared to previous lifestyle interventions. Weight loss was also higher when compared to previous studies (The Look AHEAD Research Group, 2010).

One strength of the trial was that it was conducted in multiple centers across the country. However, there are several limitations related to its generalizability including the use of liquid meal replacements and the intensive nature of the interventions. During the first 6 months, participants met weekly for three group sessions and participated in one individual session per month. These sessions were led by an intervention team that included registered dieticians, behavioral psychologists, and exercise specialists. One limitation is that which intervention strategies mediated the effect of the intervention on the outcomes was not examined. Therefore, it is unclear if changes in diet or physical activity accounted for the reduction in risk factors. The ILI has the potential to be implemented at the community level; however, it would be costly and labor intensive.

The Early ACTID trial was a randomized controlled trial evaluating the effect of diet or diet plus physical activity versus a usual care group on blood glucose control and blood pressure

(Andrews et al., 2011). The trial included 593 adults diagnosed with type 2 diabetes within the previous 5-8 months. The intensive diet intervention received dietary consultation every three months and monthly nurse support. The diet plus physical activity received the same intervention as the diet group plus a pedometer-based activity program (Andrews et al., 2011). The control group received a dietary consultation and follow-up at six months.

Results indicated that at six months, HbA1c had improved significantly in the diet and diet plus physical activity groups compared to the control group. There were no significant differences between the two active intervention groups (diet HbA1c -0.28% $p=0.005$; diet plus physical activity HbA1c -0.33% $p<0.001$; Andrews et al., 2011). Improvements in weight and insulin resistance were also seen in the diet and diet plus physical activity groups relative to control but no differences were found between the two active arms of the study. The practical implications of the study are that early diet intervention in recently diagnosed type 2 diabetics greatly improves blood glucose control over a one year period compared to a control group (Andrews et al., 2011).

One limitation is that this study did not use theory-based behavioral strategies to increase physical activity among the participants. The participants in the intensive activity and diet intervention increased their steps per day by 17% from 6399 to 7680 (Andrews et al., 2011). However, the addition of physical activity to the intensive diet intervention produced no additional benefit suggesting that greater increases in physical activity are needed. Perhaps a theory-based intervention focusing on physical activity would have produced greater increases in physical activity. Therefore, this study did not effectively test the effect of physical activity on Type 2 diabetes. Another limitation is that many individuals altered their diabetic medications during the study. Further research is needed to determine the dose and modality of exercise that is needed along with diet changes to treat type 2 diabetics.

Kahleova and colleagues (2010) conducted a study examining the efficacy of a vegetarian diet and physical activity for treating type 2 diabetes. Seventy-four participants were randomly assigned to either a vegetarian diet or a conventional diabetic diet alone and then in combination with physical activity. The meals for the vegetarian and control interventions were provided. The meals were isocaloric and both groups had a caloric restriction of 500 kcals based on the measurement of the individual's resting energy expenditure. During the initial 12 weeks of the study, the experimental and conventional diet groups received the diet intervention alone. Following the first 12 weeks, both arms of the study received a 12-week physical activity intervention in addition to the experimental or conventional diet. The experimental group exhibited greater reductions in body weight, waist circumference, visceral and subcutaneous fat, and oxidative stress markers than the control group. There was also a significant reduction in HbA1c in the experimental group from baseline to 24 weeks relative to the control. Physical activity augmented the reductions in HbA1c in the experimental group but not in the control group. Visceral and subcutaneous fat decreased significantly in the experimental group with the addition of physical activity (4% and 2% respectively, $p<0.05$; Kahleova et al., 2010) but increased in the control group. Therefore, it appears that diet changes were necessary to produce a beneficial effect of exercise. Specifically, the only reduction in HbA1c was in the experimental group and this occurred in the latter 12 weeks of the intervention suggesting a benefit of physical activity in the reduction of the HbA1c.

Limitations of the study include the use of provided meals. This strategy is not representative of interventions occurring in the real world nor would they be sustainable in the long run. This protocol attempts to control caloric intake; however, it is possible that participants chose to consume more than the metabolically controlled meals. Another limitation is that participants self-reported their physical activity and no objective measure of physical activity was

used. It is also possible that the short duration of the study may have blunted the possible effects of exercise in the control group.

A six-year randomized controlled clinical trial was conducted among individuals with impaired glucose tolerance (IGT) in Da Qing, China (n=577; Pan et al., 1997). The previous studies identified the increased risk of diabetes among high risk individuals and therefore, this intervention was targeted to those at high risk with IGT. High risk participants with IGT were randomized to one of four conditions including: (1), diet; (2), exercise; (3) diet plus exercise group; or (4) control. At six years, cumulative incidence rates of diabetes were 67.7% in the control group, 43.8% in the diet group, 41.1% in the exercise group, and 46% in the diet and exercise group (Pan et al., 1997). When baseline body mass index (BMI) and fasting glucose were controlled, the intervention groups still maintained significant reductions in their risk of developing diabetes. The exercise group was associated with a 46% reduction, the diet and exercise group had a 42% reduction, and the diet only group had a 31% reduction in the risk of developing diabetes (Pan et al., 1997). The diet and diet plus exercise groups were associated with significant risk reductions. Cumulative incidence rates of diabetes were the lowest in the diet plus exercise group and this group exhibited the greatest risk reduction compared to the other groups. These interventions, especially the diet plus exercise condition, led to significant reductions in the risk of developing diabetes in a high risk population.

A similar intervention was conducted in Finland in which overweight, middle-aged participants (n=522) with IGT were assigned to a control or lifestyle intervention group (Tuomilehto et al., 2001). The average follow-up was three years and the cumulative incidence of diabetes after four years was 23% in the control group and 11% in the intervention group (Tuomilehto et al., 2001). The intervention group exhibited a 58% reduced risk of developing diabetes during the study (Tuomilehto et al., 2001). More specifically, those who attained the target level of approximately four hours of moderate intensity physical activity per week had a

70% lower risk of developing diabetes compared to the control group (Tuomilehto et al., 2001). These reductions in risk are even greater than those found in the Pan et al. (1997) study and indicate the importance of physical activity for preventing diabetes.

In the US, a similar diabetes prevention trial was conducted among 3,234 participants with IGT (Diabetes Prevention Program Research Group [DPP], 2002). The participants were randomized to a placebo group, a metformin group, or a lifestyle intervention program. The goals of the lifestyle intervention program were to reduce body weight by 7% and to accumulate at least 150 minutes of physical activity per week. The results in the intervention group were identical to the Finnish study in that the experimental group exhibited a 58% reduction in the risk of developing diabetes compared to the placebo group (DPP, 2002). Specifically, the metformin group had a 31% risk reduction and the lifestyle group had a 58% risk reduction (DPP, 2002). The DPP demonstrated that a lifestyle intervention was effective at reducing the progression of IGT to overt diabetes. Physical activity and weight reduction resulted in a decreased risk of diabetes development. The lifestyle intervention was even more effective than the metformin intervention.

2.5 Physical Activity Intensity and Dose

The previous research reviewed suggests that there may be an intensity and/or dose-response relationship between physical activity and the development of diabetes. The previously mentioned Manson et al. (1991, 1992) articles reported that women who exercised vigorously at least once a week had a 33% reduction in the risk of diabetes (Manson et al., 1991; Manson et al., 1992). The study among the male physicians also reported a greater reduction in risk with vigorous activity but those who participated in moderate-intensity activities also experienced a reduction in risk. The inverse association between physical activity and diabetes found in this study does suggest that benefits can still be attained at lower intensities and dose of physical activity.

A study by Lynch and colleagues (1996) examined the association between physical activity intensity and the incidence of diabetes (Lynch et al., 1996). The results of this study suggested that moderate-intensity physical activity of at least 5.5 metabolic units (METS) and 40 minutes in duration are necessary to reduce the risk of type 2 diabetes (Lynch et al., 1996). This protective effect was not attained at intensities less than 5.5 METS regardless of the duration. In a sub-group of men at high risk for the development of diabetes, the effect was even more prominent. Similar results were found by Wei and colleagues (1999) who demonstrated the importance of moderate and higher cardiorespiratory fitness levels in the prevention of diabetes (Wei, Gibbons, Mitchell, Kampert, Lee, & Blair, 1999). The results of this study suggest that chronic, moderate and vigorous-intensity physical activities that produce higher levels of cardiorespiratory fitness are essential in the prevention of diabetes.

In slight contrast, a study was conducted among Australian men and women examining the relationship between sedentary time, light-intensity, and moderate to vigorous-intensity physical activity on two-hour plasma glucose (Healy et al., 2007). The results revealed a positive association between sedentary time and two-hour plasma glucose while light, moderate, and vigorous-intensity physical activity were negatively associated with two-hour plasma glucose (Healy et al., 2007). In addition, the association between light-intensity physical activity and 2-hour plasma glucose remained significant when moderate to vigorous intensity activity was controlled for (Healy et al., 2007). These data suggest that light-intensity physical activity may lead to enhanced blood glucose regulation and that replacing sedentary time with light-intensity activity can be effective in reducing the risk of type 2 diabetes and controlling blood sugar. The negative association between two-hour plasma glucose and higher intensity activity does provide consistent support for the benefit of moderate to vigorous-intensity activity in the management of blood sugar dysfunction.

Similar to these results, another study reported that sedentary time predicted levels of fasting insulin independent of the amount of moderate to vigorous-intensity physical activity (Helmerhorst, Wijndaele, Brage, Wareham, & Ekelund, 2009). Results from both of these studies suggest that sedentary time is just as important as the time spent accumulating light, moderate, and vigorous-intensity physical activity.

In the Nurse's Health Study, the benefit of walking was compared to vigorous physical activity for the risk of developing diabetes (Hu et al., 1999). Vigorous and moderate-intensity activities resulted in similar significant reductions in diabetes risk. The age-adjusted relative risk for diabetes progressively decreased as physical intensity increased. These results were independent of BMI and indicated that faster walking paces were associated with greater reductions in the risk of diabetes (Hu et al., 1999). Physical activity interventions have focused on increasing physical activity bouts and intensity however, few, if any, have primarily focused on decreasing sedentary time to promote increased energy expenditure through all daily activities other than exercise or, non-exercise activity thermogenesis (NEAT).

Part 2: Sedentary Behavior and Physical Inactivity Physiology

2.6 Non-Exercise Activity Thermogenesis and Sedentary Behavior

Physical activity research has recently shifted to becoming increasingly aware of the effect of sedentary time (Healy et al., 2008). Physical activity and sedentary time are two separate constructs with independent effects on energy expenditure and the disease process. The number of calories burned in a day can vary greatly depending on the activities chosen to replace sedentary time with NEAT. NEAT is defined as the energy expenditure of all daily activities other than exercise (Levine, Vander Weg, Hill, & Klesges, 2006). There are three primary forms of energy expenditure; 1) the basal metabolic rate; 2) NEAT; and 3) physical activity/exercise. Examples of NEAT activities include walking, standing, stair climbing, dancing, and fidgeting.

Sedentary behavior and reductions in NEAT have been found to be risk factors for cardiovascular disease (CVD) and to have detrimental associations with related biomarkers for CVD risk (Owen, Healy, Matthews, & Dunstan, 2010). A cross-sectional analysis of the US National Health and Nutrition Examination Survey (NHANES) revealed unfavorable linear associations between sedentary time and waist circumference, HDL, C-reactive protein, insulin, triglycerides, HOMA-%B, and HOMA-%S (Healy, Matthews, Dunstan, Winkler, & Owen, 2010). Actigraph accelerometers were used to measure activity levels. These findings were independent of moderate-vigorous physical activity levels and potential confounders. Frequent breaks in sedentary time were positively related to waist circumference and C-reactive protein (Healy et al., 2010). This objectively-measured data demonstrates the beneficial effects of breaking up sedentary time to promote reductions in CVD risk factors and inflammatory biomarkers.

Obese individuals are sedentary for at least 2.5 hours more and expend 350 kilocalories less than their lean counterparts per day (Levine et al., 2006). Levine and colleagues (2007) examined levels of free-living walking among obese and lean participants and found that lean participants walked, on average, 3.5 miles more per day than the obese participants (Levine et al., 2007). Additional research has shown that frequent breaks in sedentary time resulted in significant benefits for changes in waist circumference, BMI, triglycerides, and 2-hour plasma glucose (Healy et al., 2008).

These studies suggest that increases in NEAT and reductions in sedentary time lead to increased total daily energy expenditure, which has led to improvements in anthropometric measurements and metabolic risk markers. They also suggest that light-intensity physical activity is associated with improvements in blood glucose regulation while sedentary time is negatively associated with blood glucose regulation. Frequent, short-duration, light-intensity activity and

reductions in sedentary time have the potential to improve blood glucose regulation among type 2 diabetics.

Levine and Miller (2006) conducted a study utilizing walk-and-work desks in an occupational setting among obese workers (Levine & Miller, 2006). Participants worked on their computer while walking on a treadmill at a self-selected pace. Energy expenditure was measured at rest, seated and working, standing, and walking while working. The mean increase in energy expenditure using a walking while working desk was 119 kcals/hour (Levine & Miller, 2006). Therefore, this rate of daily energy expenditure performed 2-3 hours per day with other components remaining constant, could result in a 20-30 kg/year weight loss (Levine & Miller, 2006). This article provides an example of the potential for weight loss produced by increasing NEAT and light-intensity activity. Although walk-and-work desks may not be feasible, increasing NEAT can lead to increased total daily energy expenditure and subsequent weight loss. The literature is not; however, conclusive to suggest that increasing NEAT and reducing sedentary time is sufficient enough to produce the cardiovascular and metabolic improvements associated with moderate and vigorous intensity exercise.

Energy expenditure was examined in a simulated classroom setting. The effect of sitting versus standing on caloric expenditure was examined in young, healthy participants (n=10 male, n=10 female; Reiff, Marlatt, & Dengel, 2012). Participants fasted for 12 hours and abstained from exercise for 48 hours prior to testing. In a simulated classroom setting, inspired and expired gases were measured for 45 minutes while the participants performed activities such as word finds and crossword puzzles. Kilocalorie (kcal) expenditure per minute significantly increased from sitting to standing ($p \leq .0001$; Reiff et al., 2012). The generalizability of the results is limited to young, healthy adults. However, a strength of the study was that caloric expenditure was measured objectively. This study provides physiological evidence that standing while performing desk work increases energy expenditure.

In contrast, a pilot study examining standing versus sitting or sitting on an exercise ball was conducted in a work setting. The study aimed to test the hypothesis that standing would increase daily energy expenditure by 384 kcals (Speck & Schmitz, 2011). Oxygen consumption was measured while sitting on a chair, sitting on an exercise ball, and standing while working on a computer for seven minutes. No significant differences were found in energy expenditure for the different working positions. Limitations of the study include the short duration of measurement and failure to examine the effects of intermittent activity during the workday. Additionally, the purpose of the pilot study was test whether standing would meet the requirements for the recommended daily physical activity (300 kcal/day). The epidemiological evidence demonstrates an increase in all-cause mortality from excessive sitting and prolonged sedentary time (Dunstan, Howard, Healy, & Owen, 2012). The evidence does not; however, suggest that standing while working could or should replace daily physical activity. Further experimental studies are needed to determine an appropriate dose and the long-term effect of reducing sedentary behavior at work.

Another study was conducted by Duvivier and colleagues (2013) examining the effect of increased walking and standing compared to sitting with a short period of moderate to vigorous exercise in healthy adults. The previously sedentary participants (n=18) were randomized to one of the following three different activity programs each lasting four days: (1) Sitting for 14 hours per day; (2) sitting for 13 hours and substituting one hour of sitting for one hour of vigorous intensity exercise; and (3) substituted six hours of sitting with four hours of minimal physical activity (walking) and two hours of standing (Duvivier et al., 2013). Physical activity was assessed with the activPAL continuously and a physical activity diary. The number of hours spent sitting were comparable between the sitting and vigorous exercise groups and energy expenditure was matched between the exercise and minimal intensity groups.

The minimal intensity group stood approximately two hours more and performed non-exercise activity (walking around) almost four hours more than the sitting and exercise groups ($p < .001$; Duvivier et al., 2013). The exercise and minimal intensity groups expended 500 more calories daily ($p<.001$) compared to the sitting group. Additionally, the insulin area under the curve during an oral glucose tolerance test was significantly smaller for the minimal intensity group relative to the sitting ($p=.010$) and exercise ($p=.002$) groups (Duvivier et al., 2013). However, glucose and C-peptide levels were not significantly different during the oral glucose tolerance test. Therefore, one hour of vigorous exercise does not compensate for the negative effects of excessive sitting.

Another study examined the effect of breaking up prolonged sitting on postprandial glucose (Peddie et al., 2013). The study was a randomized crossover trial of apparently healthy adults with normal weight (n=70). The participants were randomized to one of six possible orders consisting of the following three; (1) Prolonged sitting (nine hours), (2) walking for 30 minutes and then sitting, and (3) 1 minute 40 second breaks every 30 minutes. Standardized, weight-based meal replacements were consumed at 60, 240, and 420 minutes (Peddie et al., 2013). The activity break intervention resulted in significant reductions in insulin incremental area under the curve (iAUC; $p<0.001$) and significantly lower plasma glucose iAUC ($p<0.001$; Peddie et al., 2013) than the other two conditions.

The study provides further evidence of the beneficial effect of breaking up prolonged sitting. Regular activity breaks resulted in reduced postprandial glucose and insulin levels. The findings are important for recommending the reduction of prolonged sedentary time among all adults. Additionally, regular activity breaks were more beneficial than one sustained bout of physical activity, which is consistent with the previously reviewed literature. The study was however conducted in a laboratory setting and among healthy, normal weight adults. A

consistent gap in the literature is the absence of studies examining the effect of breaking up prolonged sitting in adults with abnormal glucose regulation.

Acute bouts of light or moderate intensity activity consistently result in beneficial glucose and insulin responses. The effect of standing breaks has not been widely researched. In a crossover study of non-obese, healthy adults (n=10), three conditions were completed: (1) Uninterrupted sitting; (2) 2-min standing breaks every 20 minutes; and (3) 2-min light-intensity walking breaks every 20 minutes (Bailey & Locke, 2014 in press). Consistent with previous data, the light-intensity walking breaks reduced postprandial glucose; however, standing breaks did not significantly reduce postprandial glucose. Conducting the study in a laboratory setting is a limitation; however, this limitation is somewhat attenuated given the novelty of the research topic. While the study isolated the effect of standing, the participants were instructed to stand completely still during the 2-min standing break. This behavior is not consistent with the real-world work setting (people do not stand completely still naturally). Current research is continuing to examine the effect of increased standing at work and the subsequent increased movement (or light-intensity activity) around the office space once individuals are standing.

In summary, the experimental literature contains primarily acute studies and studies lasting longer in duration are needed. The prolonged and sustained effect of standing on glucose is unknown. Additionally, the sedentary literature has studied apparently healthy adults and therefore, further examination of individuals at risk for chronic disease is needed.

Part 3: Continuous Glucose Monitoring

2.7 CGM Technology

Continuous glucose monitoring (CGM) technology has been studied primarily in type I and type II diabetic populations. Continuous glucose monitors measure interstitial blood glucose using an electrochemical system. The devices can be worn for up to seven days. The market is currently dominated by three major manufacturers – Medtronic (Medtronic, USA), DexCom

(Dexcom, San Diego, CA), and Abbott (Abbott, United Kingdom). The devices function in a blinded fashion or with real-time feedback. The primary goal of CGM technology is to reduce glycemic variability. Glycemic variability was shown to be associated with increased microvascular complications associated with diabetes. Specifically, results from the Diabetes Control and Complications Trial (DCCT) demonstrated increased microvascular complications with variable glycated hemoglobin (HbA1c) in a conventional glycemic control group compared to an intensive control group (Kilpatrick, Rigby, & Atkin, 2008). Therefore, through the use of CGM technology, glycemic variability and hypoglycemic events (in type 1 diabetics) can be reduced which in turn reduces vascular risk (Liebl et al., 2013).

Currently, the literature does not contain data on the use of CGM in pre-diabetic adults; however, the technology has been studied in apparently healthy individuals. Beck and colleagues (2010) conducted a study to evaluate glucose patterns in apparently healthy adolescents and adults. The participants wore the CGM for 3-7 days and, by the nature of the device, were blinded to the results. The study group found that the majority of glucose concentrations (91%) were between 71-120 mg/dl, which suggests normal blood sugar regulation in these apparently healthy participants. This study provides baseline data confirming normal function of the device in a population free of disease.

More recently, CGM was used to examine responses to sitting and standing in apparently healthy, desk-based office workers (Buckley, Mellor, Morris, & Joseph, 2014). The study was an open, repeated-measures design performed in a real-world office setting. Participants (n=2 male, n=8 female) wore a CGM, an accelerometer, and a heart rate monitor. The study was conducted over two days. The participants were fed a standardized lunch prior to the first afternoon of data collection. Following the meal, they proceeded to work as usual in the seated position. Sit-stand desks were installed (Ergotron WorkFit-D, Minnesota, USA). The next day a standardized meal was consumed for lunch but then the participants worked in the standing position for the

afternoon. The CGM was removed on the third day. Cycle ergometry, measurement of expired gases, and heart rate were performed on two days after the study. The measurements were used to calculate energy expenditure.

The study resulted in a 43% reduction in postprandial glucose area under the curve in the standing condition compared to sitting (p=0.022; Buckley et al., 2014). Additionally, mean blood glucose continued to rise for 85 minutes prior to reaching the peak whereas the standing condition peaked at 50 minutes. Standing work peaked earlier and at a lower mean blood glucose (1.8 mmol/l vs. 3.1 mmol/l; Buckley et al., 2014). Finally, mean energy expenditure for the afternoon of work was 174±66 kcals greater in the standing compared to the seated work (p=0.028; Buckley et al., 2014).

Overall, the standing work resulted in a reduced glucose response to the standardized meal. The reduction in the area under the curve corresponded to lower glucose levels while standing and to lower peak glucose. While confirmed previously within the NEAT literature, this study confirms increased energy expenditure while performing work standing compared to sitting. The study did, however, contain limitations. Specifically, it lacked randomization and the meals consumed the evening and morning before testing were not controlled. One strength of the study is that it included a standardized meal. The results provide encouraging evidence for the usefulness of acutely reducing postprandial blood glucose responses. Further long-term research is needed among individuals at risk for or with abnormal blood glucose metabolism.

2.8 Summary and Conclusions

Traditional physical activity interventions produce beneficial outcomes for glucose regulation and diabetes management (Andrews et al, 2011; The Look AHEAD Research Group, 2010; ACTID). These interventions also significantly increase physical activity levels, which contributes to health improvements in diabetics. In addition to traditional physical activity prescriptions, the literature suggests that reducing sedentary time and increasing NEAT may be

an additional strategy for improving blood sugar regulation and producing beneficial changes in weight (Levine & Miller, 2006; Healy et al., 2008). The detrimental effects of sitting occur independent of physical activity level (van der Ploeg, Chey, Korda, Banks, & Bauman, 2012). Therefore, interventions are needed to address sedentary time in all individuals regardless of physical activity level. Additionally, an at-risk group, such as those with prediabetes, warrant further investigation in order to provide strategies that prevents the progression to type 2 diabetes. There is a lack of studies examining the effect of short-term interventions on reducing sedentary time in pre-diabetics. The research has demonstrated that reducing sedentary time and incorporating frequent breaks can produce beneficial health outcomes such as improved blood glucose regulation, reduced CVD risk, and reduced inflammatory biomarkers in healthy adults (Owen, Healy, Matthews, & Dunstan, 2010). Therefore, adults performing desk-based work with prediabetes represent a population in need of further research to prevent disease progression and improve health.

3

METHODS

Study Design

This dissertation includes two separate trials conducted among the same participants. The participants for the two trials were recruited concurrently from a larger worksite wellness study. The participants were involved in both the larger study and the sub-studies. The larger study was a randomized controlled trial examining a six-month worksite wellness intervention. The study recruited sedentary office workers (n=163) who were randomly assigned to one of four groups; 1) the control group (usual behavior at work), 2) standing at work at least 50% of the workday, 3) accruing 30 minutes of walking during the workday through multiple brief bouts, or 4) the combined standing and walking intervention.

Twenty female participants were recruited from the larger study for the two separate trials presented in the three manuscripts of this dissertation.

1) The first trial performed was the oral glucose tolerance test (OGTT) study. Within a randomized crossover trial, 20 female participants were randomly assigned to one of two conditions: (1) sitting for a 2-hour oral glucose tolerance test; or (2) standing for a 2-hour oral glucose tolerance test. The participants served as their own controls within the crossover design.
2) The second trial was the continuous glucose monitor (CGM) trial. This study was a repeated measures pilot study in which 10 of the initial 20 participants completed two study conditions: (1) First, sitting at their desk for one work week while wearing a continuous glucose monitor and an accelerometer; and (2) Using their sit-stand desk for one work week while wearing the CGM and the accelerometer with a goal of standing for at least half of their work day.

The study was approved by the University of Minnesota's Institutional Review Board (IRB) and was registered as 1208M18741 at ClinicalTrials.gov.

Participants and Inclusion/Exclusion Criteria

Twenty-seven female participants were recruited from two companies in the Midwest. Participants with a fasting blood glucose greater than 100 mg/dl were recruited concurrently from a larger study being conducted in the same workplaces. Participants were recruited from informational sessions that were provided to prospective participants for both the current study and the larger trial. Additionally, participants whose blood sugar was greater than 100 mg/dl were recruited during the baseline data collection for the current study. Inclusion criteria were a fasting blood sugar greater than 100 mg/dl, ages 18-65 years, and, if taking any, on stable medications during the past six months. Participants were required to work full-time (at least 35 hours per week) and spend at least 75% of their workday sitting. Participants were required to be able to safely begin a physical activity regimen that primarily involved increased standing, walking, and using the stairs. Exclusion criteria were prior history of manifest heart disease, renal disease with a creatinine >1.5 mg/dl, peripheral neuropathy, retinopathy, peripheral artery disease (PAD), lower limb amputation, pregnancy, active substance abuse, hospitalized in the past six months for psychiatric disorder, severe visual impairment, enrollment in a physical activity study, and the use of insulin or an insulin pump.

Measures

Study measures included sedentary time, physical activity, blood glucose, oral glucose tolerance testing (OGTT), continuous glucose monitoring (iPro2®, Medtronic, USA), blood pressure, weight, body fat percent, sitting time, and 24-hour dietary records.

Sedentary time

Sedentary time and physical activity were measured objectively with the Kinetic Activity Monitor (KAM®; Kersh Health, Plano, TX). The KAM is an accelerometer that measures activity intensity and duration. The KAM was worn on the waistband in line with the knee and measured activity counts at low, moderate, and vigorous intensities. The intensity zones are life (<2 mph), health (>2-4.5 mph), and sport (>4.5mph). The KAM accelerometer was worn during

each oral glucose tolerance test and for two weeks while the CGM was worn. Two OGTT's were performed with the KAM worn at the start of the 2hr test and removed upon completion. The KAM was worn again for two one-week periods while the CGM was worn. Participants self-reported daily standing time by recording the total daily amount of standing in their diary for each day while wearing the CGM.

Physiological Measures

Blood glucose was measured with a glucometer, glucose strip, and lancet (Bayer Breeze 2, Whippany, NJ). Oral glucose tolerance testing (OGTT) was conducted two times; once standing and once sitting. A 75g glucose load beverage was consumed and blood glucose was measured with a glucometer at 30 minute intervals up to 120 minutes (Trutol, ThermoScientific Inc., USA).

During the second trial, the continuous glucose monitor was worn (CGM). The CGM included the sensor that was inserted in the interstitial fluid and the transmitting device that was attached to the sensor on the outside of the skin. The iPro2® by Medtronic is a blinded device that uses an electrochemical system. The sensor is contains three electrodes; (1) reference, (2) working, and (3) counter electrodes that complete a circuit (Medtronic, Northridge, CA). Additionally, the sensor has three layers. The outermost layer is a semi-permeable layer that is selectively permeable to glucose and oxygen. The second layer is an enzyme layer, coated with glucose oxidase, where the chemical reaction occurs producing hydrogen peroxide and gluconic acid. The gluconic acid is reabsorbed into the body while the hydrogen peroxide travels from the enzyme layer to the electrode layer. A small nano-amp runs through the electrode layer. A second chemical reaction occurs when the hydrogen peroxide comes in contact with the nano-amp. The hydrogen peroxide is broken down into hydrogen, oxygen, and two electrons. The sensor measures the two electrons and sends the electron current, the ISIG, to the transmitter.

Upon download of the transmitter, the ISIG values were converted to glucose values for every five minutes the monitor was worn.

Height and weight were measured using a calibrated scale and stadiometer (Seca; Chino, CA). Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Body fat percent was obtained by dual energy x-ray absorptiometry (DXA). Resting blood pressure was measured with an automatic sphygmomanometer (BPTru, BPM-100; BPM Medical Devices). Cholesterol was measured in a fasted state (Alere Cholestech LDX). The fasted state was considered the absence of food and caloric beverage intake for eight or more hours and was verified by self-report.

Procedure

Participants were recruited from two office buildings in the Twin Cities metro area. Flyers were posted and emails were sent to employees at one worksite while an advertisement was placed on the electronic company newsletter of the other. Interested participants sent an email using the study email address. Potential participants were screened for eligibility via an electronic survey, which included a standard set of questions to determine if they met the inclusion and/or exclusion criteria. Following determination of eligibility, participant consent was obtained. Participants were instructed to fast for eight hours prior to the baseline data collection. Baseline blood sugar was determined prior to randomization to verify eligibility. The finger was prepped with an alcohol swab, lanced, and the initial drop of blood was wiped away. A drop of blood was then placed on the glucose strip for the glucometer to analyze (Bayer Breeze 2; Whippany, NJ).

Blood pressure was measured with an automatic sphygmomanometer (BPTru, BPM-100; BPM Medical Devices). Participants sat quietly for five minutes prior to the readings and the same arm was measured for all readings. The blood pressure was measured six times. The average of those six readings was recorded as the baseline blood pressure. Height was measured

using a stadiometer and weight was measured using a digital scale (Seca; Chino, CA). Cholesterol was measured by a finger stick using the Cholestech LDX system. The finger was cleaned with an alcohol swab, lanced, and the initial drop of blood was wiped away. The capillary tube was then filled with blood, which was transferred to the test cassette. Body fat percentage was obtained via DXA. Participants fasted for at least three hours prior to testing and removed shoes, excess outer clothing, metal jewelry, and/or belts. The participant then laid flat on the DXA table with their arms at their sides. The entire body was scanned lasting approximately five minutes.

Participants were then randomly assigned to sit or stand for the OGTT test utilizing simple randomization and computer-generated random numbers. Using the random numbers generated (0=sit, 1=stand), the participant's assigned zero sat for the first test and those who received one, stood for the first test.

Sit-stand desks were installed at one of the workplaces. The other workplace already had sit-stand desks and they were instructed how to use the desk with proper ergonomics. Participants received an ergonomic evaluation, instructions, and an informational website relating to the sit-stand desk. If assigned to sit for the first test, the participants were instructed to remain seated at their desk for the entire two hour test and to avoid any activity that would require leaving their desk or walking around. The OGTT was performed in the morning after fasting for at least eight hours. Abstinence from physical activity in the previous 48 hours was required and verified. Baseline blood glucose was measured followed by consumption of a 75g glucose beverage (Trutol, Thermo Fisher Scientific, Inc.). The beverage had to be consumed within five minutes. Blood glucose was measured over the 2h period at 30, 60, 90, and 120 minutes. The participant continued to work as usual during the test. The researcher reported to the participant's desk every 30 minutes to obtain the blood sample. Symptoms in response to ingestion of the glucose load, if any, were recorded by the researcher.

The KAM accelerometer was placed on the participant at the start of the test and worn on the front of the pants, in line with the knee. The KAM was collected at the end of the test. Testing was not performed on consecutive days. A minimum of one day was placed between each test. For the standing OGTT, participants were instructed to stand at their desk for the entire two hour period. They were again instructed to remain at their desk for the entire two hour period. The same blood glucose measuring and beverage consumption procedures were completed for the standing test. Following completion of both oral glucose tolerance tests, the participant was scheduled for the first week of continuous glucose monitoring (CGM).

The second trial, wearing the continuous glucose monitor (CGM), was completed once both OGTT tests were finished. During the first week, the participants continued to work in the seated position. The KAM was given to the participant on the first day of the week and worn during waking hours until the CGM was removed. The CGM sensor was inserted on the first day of the week. The sensor was placed in a position that would not interfere with the participant's daily life, which was generally on either side of the low back or the upper portion of the gluteus maximus. A site that was primarily fat tissue and free of stretch marks, scarring, or hardened tissue beneath the skin was chosen. The sensor was inserted using an insertion device. The sensor was allowed to "wet" for at least 15 minutes under the skin. The iPro2® was then attached to the sensor and taped down securely with transparent film dressings (3M Tegaderm®). The participant was told the requirements while wearing the CGM.

The participant was required to measure their blood glucose while wearing the iPro2®. A calibration blood sugar was required at least four times per day (before breakfast, lunch, dinner, and before going to bed) but absolutely had to be measured every 12 hours. They were supplied with daily diaries for recording blood glucose readings, dietary intake, and physical activity. Meals, beverages, snacks, and the amount of each consumed was recorded daily. Amount and type of physical activity, if any, was recorded daily. While wearing the device, the participant

was able to shower and perform all other activities as usual. They were told to refrain from using a hot tub as the sensor and iPro2® could not be guaranteed to function in that setting. The sensor and iPro2® were removed at the end of the week. The tape was peeled off and the sensor was removed from the skin and discarded in a sharps container. The iPro2® was cleaned according to Medtronic and the Food and Drug Administration (FDA) guidelines. Once clean, the iPro2® was connected to a computer and the data was downloaded. The daily diaries were collected and the calibration blood sugars, meals, and physical activity were entered into the software (CareLink, Medtronic, USA). The software used the calibration blood sugars to produce blood glucose readings from the sensor measurements. A blood glucose reading was computed in five minute intervals while the sensor was worn. The KAM was collected on the last day of the week and downloaded.

Participants performed an acclimation period of at least three weeks prior to wearing the CGM again. Following the first CGM session, participants were instructed to gradually increase their daily standing to achieve a cumulative total of four hours of standing per day. They were not required to stand for four continuous hours but rather to accumulate four hours throughout their work day. They were also instructed to wear appropriate footwear while standing such as tennis shoes rather than high heels or dress shoes. The KAM was worn again for the entire work week. The device was delivered and picked up from the participant at their workplace. The data from the KAM was downloaded to a software program, which resulted in total KAM points and minutes spent in life, health, and sport zones. The same CGM procedures were followed during the second week of data collection. However, daily standing time was recorded in addition to blood glucose readings, dietary intake, and physical activity. Participants were provided with a study email to send questions to the researcher as needed and a phone number had any emergent issues arisen. A supervising physician was part of the study team and was available to contact with questions and concerns that developed during the study. One participant was compensated

$150.00 for participation in both trials ($10 for the first OGTT, $20 for the second, $40 for the first CGM, $80 for the second). The remainder of the participants were employees of the state of Minnesota and could not accept compensation.

Data Analysis

Data were analyzed using SPSS (v21.0) for Windows and Microsoft Excel (2010). Participant characteristic data was analyzed in SPSS (v21.0) and Microsoft Excel (Windows 2010). Area under the curve (AUC) was calculated for the sitting and standing OGTT data. For each glucose interval, the values were subtracted from baseline. The trapezoidal area was then found for the sitting and standing conditions. Finally, AUC was calculated in the sitting and standing conditions followed by the difference in the two conditions.

The CGM data were evaluated using a linear mixed model regression analysis for a crossover design in SAS (v9.3). Dietary, physical activity, sedentary time covariates (i.e. carbohydrates, protein, fat, and fiber) were controlled for within the model. The KAM data was analyzed in Microsoft Excel (Windows 2010). The mean difference of minutes spent in the life, health, sport, and combined life and health zones was calculated. Values are reported as mean [SD and SE] and 95% CI.

4

The Acute Effect of Standing on Oral Glucose Tolerance Testing among Working Women with Impaired Fasting Glucose

Abstract

Objective: Sedentary time and physical inactivity are related to deleterious effects on cardiometabolic risk markers. The purpose of this study was to examine the effect of sitting versus standing on glucose tolerance during a 2-h oral glucose tolerance test (OGTT) among working adults with prediabetes. **Research Design and Methods:** This study was a randomized cross-over pilot study in which participants performed two 2-hr OGTT's; one sitting and one standing. The study was conducted under free living conditions at the participant's workplace. Participants were female volunteers (n=14) recruited from two Midwest-based companies. On average, participants were 49 years of age and obese (mean BMI was 31.2). Inclusion criteria included a fasting blood sugar >100 mg/dl (m = 108 ± 5.2 mg/dl), full-time employment (working at least 35 hours per week), a sedentary job (sitting for 75% of the work day), stable medications for 6 months among individuals taking medications, able to safely participate in low-moderate physical activity, and 18-65 years of age. **Results:** Results indicated an increased postprandial glucose response in the standing group (Glucose iAUC = -124.9 ± 481.7, 95% CI [-386.7, 137]) relative to the sitting group. **Conclusions:** The data suggest that continuous standing following consumption of a glucose load is detrimental. Future research is needed with larger sample sizes to evaluate the acute and prolonged effects of standing among individuals at risk for diabetes.

Introduction

Diabetes and obesity have reached epidemic levels across the world (Naser, Gruber, & Thomson, 2006). Currently, an estimated 79 million Americans have prediabetes, which puts those individuals at risk for type 2 diabetes (CDC, 2011). Prediabetes is diagnosed by one of three tests; (1) a Hgb A1C of 5.7-6.4%; (2) a fasting blood glucose of 100-125 mg/dl; or (3) a blood glucose reading of 140-199 mg/dl during an oral glucose tolerance test (American Diabetes Association, 2013). An estimated 70% of individuals with prediabetes are predicted to develop type 2 diabetes (Nathan et al., 2007). Diagnosed diabetes has increased 176% between 1980 and 2010 (CDC, 2012). In 2010 alone, 1.9 million adults were diagnosed with diabetes (CDC, 2011). Assuming the incidence rate of diabetes diagnoses have remained constant since 2010, the current estimate would suggest that 86.6 million Americans have prediabetes. Therefore, it is important to intervene among adults with prediabetes in order to prevent the onset of type 2 diabetes. Increasing physical activity and decreasing sedentary time is one potential strategy for improving blood sugar regulation problems among individuals with prediabetes.

Extended periods of sitting and sedentary behavior are prevalent among office-based workers (Jans, Proper, & Hildebrandt, 2007). Individuals who have occupations that involve prolonged sedentary time spend approximately 77% of their day engaged in sedentary behavior (Thorp et al., 2012). A majority of workers have sedentary jobs and this number is projected to increase through 2022 (Bureau of Labor Statistics, 2012). Adults spend about one-third of their life at their highly sedentary job (Jans et al., 2007). Studies indicate a strong relationship between sedentary behavior and all-cause mortality and cardiovascular disease mortality risk (Hamilton, Healy, Dunstan, Zderic, & Owen, 2008; Dunstan, Thorp, & Healy, 2011; Dunstan, Howard, Healy, & Owen, 2012). Epidemiological evidence has also demonstrated an increased risk of all-cause mortality in individuals with high levels of daily sitting time (van der Ploeg, Chey, Korda, Banks, & Bauman, 2012). Additionally, sedentary behaviors have been associated with

metabolic syndrome, adverse insulin and glucose profiles, and type 2 diabetes (Dunstan et al., 2004; Dunstan et al., 2005; Dunstan et al., 2007; Hu et al., 2001; Thorp et al., 2010).

Sedentary behavior is defined as activities in either the sitting or reclining position and those of very low intensity (MET levels of 1.0-1.5; Owen et al., 2010). In one study, interrupting prolonged sedentary time with frequent breaks was associated with decreased waist circumference, body mass index (BMI), triglycerides, and 2-h plasma glucose (Healy et al., 2008). The beneficial associations of frequently interrupting sedentary time did not depend on the overall amount of sedentary time and moderate-to-vigorous intensity physical activity (Healy et al., 2008).

In another study among overweight and obese adults without diabetes, the acute effect of breaking up prolonged sitting was examined (Dunstan et al., 2012). Specifically, participants consumed a standardized test drink and randomly completed three treatments in an acute crossover trial; 1) uninterrupted sitting; 2) sitting with two-min bouts of light-intensity walking every 20 minutes; and 3) sitting with two-min bouts of moderate-intensity walking every 20 minutes (Dunstan et al., 2012). Light and moderate-intensity bouts of walking reduced postprandial glucose and insulin relative to uninterrupted sitting (Dunstan et al., 2012). There were no differences between the light and moderate intensities on glucose and insulin incremental area under the curve (i.e., the area under the blood glucose and insulin response curves following ingestion of a standard test drink; Dunstan et al., 2012). Therefore, light intensity activity was as effective as moderate intensity activity in reducing postprandial glucose and insulin. The associations of objectively measured sedentary time and light, moderate, and vigorous-intensity physical activity with 2-h OGTT were examined in a sample of Australian adults (Healy et al., 2007). Light, moderate, and vigorous-intensity activity were negatively associated with 2-h plasma glucose while sedentary time was positively associated (Healy et al., 2007). Additional research indicates that light-intensity physical activity is related to improvements in blood sugar

regulation. Also, sedentary behavior is negatively associated with proper blood glucose metabolism, continuous blood glucose measures and the metabolic syndrome (Healy et al., 2008; Sugiyama, Healy, Dunstan, Salmon, & Owen, 2008).

In summary, the epidemiological and observational evidence demonstrate the deleterious effect of prolonged sitting. There are no specific guidelines and recommendations for the proper prescription for standing for the general population and individuals with impaired fasting glucose. Research is needed to better understand the effect of standing on at-risk adults with impaired fasting glucose who work at a sedentary job. The purpose of this study was to examine the effect of sitting vs. standing on glucose responses during a 2-hr OGTT among adult females with impaired fasting glucose. No study has examined the effect of standing while working on 2-hr OGTT in adults with impaired fasting glucose. It was hypothesized that participants would have significantly lower glucose responses during a 2-hr OGTT after standing compared to when sitting.

Methods

Study Design and Participants

This study was a randomized, cross-over pilot study examining blood sugar measured by an oral glucose tolerance test (OGTT) in adults with impaired fasting glucose. The participants served as their own control. The study was performed under free living conditions at the participant's place of work. Each participant completed two conditions, which were randomly counterbalanced; (1) sitting and (2) standing for the entire two-hour test. Volunteers (n=27 females) were recruited from two worksites in the upper Midwest via an advertisement within the electronic employee newsletter and flyers posted in the building. The participants were recruited simultaneously with a larger worksite wellness study (n=144 females; n=19 males). All participants in the current study also participated in this larger worksite study (a workplace wellness study examining the effect of sit-stand desks on reducing sedentary time relative to a

weekly wellness program). Informational in-person sessions were conducted at the worksites where both studies were discussed followed by question and answer sessions. Interested participants contacted the study coordinator via email and were then sent a screening questionnaire to determine their eligibility.

Inclusion criteria included a fasting blood glucose greater than 100 mg/dl, stable medications for the last six months, working full-time (at least 35 hours per week) with at least 75% of the work day spent sitting, and able to safely begin a physical activity regimen that primarily involved increased standing, walking, and using the stairs. Exclusion criteria included prior history of manifest heart disease, type 1 or type 2 diabetes, renal disease with a creatinine >1.5 mg/dl, peripheral neuropathy, retinopathy, peripheral artery disease (PAD), lower limb amputation, pregnancy, active substance abuse, hospitalization in the past six months for psychiatric disorder, severe visual impairment, enrollment in a physical activity study, and the use of insulin or an insulin pump. Informed consent was completed by each participant followed by the collection of health and medical history. Data for this study was collected between February-July 2013. The study was approved by the University of Minnesota's Institutional Review Board and registered as 1208M18741 at ClinicalTrials.gov.

Measures

Anthropometric Measures

Height and weight were measured using a calibrated scale and stadiometer (Seca; Chino, CA). Body mass index (BMI) was calculated and body fat percent was obtained by dual energy x-ray absorptiometry. Resting blood pressure was measured following five minutes of sitting quietly (BPTru, BPM-100; BPM Medical Devices). Cholesterol was measured in the fasting state (Alere Cholestech LDX) using a finger stick sample. Finally, fasting glucose was measured at baseline to determine eligibility (Bayer Breeze 2; Whippany, NJ).

Oral Glucose Tolerance Testing (OGTT)

The Oral Glucose Tolerance Test (OGTT) was used as the measure of insulin sensitivity due to its feasibility to administer and its correlation with hyperinsulinemic euglycemic clamp, the gold standard ($r=-0.61$, $p<0.001$; Tran et al., 2003). Oral glucose tolerance testing involves blood sugar measurements and the consumption of a glucose or mixed-meal beverage. A 75g glucose beverage was consumed for the OGTT (Trutol, ThermoScientific). All tests were completed in the morning at the start of the work day.

Physical Activity Monitoring

Participants wore an accelerometer (Kinetic Activity Monitor [KAM]; Kersh Health, Plano, TX) during each test to detect any excessive activity in either condition. The KAM detects low intensity to vigorous-intensity activity. Therefore, it can detect the low levels of activity associated with moving around one's desk and office space. The KAM divides activity into three intensities; life (<2 mph), health (2-4.5 mph), and sport (>4.5 mph). Each KAM point obtained from the monitor corresponded to a 1% increase above basal metabolic rate.

Procedures

Following the informational sessions, interested participants contacted the study email and an eligibility questionnaire was sent by the study coordinator via SurveyMonkey. Informed consent was obtained prior to baseline anthropometric data collection. Fasting blood glucose, cholesterol, height, weight, blood pressure, and body fat percentage were measured at baseline. Individuals with a FBG > 100 mg/dl were eligible for the present study. The testing was scheduled on two separate mornings at the participant's workplace. Following baseline data collection, OGTT testing was scheduled. Tests were performed at the participant's desk and therefore, all participants were scheduled individually for each test. One 2-h OGTT was performed sitting and one performed standing in random order. Testing was not performed back to back; however, the number of days between testing was different between participants based on their availability and work schedule (i.e. days between tests ranged from 1-22 days).

Participants were instructed to eat the same meal the night before each test, refrain from intense physical activity for 48 hours before the test, and to fast for eight hours before the tests. Prior to each test, the researcher recorded dietary intake from the previous evening, verified the participant was in the fasting state, and had abstained from physical activity within the past 48 hours. Participants were instructed to remain at their desk for the entire two-hour test and to continue work as usual. It was suggested that the restroom be used prior to beginning the test to avoid movement away from their desk during each test. They were instructed to avoid any additional walking around the office such as picking up papers from a printer.

A baseline blood sugar was measured prior to consumption of the beverage. The subject's skin was cleaned and prepped using sterile techniques. The finger was then lanced and the initial drop of blood was wiped away. The sample was then applied to the glucose test strip for measurement by the glucometer (Bayer Breeze 2; Whippany, NJ). A 75g glucose beverage (Trutol, ThermoScientific) was consumed within five minutes. Blood sugar was measured by finger stick again at 30, 60, 90, and 120 minutes following beverage consumption. Any symptoms experienced during the test were recorded for each participant. In the event of a questionable blood sugar measurement during the test, another sample was measured to maintain reliability of the glucometer. A sample of participants (n=5) were re-tested because of unreliable glucose readings due to a glucometer malfunction. However, re-testing was stopped following analysis of the data due to the suspected adverse effect of standing continuously for two hours. Finally, physical activity was monitored with the KAM during each test. The participant was given the KAM at the start of each test and it was removed after the 2-h tests were completed. The participant was instructed to wear the KAM on the front of their pants, in line with the knee. One participant received compensation for participating in the study ($30). The other participants were unable to accept compensation because they work for the government.

Statistical Analyses

All data were analyzed using SPSS (v21.0) for Windows and Microsoft Excel (Windows 2010). Incremental area under the curve was calculated for the glucose values. For each glucose interval, the values were subtracted from baseline. The trapezoidal area was then found for the sitting and standing conditions. Finally, area under the curve (AUC) was calculated in the sitting and standing conditions followed by the difference in the two conditions. Values are reported as means [SD] and 95% CI in the text and tables.

Results

Twenty seven females enrolled into the study. Twenty eligible female participants completed the study (three withdrew and four were ineligible due to meeting exclusion criteria). Ten participants had baseline glucose values that were deemed inaccurate suggesting malfunction of the glucometer. Blood glucose values that differed by greater than 10 mg/dl between the baseline sitting and standing measures were excluded. Therefore, the analysis was conducted on the remaining 10 participants. Participants were recruited between January-February, 2013. As shown in Table 1, the participants were primarily middle aged female adults with BMI levels in the overweight and obese ranges and corresponding body fat percentages in the overfat and obese ranges. Fasting glucose was on average 108 mg/dl. Participants on average had normal blood pressure, slightly elevated cholesterol levels, and elevated triglyceride levels. Three participants were taking chronic prescription medications for disorders unrelated to impaired fasting glucose.

Table 4-1

Participant Characteristics (n=10)

Variables	*M* (SD)	
Age (years)	50.6	(8.5)
Height (m)	1.65	(.06)
Weight (kg)	91.9	(15.6)
BMI	32.9	(3.9)
Body fat %[a]	48.7	(4.0)
SBP	122.3	(11.0)
DBP	81.9	(7.5)
Fasting blood glucose (mg/dl)	108.4	(5.6)
Total cholesterol[a] (mg/dl)	207.1	(37.6)
LDL – cholesterol[a] (mg/dl)	121.3	(40.0)
HDL – cholesterol[a] (mg/dl)	50.8	(14.8)
Triglycerides (mg/dl)	176.6	(84.1)

Note. BMI=Body Mass Index; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; LDL=low-density lipoprotein; HDL=high-density lipoprotein.
[a]n=8.

Oral Glucose Tolerance Testing

The mean postprandial blood glucose values were 135.4 ± 26.0 mg/dl and 149.4 ± 28.6 mg/dl for the sitting and standing conditions, respectively. The mean difference for the glucose area under the curve (AUC) was -124.9 ± 481.7, 95% CI [-386.7, 137]. Figure 4-1 shows the glucose incremental area under the curve (iAUC) for each study condition. While the results are not statistically significant, a trend toward improved glucose clearance is evident in the standing compared to the sitting group.

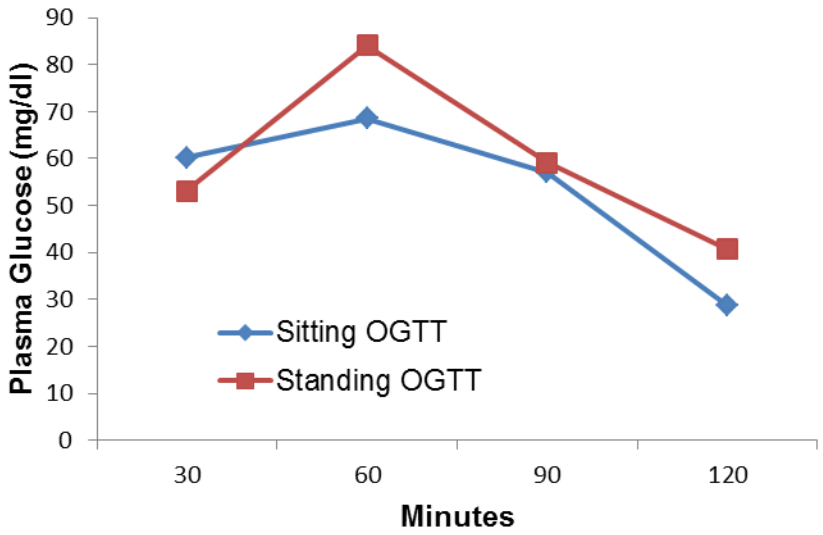

Figure 4-1. Two-hour postprandial glucose incremental area under the curve (n=10). Incremental values were subtracted from baseline. Mean values are plotted.

Four participants met the diagnostic criteria for impaired glucose tolerance (IGT; BG 140-199 mg/dl) during the sitting test and six during the standing test. A total of four participants demonstrated IGT in both conditions. The participants with positive OGTT results had impaired fasting glucose (IFG) and IGT; otherwise known as combined glucose intolerance (CGI; Abdul-Ghani, Tripathy, & DeFronzo, 2006). Finally, one participant met the diagnostic criteria for diabetes during the standing test (BG ≥ 200 mg/dl). The participant was given the results of both tests and instructed to follow-up with her primary care doctor regarding the results.

Discussion

This study is the first study, to our knowledge, to examine the effect of standing on postprandial glucose during a 2-h OGTT in adults with impaired fasting glucose (IFG) in free-living conditions. The results provide preliminary evidence for the effect of standing while working on postprandial glucose in adults with impaired fasting glucose. All participants met the criteria for impaired fasting glucose (IFG) at baseline (FBG 100-125 mg/dl). In addition to IFG

at baseline, participants then met impaired glucose tolerance (IGT) diagnostic criteria (140-199 mg/dl) and diabetes diagnostic criteria (>200 mg/dl). Considering all participants had IFG at baseline, the participants who additionally demonstrated IGT and diabetes possess underlying metabolic differences in blood glucose regulation compared to those with IFG alone. Explanations for the differing responses to the glucose load include changes in diagnostic criteria, a stress response, metabolic differences between IFG and IGT, inaccurate glucose readings, and a small sample size.

The change in IFG diagnostic criteria now identifies individuals early in the blood glucose regulation disease process. In 2003, the threshold for prediabetes and diabetes diagnoses was lowered from 110 mg/dl to 100 mg/dl and 140 mg/dl to 126 mg/dl, respectively. (Follow-up Report on the Diagnosis of Diabetes Mellitus, 2003). This change has resulted in the increased identification of early glucose regulation abnormalities. Therefore, the current study included participants with varying degrees of blood glucose regulation abnormalities. Increasing the inclusion threshold to 110 mg/dl may have attenuated this problem. In addition to changes in the diagnostic criteria, differences exist metabolically between individuals with IFG alone, IGT alone, or the combination of IFG and IGT.

While both IFG and IGT are insulin-resistant states, the site of insulin resistance is different (Abdul-Ghani et al., 2006). Therefore, the pathophysiology of progression to type 2 diabetes is different. Individuals with IFG primarily have hepatic insulin resistance with normal muscle insulin sensitivity (Abdul-Ghani et al., 2006). In contrast, hepatic insulin is slightly reduced and severe muscle insulin resistance occurs with IGT (Abdul-Ghani et al, 2006). Reducing sedentary time will likely benefit these individuals; however, the duration and amount is unknown. Little research exists specifically examining the effect of standing, separate from low-moderate intensity activity, on postprandial blood glucose, especially in adults with prediabetes. In a recent laboratory-based study of healthy adults, sitting with light intensity

activity breaks (two minutes) during a 5-h test period significantly reduced postprandial glucose and insulin compared to uninterrupted sitting. In contrary, sitting with standing breaks (two minutes) did not (Bailey & Locke, 2014 in press). Standing breaks did not significantly reduce postprandial glucose in healthy adults; however, the duration of standing may not have been sufficient.

A precise dose of standing while working is unknown; however, the current recommendation for apparently healthy adults is to avoid prolonged sitting by getting up approximately every 20 minutes (Dunstan et al., 2012). In the current study, an initial 2-h bout of standing (rather than intermittent standing) in a naïve population may have produced a stress response that could have attenuated the glucose response. Specifically, the stress response impairs insulin sensitivity and would therefore explain, in part, the higher responses in the standing condition. This could have been caused by other factors as well (i.e., Adverse symptoms from the glucose beverage, musculoskeletal discomfort from standing, and anxiety over multiple blood sugar measurements). Six participants reported adverse symptoms following consumption of the beverage while standing compared to only two while sitting. Therefore, standing for an extended duration may have produced a stress response that affected blood sugar and produced outward symptoms. However, these differences were not statistically significant in this small sample so additional research is needed.

Limitations of the study include the sample size, eligibility criteria (FBG > 100 mg/dl), and the study protocol. The sample size was small; however the study was conducted as a pilot study to provide baseline findings to inform future research. Increasing the eligibility criteria for FBG to 110 mg/dl would have led to a sample with comparable metabolic abnormalities (i.e. all subjects would demonstrate true and consistent impaired fasting glucose). The study protocol required a continuous bout of standing whereas the appropriate protocol would have alternated sitting and standing bouts. A revised protocol would aim to eliminate the stress response to the

continuous bout of standing. Additionally, the participants were not monitored continuously so it is unknown how often the participant went from a sitting to standing position during the seated test. The inaccurate readings related to glucometer malfunction were an additional limitation. The fasted state was verified by self-report and is another limitation that may have impacted the inaccurate glucose readings. Duplicate measuring in future studies will reduce measurement error. Additionally, the present study was comprised of female volunteers and therefore, the generalizability of the outcomes is limited to females. Finally, the pre-test diet was not controlled, which may have influenced the glucose response between and within persons.

Considering the current obesity and diabetes epidemics, additional research is needed to further examine the effect of low-level activity in the workplace, especially among individuals with blood glucose metabolism abnormalities. A follow-up study based on the lessons learned from the current study would include a revised protocol and would consider administering a mixed-meal beverage rather than the glucose load. A protocol with alternating sitting and standing bouts would increase the use of the large muscles in the legs and hypothetically lead to increased glucose clearance. The mixed-meal beverage may lead to a reduction in symptoms compared to the 75g glucose load. Consequently, a follow-up to the current study with an improved protocol will be equipped to examine the effect of increased activity on postprandial glucose in adults with impaired fasting glucose.

Additionally, a group of participants demonstrated combined glucose intolerance (CGI; IFG and IGT). Individuals with CGI represent approximately 15-20% of those with glucose intolerance and they have double the risk of developing type 2 diabetes (Unwin, Shaw, Zimmet, & Alberti, 2002). The increased risk is due to the severity of the combined hepatic and muscle insulin resistance. Therefore, this group warrants attention and further research on how activity in the workplace can reduce the risk of disease progression. Furthermore, males should be recruited in future studies to identify the effects of standing in males and to allow generalizability

of the results to both genders. Finally, the long-term effect of intermittent standing in the workplace on blood glucose control should be examined in this population.

Intermittent standing while working has the potential to produce beneficial responses in postprandial glucose in female adults with prediabetes. A prolonged bout of standing following glucose ingestion; however, is not recommended. Further research will increase the knowledge base of the response to low-level activity such as standing in the workplace among those with IFG and IGT. This knowledge will inform the development of specific recommendations for standing while working in this population.

5

The Short-term Effect of Sit-Stand Workstations on Blood Glucose in Women with Impaired Fasting Glucose While Working

Abstract

Objective: The purpose of this study was to examine the effect of using a sit-stand desk while working on blood glucose control (monitored continuously) among women with impaired fasting glucose. **Research Design and Methods:** The study was a repeated measures pilot study. Participants (n=10) were overweight or obese adult females with impaired fasting glucose (blood glucose >100 mg/dl) who performed a sedentary job. Participants were recruited from two upper Midwest office buildings. Blood glucose was monitored with continuous glucose monitoring technology (CGM) during two, one-week periods at work. Participants first completed a pre-test for one week in the traditional seated position while working. The second week participants were instructed to alternate bouts of sitting and standing (by adjusting their desk) with the goal of standing for half of the workday. **Results:** The sit-stand condition resulted in reduced blood glucose levels relative to the sitting condition; however, this trend was not significant. Carbohydrates, protein, and fat, significantly predicted blood glucose ($p<.0001$). Specifically, carbohydrate and protein consumption increased blood glucose while fat reduced blood glucose. Sedentary time also significantly predicted blood glucose independent of overall physical activity ($p = .015$). **Conclusions:** Our findings suggest that there is no effect of standing on blood glucose levels in pre-diabetic women. Sedentary time is however a strong predictor of increased blood glucose. Future research with larger sample sizes and longer intervention periods are needed to further examine the effect of reducing sedentary time in the workplace on blood glucose among individuals with impaired fasting glucose.

Introduction

Sedentary behavior is a distinct cardiometabolic risk factor that has been shown to occur independently of habitual physical activity (Wilmot et al., 2012, Saunders et al., 2012). More specifically, prolonged bouts of sedentary time are associated with adverse health outcomes including type 2 diabetes and premature mortality (Dunstan, Howard, Healy, & Owen, 2012). Additionally, sedentary behavior is inversely associated with insulin action (Dunstan et al., 2007; Healy et al., 2007; Healy et al., 2008). Breaking up prolonged sedentary time is associated with beneficial effects on cardiometablic risk markers such as reducing BMI, waist circumference, triglycerides, and postprandial glucose, regardless of both total sedentary time and moderate-vigorous intensity activity (Healy et al., 2008). Laboratory-based studies have demonstrated reductions in postprandial glucose and insulin concentrations following short activity breaks (e.g., low intensity walking; Dunstan et al., 2012, Peddie et al., 2013).

Working adults spend approximately one-third of their lives at work and 77% of this time is spent engaged in sedentary behavior (Jans, Proper, & Hildebrandt, 2007; Thorp et al., 2012). Recent studies have demonstrated the feasibility of replacing traditional desks with height-adjustable workspaces to reduce sedentary time (Alkhajah et al., 2012; Healy et al., 2013). These height-adjustable workspaces could have important implications for decreasing sedentary time and improving cardiometabolic risk factors such as impaired fasting glucose.

Impaired fasting glucose (IFG) affects an estimated 79 million Americans over the age of 20 (Centers for Disease Control and Prevention [CDC], 2011). Impaired fasting glucose increases an individual's risk of developing type 2 diabetes, cardiovascular disease, and stroke (CDC, 2011). Weight reduction and increased physical activity are effective strategies for preventing or delaying the onset of type 2 diabetes (CDC, 2011). Additionally, research indicates

that reducing sedentary time is an effective strategy for reducing the risk of type 2 diabetes (Dunstan et al., 2012; Peddie et al., 2013). A limitation of these studies is that they did not did not continuously monitor glucose levels. Continuous glucose monitoring technology generates 288 (every five minutes) glucose measures in a single day (Medtronic, Northridge, CA). Therefore, this technology enables near continuous examination of glycemic variability, which can be tracked for up to seven days.

Continuous glucose monitoring (CGM) technology was developed in response to the need for improved glucose control to reduce complications related to diabetes and to decrease the risk of severe hypoglycemic episodes (Stratton et al., 2000; Kim et al., 2012). Prior to CGM, HbA1c was the primary measurement tool for assessing glucose variability. One problem was that treatment responses to HbA1c levels were leading to episodes of severe hypoglycemia, primarily in individuals with type 1 diabetes. Because HbA1c reflects the average control of blood glucose, methods capable of frequently monitoring blood glucose control were needed. Additionally, diabetes-related complications were occurring inconsistently in patients with the same HbA1c levels (Hirsch & Brownlee, 2005). Clinically, CGM is currently recommended for managing type 1 diabetes and now functions simultaneously with insulin pumps to form an artificial pancreas (Medtronic, Northridge, CA). Clinical recommendations state that individuals with type 2 diabetics who have difficulty controlling hypoglycemic episodes should use CGM but in general CGM is not used daily (Kim et al., 2012). To date, CGM technology has not been studied in adults with IFG. In addition, the effect of intermittent standing on glucose control in adults with IFG over an entire work week has yet to be examined. The observational and lab-based studies have examined healthy, overweight, and obese individuals and therefore, investigating the effect of a sit-stand workstation on blood glucose among individuals with impaired fasting glucose would address a gap in the literature.

The purpose of the current study was to examine the effect of intermittent standing during the workday on blood glucose levels among women with IFG. Specifically, women with IFG participated in a one week traditional sitting pre-test followed by a one-week sit-stand intervention both conducted at their workplace. The effect on the sit-stand intervention on continuously monitored glucose (specifically focusing on working hours) was examined. We hypothesized that blood glucose would be lower during the sit-stand intervention than during the pre-test. This study is the first to our knowledge to examine continuous blood glucose responses to intermittent standing while working among women with impaired fasting glucose.

Methods

Study Design and Participants

This study was a repeated measures pilot study examining the effect of sitting vs. standing on blood glucose responses based on continuous glucose monitoring (CGM) technology. Participants wore a Continuous Glucose Monitor (CGM) on two separate occasions: (1) one work week while using a desk in the traditional seated position (pre-test), and (2) a second work week while standing for half of the workday. Participants (n=10) were recruited from two workplaces in the upper Midwest. Recruitment methods included flyers, advertisements on the electronic company newsletter, and informational sessions at the worksites. The volunteers in the present study were recruited from and concurrently enrolled in a larger worksite wellness study (a worksite wellness study examining the effect of sit-stand desks, walking, and wellness education on reducing sedentary time in the workplace). The studies began at the same time.

Inclusion criteria included impaired fasting glucose (fasting blood glucose greater than 100 mg/dl), stable medications for the last six months, being a full-time employee (working at least 35 hours per week), daily work performed in the seated position (at least 75% of the work

day spent sitting), and able to safely participate in physical activity that involved increased walking, standing, and using the stairs. Exclusion criteria included a history of heart disease, type1 or type 2 diabetes, renal disease, peripheral neuropathy, retinopathy, peripheral arterial disease (PAD), lower limb amputation, pregnancy, active substance abuse, hospitalization in the past six months for a psychiatric disorder, severe visual impairment, enrollment in a physical activity study, and insulin therapy. Informed consent was obtained and past medical history was collected. The study is registered as 1208M18741 at ClinicalTrials.gov and was approved by the University of Minnesota's Institutional Review Board.

Measures

Anthropometric Measures

Baseline data collection included height, weight, blood glucose, cholesterol, blood pressure, and body fat percentage. Measurements were completed in the fasting state in a private room at the worksite. Height and weight were measured with a stadiometer and calibrated scale (Seca, Chino, CA). Fasting blood glucose and cholesterol were measured by a finger stick with a glucometer (Bayer Breeze 2; Whippany, NJ) and LDX Cholestech system (Alere Cholestech LDX, USA). Blood pressure was measured with an automatic sphygmomanometer (BPTru, BPM-100; BPM Medical Devices). Finally, body fat percentage was measured with dual-energy x-ray apsorptiometry (DXA).

Continuous Glucose Monitor

Blood glucose was measured using continuous glucose monitoring (CGM) technology (iPro2®, Medtronic, USA). The iPro2® system consisted of a sensor that was inserted into the interstitial fluid and a transmitting device that was attached to the sensor on the outside of the skin. The iPro2® is a blinded device that uses an electrochemical system. The sensor is made of

three electrodes (reference, working and counter electrodes) that complete a circuit. The sensor contains three layers: (1) an outer semi-permeable layer that is selectively permeable to oxygen and glucose; (2) a second layer coated with the enzyme glucose oxidase (within this layer a chemical reaction occurs producing hydrogen peroxide and gluconic acid); and (3) the innermost layer is an electrode layer. The gluconic acid produced in the second layer is reabsorbed into the body. The hydrogen peroxide from the enzyme layer travels to the electrode layer. The electrode layer contains a small nano-amp. As the hydrogen peroxide comes in contact with the nano-amp, a second chemical reaction occurs. The chemical reaction reduces the hydrogen peroxide into hydrogen, oxygen, and two electrons. The two electrons are measured by the sensor and the resulting electron current, the ISIG, is sent to the transmitter. Upon download of the transmitter, the ISIG values are converted to glucose values (in five minute intervals). The transmitter was reusable following proper sterilization and download of the previous data; however, the sensor is designed for single use. The iPro2® could be worn continuously for up to seven days.

Other Measures

An accelerometer, the Kinetic Activity Monitor (KAM; Kersh Health, Plano, TX), was worn during the trial to measure physical activity. The KAM measures activity minutes in three zones: (1) life (<2mph); (2) health (2-4.5 mph); and (3) sport (>4.5 mph). The accelerometer generates KAM points which correspond to a 1% increase above basal metabolic rate (BMR; BMR is calculated within the software using height, weight, age, and gender). The results from the KAM are reported elsewhere (Chapter 6). Additionally, dietary intake (all meals, snacks, and beverages) and physical activity were recorded daily in a diary.

Procedure

Informational sessions for both studies were conducted at the worksites with question and answer sessions following the presentation. Interested participants contacted the study email and an initial eligibility questionnaire was sent in response. Following informed consent and baseline data collection, participants were scheduled for the first week of wearing the CGM. All instructions and expectations were reviewed prior to insertion of the device. The CGM device (i.e., iPro2; Medtronic, USA) was inserted on the first day of the week at the worksite in a private room. To insert the device, a location on the body was chosen that would not interfere with normal daily movements, was free of scarring, stretch marks or hardened tissue, and in an area that was comprised primarily of fatty tissue. The device was placed on the side of the low back or the top of the gluteus maximus. The insertion site was sterilized with alcohol and allowed to dry. The sensor was placed in the inserter and the protective coverings removed. The inserter was placed on the skin at a 60° angle. The sensor was inserted with the insertion device. The inserter was removed from the sensor. The sensor and the site were monitored for bleeding (bleeding was rare, however excessive bleeding could destroy the sensor). The sensor was allowed to "wet" for a minimum of 15 minutes. During this time the instructions for wearing the device were again reviewed.

The instructions included educating the participant on how and when to take daily self-monitored blood glucose (SMBG) measurements. The SMBG measurements were required for calibration of the CGM device. Participants were instructed to measure their blood glucose before breakfast, before lunch, before dinner, and before going to bed every day while wearing the device. The participants were provided with a glucometer, a lancer, and lancets (Bayer Breeze 2, Whippany, NJ). Instructions were given on measurement of blood glucose and the participant practiced taking their blood sugar until they were confident in the skill. The SMBG measurements were recorded on the daily diary provided. Dietary intake including meals,

beverages, and snacks were recorded in a diary. Nutrient composition was derived using the USDA National Database for Standard Reference (USDA Agricultural Research Service). The database contains over 8,000 food items. Quantity and type of food were searched and the nutrient composition was recorded for all meals and beverages. Dietary compositions for meals consumed at chain restaurants were cross-checked with the database to ensure accuracy. Finally, daily physical activity was recorded in the diary. Participants were instructed to continue their normal daily activities while wearing the device. The manufacturer recommended avoiding hot tubs or spas given they could cause the device to malfunction. A phone number and email were provided for any emergencies or questions.

After 15 minutes of "wetting," the recording device was attached to the sensor. The recording device displayed a green light signifying the sensor was adequately placed. After the green light was visible, the device was secured with a transparent film dressing (Tegaderm®, 3M). The film was hypoallergenic and kept the device in place during most activities. Participants were then instructed to record the first SMBG within one hour, a second SMBG three hours after insertion, and then on the normal schedule. A Medtronic specialist was available and present for device insertion to address any questions or problems with the equipment. During week one of data collection, all participants were instructed to sit at their desk as usual. At the end of the week, the CGM device was removed at the worksite in a private room. The film was removed and the transmitter and sensor were taken out. The transmitter was removed from the sensor and the sensor was disposed in a biohazard container. The transmitter was cleaned and sterilized according to manufacturer and regulatory guidelines. The Principal Investigator completed training through Medtronic on the proper use and insertion of the device and FDA guidelines for care and cleaning. The device was then downloaded to the manufacturer software. Dietary intake and calibration SMBG measurements were recorded in the software.

After the first week, an acclimation period commenced for approximately four weeks. Throughout this period, the participants were instructed to gradually increase their daily standing time to half of their working day and accumulate standing time in intermittent bouts. After these four weeks, the second week of data collection began. At this time, participants were instructed to use their sit-stand desk for at least half of the workday for the next five days. The CGM was inserted again on the first day of the data collection week. The same procedures for device insertion and wearing instructions were followed during the second week of data collection. Daily standing time was recorded in the diary in addition to dietary intake, SMBG measurements, and physical activity. One participant was compensated but the others could not accept compensation as government employees ($40 for the first CGM and $80 for the second CGM).

Statistical Analyses

Data were analyzed using Microsoft Excel (Windows 2010) and SAS (v9.3). A linear mixed model regression analysis for a crossover design was used in SAS to analyze differences in mean blood glucose between the pre-test and intervention weeks. Working hours (9:00 am to 5:00 pm) were analyzed to examine the effect of the sit-stand workstation on blood glucose. Dietary (i.e., carbohydrate, fat, protein, and fiber intake in grams), physical activity, and sedentary time covariates were controlled for in this model. Results are reported as mean [SD or SE] and *p-values*.

Results

A total of 68 individuals expressed interest in the study (n=62 females and n=6 males). Twenty-seven females met eligibility criteria for the study. The males did not meet inclusion criteria. Data was collected February – July, 2013. Seventeen participants were lost for multiple reasons: (1) four were ineligible; (2) three withdrew; (3) five were not willing to comply with

study requirements; and (4) five experienced CGM malfunction during the pre-test and therefore, the second test week was not completed. Participants had impaired fasting glucose and were on average overweight or obese. Table 5-1 summarizes the baseline characteristics of the sample.

Table 5-1

Participant Characteristics (n=10)

Variables	*M*	(SD)
Age (years)	50.6	(8.5)
Height (m)	66.2	(2.8)
Weight (kg)	91.9	(15.6)
BMI	32.9	(3.9)
Body fat %[a]	48.7	(4.0)
SBP	122.3	(11.0)
DBP	81.9	(7.5)
Fasting blood glucose (mg/dl)	108.4	(5.6)
Total cholesterol[a] (mg/dl)	207.1	(37.6)
LDL – cholesterol[a] (mg/dl)	121.3	(40.0)
HDL – cholesterol[a] (mg/dl)	50.9	(14.8)
Triglycerides (mg/dl)	176.6	(84.1)

Note. BMI=Body Mass Index; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; LDL=low-density lipoprotein; HDL=high-density lipoprotein.
[a]n=8.

The self-reported standing time resulted in adherence to standing for approximately half of the work day ($m = 3.65 \pm 0.4$ hrs). The results of the first linear mixed model analysis (controlling for the effect of the covariates; carbohydrates, fat, protein, and fiber) indicated a nonsignificant effect of standing on blood glucose levels ($p = .549$) during working hours relative to the seated condition (see Table 5-2). Although the *p* – value was not significant, the sign of the coefficient is in line with the hypothesis that blood glucose would be lower when using the sit-

stand desk compared to sitting. In this model, blood glucose in Condition 1 (sitting) was 2.5 mg/dl higher, on average, than Condition 2 (sit-stand; see Table 5-2). Carbohydrates, fat, and protein (p <.0001) demonstrated a significant effect, although fiber (p = .099) did not. Consequently, a one gram increase in carbohydrate or protein produces .08 and .20 mg/dl increases in blood glucose, respectively. In contrast, a one unit increase in fat results in a .19 mg/dl decrease in blood glucose.

Table 5-2

Linear Mixed Model Analysis with Dietary Covariates

Solution for Fixed Effects						
Effect	Cond	Estimate	SE	DF	t Value	Pr > |t|
Intercept		81.6636	3.4869	16	23.42	<.0001
Condition	1	2.5463	4.1638	16	0.61	0.5494
Condition	2	0				
Timepoint2		0.09923	0.009395	4255	10.56	<.0001
Carbohydrates		0.07815	0.01159	4255	6.74	<.0001
Fat		-0.1924	0.02229	4255	-8.63	<.0001
Protein		0.2025	0.02319	4255	8.73	<.0001
Fiber		0.1170	0.07080	4255	1.65	0.0986

Note. Condition 1 = one week seated pre-test. Condition 2 = one week sit-stand. SE = standard error. DF = degrees of freedom.

The model was run again including the accelerometer data (KAM points; overall physical activity) with similar results (see Table 5-3). The effect of the intervention increased slightly compared to the model in Table 5-2 although there was still not a significant difference between conditions. In this model, overall physical activity is a significant predictor of blood glucose. With each one unit increase in KAM points, blood glucose was lowered by .06 mg/dl (p = .017).

Table 5-3

Linear Mixed Model Analysis with Physical Activity as a Covariate

Solution for Fixed Effects						
Effect	Cond	Estimate	SE	DF	t Value	Pr > |t|
Intercept		78.2659	4.3219	14	18.11	<.0001
Condition	1	3.1264	5.2708	14	0.59	0.5625
Condition	2	0				
Timepoint2		0.1318	0.01033	3596	12.75	<.0001
Carbohydrates		0.1024	0.01402	3596	7.30	<.0001
Fat		-0.2571	0.02922	3596	-8.80	<.0001
Protein		0.2361	0.02525	3596	9.35	<.0001
Fiber		0.05043	0.07657	3596	0.66	0.5102
KAM point		-0.06741	0.02823	3596	-2.39	0.0170

Note. Condition 1 = one week seated pre-test. Condition 2 = one week sit-stand. SE = standard error. DF = degrees of freedom.

Again, the statistical model was run, now including sedentary minutes as a covariate (Table 5-4). The effect on the intervention remained nearly identical to the previous model with overall physical activity. Time spent in sedentary activity significantly predicted blood glucose. For every one minute increase in sedentary time, blood glucose increased 0.11 mg/dl (p = .0007).

Table 5-4

Linear Mixed Model Analysis with Sedentary Time Covariate

Solution for Fixed Effects						
Effect	Condition	Estimate	SE	DF	t Value	Pr > |t|
Intercept		71.8966	4.6740	14	15.38	<.0001
Condition	1	3.1245	5.3128	14	0.59	0.5658
Condition	2	0				
Timepoint2		0.1360	0.01045	3596	13.02	<.0001
Carbohydrates		0.1024	0.01400	3596	7.32	<.0001
Fat		-0.2557	0.02920	3596	-8.76	<.0001
Protein		0.2291	0.02535	3596	9.03	<.0001
Fiber		0.05165	0.07649	3596	0.68	0.4996
Sedentary min		0.1061	0.03119	3596	3.40	0.0007

Note. Condition 1 = one week seated pre-test. Condition 2 = one week sit-stand week. SE = standard error. DF = degrees of freedom.

The final model included both overall physical activity and sedentary time (see Table 5-5). The treatment effect remained nonsignificant; however, the effect of the intervention remained in the hypothesized direction. Blood glucose was 3.1 mg/dl higher in Condition 1 (sitting) compared to Condition 2 (standing). The dietary covariates remain statistically significant. However, with physical activity and sedentary time included in the same model, overall physical activity no longer significantly predicted blood glucose. Sedentary time was significantly related to increasing blood glucose, regardless of physical activity (p = .015).

Table 5-5.

Linear Mixed Model Analysis with Physical Activity and Sedentary Time Covariates

Solution for Fixed Effects						
Effect	Cond	Estimate	SE	DF	t Value	Pr > |t|
Intercept		71.5014	5.1636	14	13.85	<.0001
Condition	1	3.1208	5.3108	14	0.59	0.5661
Condition	2	0				
Timepoint2		0.1362	0.01048	3595	12.99	<.0001
Carbohydrates		0.1025	0.01401	3595	7.32	<.0001
Fat		-0.2557	0.02921	3595	-8.75	<.0001
Protein		0.2287	0.02541	3595	9.00	<.0001
Fiber		0.05140	0.07650	3595	0.67	0.5017
KAM point		0.007521	0.04180	3595	0.18	0.8572
Sedentary min		0.1123	0.04624	3595	2.43	0.0152

Note. Condition 1 = one week seated pre-test. Condition 2 = one week sit-stand. SE = standard error. DF = degrees of freedom.

Discussion

Our main finding suggested a trend towards lower blood glucose during the work day when these prediabetic adults were using a sit-stand workstation to increase standing time, relative to the control/sitting usual workday period. However, this finding was not statistically significant, but needs to be followed up with more sophisticated modeling techniques given the richness of the dataset. Sedentary time, however, was a significant predictor of blood glucose. The epidemiological literature describes associations of increased sedentary time with risks of blood sugar dysfunction regardless of physical activity levels (Dunstan et al., 2005; Dunstan et al., 2012; Healy et al., 2008). The current study objectively demonstrates the deleterious effect of sedentary time on blood glucose. In the final analysis model, sedentary time remains the

significant predictor of blood glucose while overall physical activity is no longer predicting blood glucose.

Using the overall mean of the blood glucose readings over the five days may not be a good estimate of blood glucose. Unfortunately, the literature does not provide a standard or preferred method of analysis for CGM data and therefore, the current analysis was straightforward. The treatment effect is comparing the average blood glucose of the five days, which considerably reduces the degrees of freedom for the effect estimate, and considerably increases the magnitude of the standard error. For this reason, even though the estimated difference in daily blood glucose mean was 3.1 mg/dl between conditions, this effect was not statistically significant in the present models. Because glucose fluctuates dramatically throughout the day, this may not be the most appropriate analysis technique. Individuals with impaired fasting glucose exhibit more moderate excursions in blood glucose compared to type 1 and type 2 diabetics. These excursions may increase the difficulty of finding significant differences, especially when broadly estimating the mean. Varied levels of glucose intolerance between participants likely influenced the results as well. Glucose intolerance across the participants ranged from very mild, at the threshold criteria for impaired glucose tolerance, to more severe, near the diagnostic criteria for type 2 diabetes. This wide range of glucose intolerance further reduces the ability of the current analysis to detect significant differences. If the inclusion criteria threshold was set at a more conservative 110 mg/dl, this would have resulted in a more metabolically homogeneous sample and perhaps would have increased the likelihood of detecting significant differences. Sophisticated analysis techniques are needed to more fully explore these CGM data. Indeed, modest reductions in blood glucose can be clinically meaningful in the treatment and management of prediabetes, and the prevention of frank diabetes onset. Regression to normal glucose regulation, even if transient, significantly reduces the risk of future diabetes

(Perreault et al., 2012). Nevertheless, the blood glucose findings in the current pilot study will likely serve to be very useful for designing a full-scale study on this and related topics.

The dietary covariates were also significant predictors of blood sugar. Increased intake of carbohydrates and protein significantly increased blood glucose, whereas, as expected, increased fat intake reduced blood glucose. The effect of carbohydrates and fats are in the expected direction. The positive effect (increasing blood glucose) of protein, however, was unexpected, as protein ingestion generally does not increase peripheral glucose (in normal individuals; Gannon & Nuttall, 1999). Further examination of the dietary logs is needed to determine the type and quality of protein being consumed as this can greatly affect the rate of metabolism (Ten Have, Engelen, Luiking, & Deutz, 2007). It is also likely that the results for protein may be an artifact of the dietary log data or analysis, and this will be explored in more detail in future analyses.

Strengths of the study were the novel use of continuous glucose monitoring technology in prediabetic women and conducting the study in a natural setting. The CGM technology provides a large amount of data for each individual and provides valuable data on glucose control. The data can be used to identify problem areas, such as the postprandial period (two to three hours after eating), to develop interventions to reduce disease risk and progression. The study provided pilot data to guide future use of CGM in impaired fasting glucose. No studies to date have continuously monitored blood glucose in women with impaired fasting glucose nor has data been collected over an entire work week. Additional strengths were the objectively measured physical activity and sedentary time. Not many studies have captured these variables in the natural setting nor has blood glucose been simultaneously monitored in this population.

This study has several limitations. The participants were not randomized to the order of the two data collection periods (sitting and sit-stand). As individuals increase standing while working they may experience musculoskeletal discomfort (specifically in the low back and legs) due to the increased use of these muscles. This discomfort generally disappears following a week or two of intermittent standing. The participants may have been less likely to comply to the sitting week if they were aware of the discomforts associated with acclimating to the use of the desk. The inclusion criteria for fasting blood glucose was >100 mg/dl. An increased inclusion criteria threshold of >110 mg/dl would result in a metabolically similar sample. While six men volunteered for the study (the male volunteers did not meet inclusion criteria), the participants were all women. This limitation is possibly two-fold in that women are more likely to volunteer to participate in research and the worksites consisted of primarily female employees.

The study recruited a relatively large sample size; however, a number of participants were lost following consent. The continuous glucose monitor involved an invasive procedure in addition to monitoring blood glucose daily which led to drop outs. Others were lost due to the monitor malfunctioning. Five participants had no data upon download following the first week of the study. Because the device was blinded, the malfunction was not known until the transmitter was downloaded. The manufacturer determined the data loss was due to a bad batch of sensors. Additional limitations were self-reported dietary intake and standing time. Nonetheless, the participants were instructed to consume a similar dietary pattern during each week while wearing the monitor. Finally, the statistical analysis, as discussed previously, may be a limitation.

Future studies should recruit a larger sample size (and minimize loss of participants) and recruit from multiple worksites to increase the likelihood of recruiting male participants. The sample size of the current study is fairly consistent with similar studies within the literature, considering this area of research is novel (Speck & Schmitz, 2011; Alkhajah et al., 2012; Buckley

et al., 2013). Future studies should examine the long-term effect of reducing sedentary time on blood glucose in prediabetes. Lifestyle interventions (including weight loss, regular physical activity, and dietary modifications such as calorie restriction, increased fiber, and limited carbohydrate intake) have prevented or delayed progression from prediabetes to type 2 diabetes (Garber et al., 2008). Therefore, reducing sedentary time may be an additional component to consider in lifestyle interventions to prevent disease progression. Finally, the effect of the sit-stand desk on the postprandial period should be examined. Rather than analyzing the entire work day, reducing the analysis period to a specific time point can examine the effect of the intervention during a specific time of the work day.

Research indicates that sit-stand desks are effective for reducing sedentary time and lowering postprandial blood glucose (Alkhajah et al., 2012; Buckley et al., 2013). However, additional research is needed to determine if sit-stand workstations are an effective tool for controlling blood glucose and preventing further disease progression in this population. Long-term intervention studies with large samples are needed to further examine this research question.

6

The Short-term Effect of Using a Sit-Stand Desk to Reduce Sedentary Time in Women with Prediabetes

Abstract

Objective: The primary aim of this study was to examine the acute effect of a sit-stand desk on objectively measured sedentary time during the workday among adults with prediabetes.

Research Design and Methods: The study was a repeated measures pilot study. All measurements were collected at the participant's worksite and desk under free-living conditions. The study included 10 participants who completed the following two conditions: (1) wearing an accelerometer and sitting at their desk for one week; and (2) wearing an accelerometer and intermittently standing at their desk for one week. **Results:** Participants were females who on average were overweight or obese and middle-aged. Participants stood for approximately half of the work day during the sit-stand week (m = 3.65 ± 0.4 hrs). The participants wore an accelerometer that tracked minutes spent in three intensity zones (life <2 mph, health 2-4.5 mph, and sport >4.5 mph). There was a marginally significant reduction in sedentary time in the standing condition compared to the sitting condition. Mean differences in minutes between the zones were as follows; 1.37 ± 2.77, 95% CI [-0.35, 3.08]; 0.55 ± 1.56; [-0.42, 1.52]; and 1.92 ± 3.44; [-0.21, 4.05] for the minutes in life, health, and life and health zones combined, respectively. **Conclusions:** Sit-stand desks may be an effective method for reducing sedentary time among adults with impaired fasting glucose. Further research with a larger sample is needed to examine additional benefits associated with reducing sedentary time in this population.

Introduction

Substantial epidemiological and growing experimental evidence support the association between sedentary time and cardiometabolic disease (Hamilton, Hamilton, & Zderic, 2007; Healy, Matthews, Dunstan, Winkler, & Owen, 2010; Proper, Singh, Van Mechelen, & Chinapaw, 2011; Wilmot et al., 2012). Specifically, prolonged sedentary behavior is associated with the increased risk of obesity, blood sugar metabolism abnormalities, adverse alterations in cardiometabolic markers, certain cancers, and all-cause mortality (Hu, Li, Colditz, Willett, & Manson, 2003; Katzmarzyk, Church, Craig, & Bouchard, 2009; Healy et al., 2010; Lynch, 2010; Wilmot et al., 2012). While the epidemiological evidence supporting the association between sedentary behavior and adverse health outcomes is vast, the experimental literature has been widely lab-based. There is a need for studies to examining sedentary behavior in free-living conditions such as occupational settings.

Working adults represent half of the world's population (WHO, 1995). The majority of a working adult's day is spent performing sedentary behaviors. Specifically, adults spend an average of six hours per work day sitting (Thorp et al., 2009; Ryan, Grant, Dall, & Granat, 2011). The simple installation of a height-adjustable workstation has been shown to be effective at reducing sitting time both at work and throughout the entire week (Alkhajah et al., 2012). Objectively measured activity data demonstrated a reduction in sitting time by 143 minutes per working day (Alkhajah et al., 2012). Neuhaus and colleagues (2014) recently conducted a study in which participants were randomly assigned to height-adjustable workstations with a multi-component intervention (six emails from the staff manager supporting program participation and five emails encouraging staff to stand up, sit less, and move around more), height-adjustable workstations only, and a comparison group. The workstation plus multi-component intervention reduced sitting time by 89 minutes during an eight-hour work day while the group that received

the desk only still reduced sitting time by 33 minutes (Neuhaus et al., 2014). Taken together, research indicates that installing a height-adjustable desk is effective for reducing sitting time in healthy, working adults. Height-adjustable desks may be especially important for at risk individuals such as those with blood glucose metabolism abnormalities suggestive of prediabetes. The effect of height-adjustable desks on sedentary time is yet to be studied in this population.

Prediabetes affects an estimated 79 million Americans (Centers for Disease Control and Prevention [CDC], 2012). Excessive sitting and sedentary behavior increases the risk of developing blood glucose metabolism abnormalities, which often lead to prediabetes and type 2 diabetes (Healy et al., 2007; Dunstan, Howard, Healy, & Owen, 2012). Strategies to prevent the progression of blood glucose metabolism abnormalities are important given 70% of individuals with prediabetes will eventually develop type 2 diabetes (Nathan et al., 2007). Sedentary behaviors that lead to reduced muscle activity such as sitting, watching television, or using a computer, are inversely related to insulin action (Dunstan et al., 2007; Healy et al., 2007; Healy et al., 2008). Just one day of sitting reduces insulin action by 39% in healthy men and women (Stephens, Granados, Zderic, Hamilton, & Braun, 2011).

Interventions that reduce sedentary time among prediabetic individuals are needed. Working adults spend on average 8.8 hours of their day and one-third of their life at work and therefore, the workplace is an optimal location to intervene (Bureau of Labor Statistics, 2012; Jans, Proper, & Hildebrandt, 2007). The present study, a repeated measures pilot study, examined the acute effect of a height-adjustable workstation on sedentary time among adult females with prediabetes. Participants were employed full-time at a sedentary job. It was hypothesized that participants would exhibit less sedentary time during the week they used the height-adjustable desk than the week they used their conventional desk.

Methods

Research Design

This repeated measures pilot study was conducted at two workplaces in the upper Midwest. The physical activity data presented in this brief report were collected concurrently with a blood sugar study and a longitudinal worksite wellness study. The details of the blood sugar study are presented elsewhere (Chapter 5) while the worksite wellness study is currently being analyzed. Measurements were performed at the participant's desk under free-living conditions.

Participants

Participants were recruited through flyers and an electronic advertisement on the company newsletter. Employees were invited to attend general information sessions at the worksites that included an explanation of the study and question and answer sessions. A study email address was provided for interested participants to contact. A total of 163 individuals (n=144 females; n=19 males) contacted the study email to express interest in the worksite wellness study. Of the 163, 68 individuals (n=62 females; n=6 males) specified additional interest in the current study. A total of 27 female volunteers were initially eligible and recruited for the study. Each participant completed two, one-week conditions while wearing the accelerometer. The two conditions included the following; (1) a pre-test sitting at their desk as usual while working; and (2) intermittently standing for half of the work day using a height-adjustable desk.

Inclusion criteria included fasting blood glucose greater than 100 mg/dl, a full-time employee (defined as working at least 35 hours per week), sedentary workday (75% of their work day had to be spent sitting), stable medications for at least six months, and no contraindications to

participating in light-intensity physical activity such as standing, walking, or using the stairs. Exclusion criteria included a history of heart disease, peripheral artery disease, lower limb amputation, known type 1 or type 2 diabetes, renal disease, peripheral neuropathy, retinopathy, currently pregnant, active substance abuse, severe visual impairment, hospitalization for a psychiatric disorder in the past six months, enrolled in another physical activity study, and the use of insulin or an insulin pump. Each participant completed informed consent and past health and medical history was collected. The study was approved by the University of Minnesota's Institutional Review Board and registered as 1208M18741 at ClinicalTrials.gov.

Anthropometric and Physiological Measures

All measures were collected at the participant's worksite, in a private setting. Baseline data collection included height and weight, body mass index (BMI), body fat percent (dual energy x-ray absorptiometry [DXA]), resting blood pressure (BPTru, BPM-100; BPM Medical Devices), fasting cholesterol (Cholestech LDX, Alere), and fasting blood glucose (Bayer Breeze 2; Whippany, NJ).

Activity Measurement

The Kinetic Activity Monitor (KAM) was worn to measure activity during each one-week period (Kersh Health, Plano, TX). The KAM measured minutes of activity in three intensity zones; life (<2 mph), health (2-4.5 mph), and sport (>4.5 mph). The device also calculates KAM points. KAM points are derived from the ratio of the amount of energy used while active and the amount of energy used at rest, multiplied by 100% (Kersh Health). Each KAM point represents a 1% increase above basal metabolic rate. Activity and caloric computations are based on height, weight, age, and gender. The KAM is capable of detecting both low and vigorous-intensity activity. Therefore, low levels of activity associated with

moving around one's desk and office space are detected with this device. The device can provide real-time data on KAM points and minutes of activity at each intensity to participants; however, this output was locked during the study in order to blind participants to the data. Additionally, daily physical activity and standing time were recorded on the logs provided to the participants.

Procedures

After attending an information session or viewing one of the study advertisements, interested participants contacted the study coordinator via the email provided. An eligibility questionnaire was emailed to the interested participant via SurveyMonkey. The questionnaire determined whether the individual's job was sedentary and if exclusion criteria were present. Once eligible, informed consent was obtained, past medical history was collected, and baseline anthropometric data collection commenced. Data collection was performed at the worksites in private rooms. Participants fasted eight hours prior to data collection. Fasting blood glucose was measured by a finger stick. The skin was sterilized, lanced, and the first drop of blood was wiped away. A drop of blood was applied to the glucose test strip for the glucometer to analyze (Bayer Breeze 2; Whippany, NJ). Individuals with a fasting blood glucose (FBG) >100 mg/dl were eligible to participate in the current study.

Following anthropometric data collection, participants completed a week long pre-test assessment of their sedentary behavior in the seated position. The KAM was delivered to the participant and instructions were given. The KAM was worn on the front of the pants, in line with the knee during waking hours for the entire week (both at work and home). The KAM was not worn while sleeping or during water-based activities. Daily dietary and activity logs were provided for the participant to record all meals, snacks, beverages, and daily physical activity. A

continuous glucose monitor was worn during the same period and procedures and results are reported elsewhere (Chapter 5). The KAM was collected on the last day of the week.

Following the pre-test, a height-adjustable desk was installed at one worksite and the existing motor-driven desks were used at the other worksite. An ergonomic evaluation was completed prior to the use of the desk to inform the participant on proper ergonomics while using the sit-stand desk. An acclimation period of at least three weeks was completed prior to the second week of the study. During this time, the participants were instructed to gradually increase their total daily standing time to half of the workday, or approximately four hours. Participants were encouraged to accrue daily standing time through intermittent bouts of standing rather than continuous standing. Participants were instructed to wear proper footwear such as tennis shoes and not high heels while standing. During the second week of data collection the participants were encouraged to intermittently stand while working for half of their workday. The KAM was again given to the participant on the first day of the week and collected on the last day.

Daily standing time was recorded on the logs in addition to dietary intake and physical activity. Participants were instructed to follow similar dietary and physical activity patterns as they did during the pre-test. Following each week of data collection, the KAM was downloaded to the software provided by the manufacturer. The software provided hourly totals for KAM points and minutes spent in the life, health, and sport activity zones.

Statistical Analyses

Participant characteristic data were analyzed using SPSS (v21.0) for Windows and Microsoft Excel (Windows 2010). The KAM data was analyzed in Microsoft Excel. The mean difference in minutes between the life, health, and sport zones (minutes) while sitting and standing during working hours was computed. Results are reported as mean [SD] and 95% CI.

Results

Participants

Twenty seven participants enrolled in the study. However, three withdrew from the study, four were ineligible due to meeting exclusion criteria, five chose not to comply with the study requirements, and five only completed the first week due to equipment malfunction. Therefore, the final sample consisted of 10. The baseline subject characteristics are presented in Table 1. The participants were on average overweight and obese middle aged females with impaired fasting glucose and high triglycerides. Based on the National Cholesterol Education Program's (Adult Treatment Panel III) guidelines, 50% of the participant's baseline data met at least three of the criteria for the diagnosis of metabolic syndrome (Grundy et al., 2005). The diagnostic criteria include fasting blood glucose (≥110 mg/dl), systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, high density lipoprotein (HDL; <50 mg/dl), and triglycerides (≥150 mg/dl).

Table 6-1

Participant Characteristics (n=10)

Variables	*M*	(SD)
Age (years)	47.3	(9.3)
Height (in.)	66.2	(2.8)
Weight (kg)	93.5	(16.2)
BMI	32.4	(4.4)
Body fat %[a]	47.2	(6.7)
SBP	121.9	(11.1)
DBP	81.7	(7.3)
Fasting blood glucose (mg/dl)	106.9	(4.1)
Total cholesterol[a] (mg/dl)	199.5	(36.1)
LDL – cholesterol[a] (mg/dl)	113.8	(33.5)
HDL – cholesterol[a] (mg/dl)	48.5	(12)
Triglycerides (mg/dl)	186.8	(74)

Note. BMI=Body Mass Index; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; LDL=low-density lipoprotein; HDL=high-density lipoprotein.
[a]n=8.

Physical Activity

Participants self-reported standing time as the daily cumulative total number of hours. During the pre-test, participants worked in the seated position as usual and therefore, standing time was not reported for this period. Participants reported standing for approximately half of the work day while using the height-adjustable desk (3.65 ± 0.4; n=6). Differences in the minutes spent in the life, health and sport zones between the pre-test and sit-stand weeks during working hours were calculated. The mean differences of the minutes spent in the life, health, and the combined mean difference of the life and health zones between the pre-test and sit-stand weeks were also calculated. The differences between the pre-test and the sit-stand week were

marginally significant representing a trend toward reduced sedentary time when using the sit-stand desk (1.37 ± 2.77, 95% CI [-0.35, 3.08]; 0.55 ± 1.56, [-0.42, 1.52]; and 1.93 ± 3.44; [-0.21, 4.05] for the minutes spent in life, health, and combined life and health zones, respectively). Table 6-2 summarizes the findings for the intensity zones.

Table 6-2

Accelerometer Intensity Zone Differences (min) During Working Hours

Zone	*M*	(SD)	95% CI	
			LL	UL
Life	1.37	(2.77)	-0.35	3.08
Health	0.55	(1.56)	-0.42	1.52
Sport	-0.16	(0.35)	-0.38	0.05
Life & Health	1.92	(3.44)	-0.21	4.05

Note. CI = confidence interval; LL = lower limit; UL = upper limit.

Discussion

Increased standing while working through a simple intervention (installing a sit-stand desk and encouraging intermittent standing for at least half of the work day) has been previously shown to be an effective method for reducing sedentary time in apparently healthy adults (Alkhajah et al., 2012). The present study indicates that a similar outcome can be achieved among women with prediabetes. The self-reported standing time during the sit-stand week indicated that participants achieved the goal of standing for approximately half of an 8-hour work day while using the sit-stand desk. The accelerometer results demonstrated a nearly significant reduction in sedentary time between when the participants were using their standing instead of

their traditional desks. The marginally significant finding further confirms that the participants increased activity during the sit-stand week. The increase in standing resulted from simply installing a desk and providing instruction to gradually increase daily standing to at least half of the work day. The findings are consistent with the current literature on the reduction of sedentary time through installation of height-adjustable workstations in healthy adults (Alkhajah et al., 2012; Neuhaus et al., 2014).

Reducing sedentary time at work can lead to improvements in cardiovascular risk and, more specifically for this population, reducing the risk of progressing to type 2 diabetes. Reducing cardiovascular and diabetes risk is important in this population considering individuals with impaired fasting glucose have been found to have similar coronary atherosclerosis and plaque vulnerability as those with diabetes (Kurihara et al., 2013). Therefore, impaired fasting glucose, or prediabetes, is a risk factor for coronary artery disease (CAD) itself, which increases the necessity and urgency of reducing sedentary time in this population to reduce disease risk. In addition to the increased risk of CAD, half of the participants in the current study meet diagnostic criteria for metabolic syndrome.

Abdominal obesity and insulin resistance play key roles in the development of the metabolic syndrome. Additional factors implicated in the pathogenesis are a sedentary lifestyle, diet, and genetics (Lakka & Laaksonen, 2007)). An inverse dose-response relationship has been found between leisure-time physical activity (LTPA) and metabolic syndrome in middle-age and older adults (Halldin, Rosell, de Faire, & Hellenius, 2007). Based on this relationship, increasing LTPA while working is a promising avenue for the prevention and treatment of metabolic syndrome in this population. The precise dose and intensity of activity accumulation while working remains unknown; however the simple installation of sit-stand desks appears to be helpful for reducing sedentary time.

A strength of the study was measuring sedentary time in the natural setting. Additionally, sedentary time at work among adults with impaired fasting glucose has not been examined and therefore, this study contributes to a gap in the sedentary and inactivity literature. Limitations of the study include the subjective measurement of standing time and the lack of randomization. Participants were not randomly counterbalanced to the two conditions due to the musculoskeletal discomfort associated with acclimating to a sit-stand desk. The discomfort generally disappears quickly and may be followed by improvement in chronic low back pain and increased energy while working. If a portion of the participants stood first they would be aware of this acclimation period and may be less likely to comply with the sitting protocol due to the perceived benefits of standing while working. Another limitation was the small sample size and a significant number of participants were lost following consent. The concurrent blood sugar study involved invasive blood draw procedures, which contributed to a portion of the drop-out rate. Additional equipment malfunctions (within the blood sugar study) led to further loss. Another limitation was the measurement capability of the KAM. The KAM measures movement in the horizontal plane and activity is recorded from movements of the hips and torso. The KAM is not capable of measuring movement in the vertical plane (up and down motions such as transferring from a seated to a standing position). Therefore the device only functions as an accelerometer and not an inclinometer. Finally, the KAM may not have been sensitive enough to detect such minor movements as shifting while standing and moving around one's desk.

Future studies should use randomization and recruit a larger sample size. The KAM can be an effective tool for promoting physical activity and wellness; however, it is not equipped to measure inclinometry. Therefore, the use of a more sophisticated activity measurement device that includes an accelerometer and inclinometer should be utilized in future studies. The current study was conducted over a short period of time. Future studies should examine the long-term

effect of height-adjustable workstations (including biochemical markers such as insulin) in adults with prediabetes. Finally, multicomponent studies that incorporate wellness and physical activity education should be conducted.

Sit-stand desks may be an effective method for reducing sedentary time and combatting the deleterious effects of excessive sitting. The current study extends the knowledge of the effectiveness of sit-stand desks to adults with impaired fasting glucose. Working adults with impaired fasting glucose represent a population at high risk for future disease and therefore, require innovative interventions that decrease sedentary time to reduce disease risk and progression.

7

Summary

The purpose of this dissertation was to examine the effect of increased standing at work on blood glucose and sedentary behavior among working female adults with impaired fasting glucose. The results presented in Chapters 4-6 provide preliminary pilot data evaluating the effect of sit-stand desks on postprandial glucose responses and sedentary time among women at risk for developing type 2 diabetes. This dissertation was novel in three specific ways. First, the effect of standing on glucose responses was evaluated in a natural setting among women with impaired fasting glucose. Previous studies have been conducted in laboratory settings and on apparently healthy adults and therefore, there is a need to examine this research question in natural settings and in this population. Second, continuous glucose monitoring technology was used to examine the effect of intermittent standing on blood glucose responses. Blood glucose, monitored continuously, during working hours was examined among female adults at risk for developing type 2 diabetes. This technology is primarily used among individuals with type 1 and type 2 diabetes. Therefore, extending its use to prediabetes for potential reduction in disease progression is novel. Finally, examining the effect of a sit-stand desk on decreasing sedentary behavior among women with fasting glucose is novel. Reductions in sedentary time have not been specifically examined among this at-risk group. The results of each paper are summarized below.

The purpose of Specific Aim 1 was to examine the acute effect of a sit-stand desk on postprandial glucose in pre-diabetic women. As described in Chapter 4, postprandial glucose increased in the sit-stand desk condition relative to the traditional desk condition. It is possible that stress responses related to standing for an extended period augmented glucose responses. Future research following an improved testing protocol is needed to examine the effect of intermittent standing on postprandial glucose. The study should include a larger sample and utilize a sit-stand protocol (intermittent standing every 10 minutes rather than continuous

standing). Finally, a mixed-meal beverage should be considered in lieu of the glucose beverage to reduce adverse symptoms.

The purpose of Specific Aim 2 was to assess the effect of a sit-stand desk on blood glucose control among pre-diabetic women. The results presented in Chapter 5 demonstrate a trend toward reduced blood glucose while using the sit-stand desk for one week relative to the traditional seated position in prediabetic women. Dietary, physical activity and sedentary time covariates significantly predicted blood glucose. Increased carbohydrate and protein predicted increases in blood glucose while fat predicted decreased blood glucose. In the final analysis model, sedentary time was a strong predictor of glucose, not overall physical activity. Future research should recruit a larger sample size and examine the long-term effect of reduced sedentary time as a result of using a sit-stand desk on blood glucose regulation in women with prediabetes.

Specific Aim 3 examined the effect of a sit-stand desk on sedentary time among pre-diabetic women. The results presented in Chapter 6 suggest that a sit-stand desk may be an effective intervention tool for reducing sedentary time in women with prediabetes. Future studies with a larger sample size and additional biochemical measures are needed to further examine the effect of sit-stand desks on reducing sedentary time among pre-diabetic women.

8

References

Abdul-Ghani, M. A., Tripathy, D., & DeFronzo, R. A. (2006). Contributions of β-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes Care, 29*(5), 1130-1139.

American Diabetes Association. Standards of medical care in diabetes--2011. *Diabetes Care*, *34,* Suppl 1:S11-61.

American Diabetes Association (2013). Diagnosing diabetes and learning about prediabetes. Retrieved from http://www.diabetes.org/diabetes-basics/diagnosis/?loc=db-slabnav

Ali, S., Stone, M. A., Peters, J. L., Davies, M. J., & Khunti, K. (2005). The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. *Diabetic Medicine, 23,* 1165-1173.

Alkhajah, A. T., Reeves, M. M., Eakin, G. E., Winkler, A. H. E., Owen, N., & Healy, N. G. (2012). Sit-stand workstations: A pilot intervention to reduce office sitting time. *American Journal of Preventive Medicine, 43*(3), 298-303.

Alonso J., Ferrer, M., Gandek, B., Ware, J. E., Aaronson, N. K., Moscani, P., . . . Leplege, A. (2004). Health-related quality of life associated with chronic conditions in eight countries: results from the International Quality of Life Assessment (IQOLA) project. *Quality of Life Research, 13,* 283-298.

Andrews, R. C., Cooper, A. R., Montgomery, A. A., Norcross, A. J., Peters, T. J., Sharp, D. J., . . . Dayan, C. M. (2011). Diet or diet plus physical activity versus usual care in patients with newly diagnosed type 2 diabetes: the Early ACTID randomized controlled trial. *Lancet, 378,* 129-139.

Bailey, D. P. & Locke, C. D. (2014 in press). Breaking up prolonged sitting with light-intensity walking improves postprandial glycemia, but breaking up sitting with standing does not. *Journal of Science and Medicine in Sport.* http://dx.doi.org/10.1016/j.jsams.2014.03.008

Blake, H. (2008). Innovation in practice: mobile phone technology in patient care. *British Journal of Community Nursing, 13,* 162-165.

Bode, W. B. & Batellino, T. (2013). Continuous glucose monitoring in 2013. *Diabetes Technology & Therapeutics*, *16*(S1), S11-S16. doi:10.1089/dia.2013.1502.

Boule, N. G., Haddad, E., Kenny, G. P, Wells, G. A., & Sigal, R. J. (2003). Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *Journal of the American Medical Association, 286,* 1218-1227.

Brooks, G. A., Fahey, T. D., & Baldwin, K. M. (2005). *Exercise physiology: Human bioenergetics and its applications* (4th ed.). New York, NY: McGraw-Hill.

Brown, W. J., Miller, Y. D., & Miller, R. (2003). Sitting time and work patterns as indicators of overweight and obesity in Australian adults. *International Journal of Obesity and Related Metabolic Disorders, 27*(11), 1340-1346.

Brownson, R. C., Boehmer, T. K., Luke, D. A. (2005). Declining rates of physical activity in the United States: what are the contributors? *Annual Review of Public Health, 26*, 421- 443.

Buckley, J. P., Mellor, D. D., Morris, M., & Joseph, F. (2013). Standing-based office work shows encouraging signs of attenuating post-prandial glycaemic excursion. *Occupational and Environment Medicine, 71,* 109-111.

Bureau of Labor Statistics. American time use survey (2012). Retrieved from http://www.bls.gov/tus/charts/

Bureau of Labor Statistics. Employment by major occupational group, 2012 and projected 2022. Economic News Release. Tables 5 & 6. Dec 19, 2013. Retrieved from http://www.bls.gov/news.release/ecopro.toc.htm.

Centers for Disease Control and Prevention, National Center for Health Statistics, Division of Health Interview Statistics, data from the National Health Interview Survey. Statistical analysis by the Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Diabetes Translation. Accessed: July 2, 2012.

Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011. Available at www.cdc.org.

Centers for Disease Control and Prevention. (2009). *The state of aging and health in America report. No leisure-time physical activity*. Retrieved from http://apps.nccd.cdc.gov/SAHA/Default/IndicatorDetails.aspx?IndId=NLT~N

Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion, Division of Diabetes Translation. (2008). Facts about county-level estimates of leisure-time physical inactivity. Accessed 4/26/2012.

Cho, J. H., Lee, H. C., Lim, D. J., Kwon, H. S., & Yoon, K. H. (2009). Mobile communication using a mobile phone with a glucometer for glucose control in Type 2 patients with diabetes: as effective as an Internet-based glucose monitoring system. *Journal of Telemedicine and Telecare, 15,* 77-82.

Church, T. S., Thomas, D. M., Tudor-Locke, C., Katzmarzyk, P. T., Earnest, C. P., Rodarte, R. Q., . . . Bouchard, C. (2011). Trends over 5 decades in U.S. occupation-related physical activity and their associations with obesity. *PLoS ONE, 6*(5), e19657.doi: 10.1371/journal.pone.0019657

Dela, F., Ploug, T., Handberg, A., Petersen, L. N., Larsen, J. J., Mikenes, K. J., & Galbo, H. (1994). Physical training increases muscle GLUT4 protein mRNA in patients with NIDDM. *Diabetes, 43,* 862-865.

Devlin, J. T., Hirshman, M., Horton, E. D., & Horton, E. S. (1987). Enhanced peripheral and splanchnic insulin sensitivity in NIDDM men after single bout of exercise. *Diabetes, 36,* 434-439.

Diabetes Prevention Program Research Group. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England Journal of Medicine, 346,* 393-403.

Dustan, D. W., Salmon, J., Owen, N., Armstrong, T., Zimmet, P. T., Welborn, T. A., . . . Shaw, J. E. (2004). Physical activity and television viewing in relation to risk of undiagnosed abnormal glucose metabolism in adults. *Diabetes Care, 27*(11), 2603-2609.

Dunstan, D. W., Salmon, J., Owen, N., Armstrong, T., Zimmet, P. T., Welborn, T. A., . . . Shaw, J. E. (2005). Associations of TV viewing and physical activity with the metabolic syndrome in Australian adults. *Diabetologia, 48,* 2254-2261.

Dunstan, D. W., Salmon, J., Healy, G. N., Shaw, J. E., Jolley, D., Zimmet, P. Z., &Owen, N.; AusDiab Steering Committee. (2007). Association of television viewing with fasting and 2-h post-challenge plasma glucose levels in adults without diagnosed diabetes. *Diabetes Care, 30*(3), 516-522.

Dunstan, D. W., Thorp, A. A., & Healy, G. N. (2011). Prolonged sitting: is it a distinct coronary heart disease risk factor? *Current Opinion in Cardiology, 26,* 412-419.

Dunstan, D. W., Howard, B., Healy, G. N., & Owen, N. (2012). Too much sitting – a health hazard. *Diabetes Research and Clinical Practice, 97,* 368-376.

Duvivier, B. M., Schaper, N. C., Bremers, M. A., van Crombrugge, G., Menheere, P. P., Kars, M.,& Savelberg, H. H. (2013). Minimal intensity physical activity (standing and

walking) of longer duration improves insulin action and plasma lipids more than shorter periods of moderate to vigorous exercise (cycling) in sedentary subjects when energy expenditure is comparable. *PLOS One, 8*(2), 1-8.

Follow-up Report on the Diagnosis of Diabetes Mellitus (2003). The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care, 26*, 3160-3167.

Fukuoka, Y., Vittinghoff, E., Jong, S. S., & Haskell, W. (2010). Innovation to motivation – pilot study of a mobile phone intervention to increase physical activity among sedentary women. *Preventive Medicine, 51,* 287-289.

Gannon, M. C. & Nuttall, F. Q. (1999). *Protein and diabetes in American Diabetes Association Guide to Medical Nutrition Therapy for Diabetes* (Franz, M. J. and Bantle, J. P., eds.). pp. 107-125, American Diabetes Association, Alexandria.

Garber, A. J., Handelsman, Y., Einhorn, D., Bergman, D. A., Bloomgarden, Z. T., Fonseca, V., . . . Nesto, R. W. (2008). Diagnosis and management of prediabetes in the continuum of hyperglycemia – when do the risks of diabetes begin? A consensus statement from the American College of Endocrinology and the American Association of Clinical Endocrinologists. *Endocrine Practice, 14*(7), 933-946.

Grundy, S. M., Cleeman, J. I., Daniels, S. R., Donato, K. A., Eckel, R. H., Franklin, B. A., . . . Costa, F. (2005). Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation, 112*(17), 2735-2752.

Halldin, M., Rosell, M., de Faire, U., & Hellenius, M. L. (2007). The metabolic syndrome: prevalence and association to leisure-time and work-related physical activity in 60-year-old men and women. *Nutrition, Metabolism and Cardiovascular Diseases, 17*(5), 349-357.

Hamilton, M., Hamilton, M., Hamilton, D., Zderic, T. M., & Hamilton, D. (2004). Exercise

physiology versus inactivity physiology: An essential concept for understanding lipoprotein lipase regulation. *Exercise and Sport Sciences Reviews, 32,* 161-166.

Hamilton, M. T., Hamilton, D. G., & Zderic, T. W. (2007). Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. *Diabetes*, 56(11), 2655-2667.

Hamilton, M. T., Healy, G. N., Dunstan, D. W., Zderic, T. W., & Owen, N. (2008). Too little exercise and too much sitting: inactivity physiology and the need for new recommendations on sedentary behavior. *Current Cardiovascular Risk Reports, 2*(4), 292-298.

Healy, G. N., Dustan, D. W., Shaw, J. E., Zimmet, P. Z., Owen, N. (2006). Beneficial associations of physical activity with 2-h but not fasting blood glucose in Australian adults: the AusDiab study. *Diabetes Care, 29*, 2598-2604.

Healy, G. N., Dustan, D. W., Salmon, J., Cerin, E., Shaw, J. E., Zimmett, P.Z., & Owen, N. (2007). Objectively measured light-intensity physical activity is independently associated with 2-h plasma glucose. *Diabetes Care*, 30(6), 1384-1389.

Healy, G. N., Dunstan, D. W., Salmon, J., Cerin, E., Shaw, J. E., Zimmet, P. Z., & Owen, N. (2008). Breaks in sedentary time: Beneficial associations with metabolic risk. *Diabetes Care, 31,* 661-666.

Healy, G. N., Dustan, D. W., Salmon, J., Shaw, J. E., Zimmet, P. Z., & Owen, N. (2008). Television time and continuous metabolic risk in physically active adults. *Medicine and Science in Sports and Exercise*, 40(4), 639-645.

Healy, G. N., Matthews, C. E., Dunstan, D. W., Winkler, E. H., & Owen, N. (2010). Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003-06. *European Heart Journal, 32,* 590-597.

Helmerhorst, H. J., Wijndaele, K., Brage, S., Wareham, N. J., & Ekelund, U. (2009). Objectively measured sedentary time may predict insulin resistance independent of moderate- and vigorous-intensity physical activity. *Diabetes, 58,* 1776-1779.

Helmrich, S. P., Ragland, D. R., Leung, R. W., & Paffenberger Jr., R. S. (1991). Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *New England Journal of Medicine, 325,* 147-152.

Hu, F. B., Sigal, R. J., Rich-Edwards, J. W., Colditz, G. A., Solomon, C. G., Willet, W. C., . . . Manson, J. E. (1999). Walking compared with vigorous physical activity and risk of type 2 diabetes in women: A prospective study. *Journal of the American Medical Association, 282,* 1433-1439.

Hu, F. B., Leitzmann, M. F., Stampfer, M. J., Colditz, G. A., Willett, W. C., & Rimm, E. B. (2001). Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Archives of Internal Medicine, 161,* 1542-1548.

Hu, F. B., Li, T. Y., Colditz, G. A., Willett, W. C., & Manson, J. E. (2003). Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *Journal of the American Medical Association, 289(14),* 1785-1791.

Jans, M. P., Proper, K. I., & Hildebrandt, V. H. (2007). Sedentary behavior in Dutch workers: differences between occupations and business sectors. *American Journal of Preventive Medicine, 33*(6), 450-454.

Kahleova, H., Matoulek, M., Malinska, H., Oliyarnik, L. Kazdova, Neskudla, T., . . . Pelikanova, T. (2010). Vegetarian diet improves insulin resistance and oxidative stress markers more than conventional diet in participants with type 2 diabetes. *Diabetic Medicine, 28,* 549-559.

Katzmarzyk, P. T., Church, T. S., Craig, C. L., & Bouchard, C. (2009). Sitting time and morality from all causes, cardiovascular disease, and cancer. *Medicine and Science in Sports and Exercise*, 41(5), 998-1005.

Kern, M. J., Wells, J. M., Stephens, C. W., Elton, J. E., Friedman, E. B., Tapscott, P. H., . . . Dohm, G. L. (1990). Insulin responsiveness in skeletal muscle is determined by glucose transporter (GLUT4) protein level. *Biochemical Journal, 270,* 391-400.

Kim, H. S. & Jeong, H. S. (2007). A nurse short message service by cellular phone in type-2 diabetic patients for six months. *Journal of Clinical Nursing, 16,* 1082-1087.

Kim, H. S., Shin, J. A., Chang, J. S., Cho, J. H., Son, H. Y., & Yoon, K. H. (2012). Continuous glucose monitoring: current clinical use. *Diabetes Metabolism Research and Review, 28*(2), 73-78.

Kleefstra, N., Landman, G. W. D., Houwelilng, S. T., Ubink-Veltmaat, L. J., Logtenberg, S. J., Meyboom-de Jong, B., . . . Bilo, H. J. (2008). Prediction of mortality in type 2 diabetics from health-related quality of life (ZODIAC-4). *Diabetes Care, 31,* 932-933.

Kohl, H. W., Gordon, N. F., Villegas, J. A., & Blair, S. N. (1992). Cardiorespiratory fitness, glycemic status, and mortality risk in men. *Diabetes Care, 15,* 185-192.

Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2001). Validity of a brief depression severity measure. *Journal of General Internal Medicine, 16,* 606-613.

Kurihara, O., Takano, M., Yamamoto, M., Shirakabe, A., Kimata, N., Inami, T., . . . Mizuno, K. (2013). Impact of prediabetic status on coronary atherosclerosis: a multivessel angioscopic study. *Diabetes Care, 36*(3), 729-733. doi: 10.2337/dc12-1635

Lakka, T. A. & Laaksonen, D. E. (2007). Physical activity in prevention and treatment of metabolic syndrome. *Applied Physiology, Nutrition & Metabolism, 32*, 76-88.

Levine, J.A., Vander Weg, M. W., Hill, J. O., & Klesges, R. C. (2006). Non-exercise activity thermogenesis: The crouching tiger hidden dragon of societal weight gain. *Arteriosclerosis, Thrombosis, and Vascular Biology, 26,* 729-736.

Levine, J. A. & Miller, J. (2006). The energy expenditure of using a "walk-and-work" desk for office-workers with obesity. *British Journal of Sports Medicine, 000,*1-4. doi:10.1136/bjsm.2006.032755

Levine, J. A., McCrady, S. K., Lanningham-Foster, L. M., Kane, P. H., Foster, R. C., & Manohar, C. U. (2007). The role of free-living daily walking in human weight gain and obesity. *Diabetes, 57,* 548-554. doi: 10.2337/db07-0815.

Liebl, A., Henrichs, H. R., Heinemann, L., Freckmann, G., Biermann, E., & Thomas, A. (2013). Continuous glucose monitoring: evidence and consensus statement for clinical use. *Journal of Diabetes Science and Technology, 7*(2), 500-519.

Loge, J. H. & Kaasa, S. (1998). Short-form 36 (SF-36) health survey: normative data from the Norwegian population. *Scandinavia Journal of Social Medicine, 26,* 250-258.

Lynch, J., Helmrich, S. P., Lakka, T. A., Kaplan, G. A., Cohen, R. D., Salonen, R., & Salonen, J. T. (1996). Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. *Archives of Internal Medicine, 156,* 1307-1314.

Lynch, B. M. (2010). Sedentary behavior and cancer: a systematic review of the literature and proposed biological mechanisms. *Cancer Epidemiology Biomarkers and Prevention*, 19(11), 2691-2709.

Manson, J. E., Stampfer, M. J., Colditz, G. A., Willett, W. C., Rosner, B., Hennekens, C. H., . . . Krolewski, A. S. (1991). Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *The Lancet, 338,* 774-778.

Manson, J. E., Nathan, D. M., Krolewski, A. S., Stampfer, M. J., Willett, W. C., & Hennekens, C. H. (1992). A prospective study of exercise and incidence of diabetes among US male physicians. *Journal of the American Medical Association, 268,* 63-67.

Masse, L. C., Fulton, J. E., Watson, K. L., Heesch, K. C., Kohl, H. W., Blair, S. N., & Tortolero, S. R. (1999). Detecting bouts of physical activity in a field setting. *Research Quarterly for Exercise & Sport, 70,* 212-219.

Meigs, J. B., Nathan, D. M., D'Agostino, R. B., & Wilson, P. W., (2002). Fasting and postchallenge glycemia and cardiovascular disease risk: the Framingham Offspring Study. *Diabetes Care, 10*, 1845–1850.

Melanson, E. L. & Freedson, P. S. (1995). Validity of the Computer Science and Applications, Inc. (CSA) activity monitor. *Medicine and Science in Sports and Exercise, 27,* 934-940.

Minuk, H. L., Vranic, M., Marliss, E. B., & Hanna, A. K. (1981). Glucoregulatory and metabolic response to exercise in obese noninsulin-dependent diabetes. *American Journal of Physiology – Endocrinology and Metabolism, 240,* E458-E464.

Naser, K. A., Gruber, A., & Thomson, G. A. (2006). The emerging pandemic of obesity and diabetes: are we doing enough to prevent a disaster? *International Journal of Clinical Practice, 60,* 1093-1097.

Nathan, M. D., Davidson, B. M., DeFronzo, A. R., Heine, J. R., Henry, R. H., Pratley, R., & Zinman, B., Impaired Fasting Glucose and Impaired Glucose Tolerance Implications for care. *Diabetes Care March 2007, 30*(3), 753-759.

Neuhaus, M., Healy, G. N., Dunstan, D. W., Owen, N., & Eakin, E. G. (2014). Workplace sitting and height-adjustable workstations: a randomized controlled trial. *American Journal of Preventive Medicine, 46*(1), 30-40.

Ng, S. W. & Popkin, B. M. (2012). Time use and physical activity: a shift away from movement across the globe. *Obesity Reviews: an official journal of the International Association for the Study of Obesity., 13*(8), 659-680.

Office of Disease Prevention & Health Promotion, U.S. Department of Health and Human Services. (2008). 2008 physical activity guidelines for Americans. Available at: www.health.gov/paguidelines.

Owen, N., Healy, G. N., Matthews, C. E., & Dunstan, D. W. (2010). Too much sitting: the population health science of sedentary behavior. *Exercise and Sport Sciences Reviews, 38,* 105-113. *doi:10.1097/JES.0b013e3181e373a2*.

Pan, X. R., Li, G. W., Hu, Y. H., Wang, J. X., Yang, W. Y., An, Z. X., . . . Howard, B. V. (1997). Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: The Da Qing IGT and diabetes study. *Diabetes Care, 20,* 537-544.

Peddie, M. C., Bone, J. L., Rehrer, N. J., Skeaff, C. M., Gray, A. R., & Perry, T. L. (2013). Breaking prolonged sitting reduces postprandial glycemia in healthy, normal-weight adults: a randomized crossover trial. *American Journal of Clinical Nutrition, 98,* 358-66.

Pereira, M. A., FitzerGerald, S. J., Gregg, E. W., Joswiak, M. L., Ryan, W. J., Suminski, R. R., . . . Zmuda, J. M. (1997). A collection of Physical Activity Questionnaires for health-related research. *Medicine & Science in Sports & Exercise*, *29(6 Suppl),* S1-205.

Perrault, L., Pan, Q., Mather, K. J., Watson, K. E., Hamman, R. F., & Kahn, S. E.; DPP Research Group (2012). Regression from pre-diabetes to normal glucose regulation is associated with long-term reduction in diabetes risk: results from the Diabetes Prevention Program outcomes study. *Lancet, 379*(9833), 2243-2251.

Proper, K. I., Singh, A. S., van Mechelen, W., Chinapaw, M. J. (2011). Sedentary

behaviors and health outcomes among adults: a systematic review of prospective studies. *American Journal of Preventive Medicine*, 40(2), 174-182.

Rogers, M. A., Yamamoto, C., King, D. S., Hagberg, J. M., Ehsani, A. A., & Holloszy, J. O. (1988). 1 wk of exercise in patients with mild NIDDM. *Diabetes Care, 11,* 613-618.

Ryan, C. G., Grant, P. M., Dall, P. M., & Granat, M. H. (2011). Sitting patterns at work: objective measurement of adherence to current recommendations. *Ergonomics, 54*(6), 531-538.

Saunders, T. J., Larouche, R., Colley, R. C., & Tremblay, M. S. (2012). Acute sedentary behavior and markers of cardiometabolic risk: a systematic review of intervention studies. *Journal of Nutrition and Metabolism, 2012,* 1-12. doi:10.1155/2012/712435

Schneider, S. H., Amorosa, L. F., Khachadurian, A. K., & Ruderman, N. B. (1984). Studies on the mechanisms of improved glucose control during regular exercise in type 2 (non-insulin-dependent) diabetes. *Diabetologia, 26,* 325-360.

Sisson, S. B., Camhi, S. M., Church, T. S., Martin, C. K., Tudor-Locker, C., Bouchard, C., . . . Katzmarzyk, P. T. (2009). Leisure time sedentary behavior, occupational/domestic physical activity, and metabolic syndrome in U.S. men and women. *Metabolic Syndrome and Related Disorders, 7*(6), 529-536.

Speck, R. M. & Schmitz, K. H. (2011). Energy expenditure comparison: a pilot study of standing instead of sitting at work for obesity prevention. *Preventive Medicine, 52,* 283-284.

Stephens, B. R., Granados, K., Zderic, T. W., Hamilton, M. T., Braun, B. (2011). Effects of 1 day of inactivity on insulin action in healthy men and women: interaction with energy intake. *Metabolism: Clinical and Experimental, 60*(7), 941-949.

Stoll, T., Gordon, C., Seifert, B., Richardson, K., Malik, J., Bacon, P. A., & Isenberg, D. A. (1997). Consistency and validity of patient administered assessment of quality of life by

the MOS SF-36; its association with disease activity and damage in patients with systemic lupus erythematosus. *The Journal of Rheumatology, 24,* 1608-1614.

Stratton, I. M., Adler, A. I., Neil, H. A., Matthews, D. R., Manley, S. E., Cull, C. A., . . . Holman, R. R. (2000). Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *British Medical Journal, 12*(312), 405-412.

Stuckey, M., Fulkerson, R., Read, E., Russell-Minda, E., Munoz, C., Kleinstiver, P., & Petrella, R. (2011). Remote monitoring technologies for the prevention of metabolic syndrome: the Diabetes and Technology for Increased Activity (DaTA) study. *Journal of Diabetes Science and Technology, 5,* 936-944.

Sugiyama, T., Healy, N. G., Dustan, W. D., Salmon, J., & Owen, N. (2008). Is television viewing time a marker of a broader pattern of sedentary behavior? *Annals of Behavioral Medicine, 35,* 245-250.

Ten Have, G. A. M., Engelen, M. P., Luiking, Y. C., & Duetz, N. E. P. (2007). Absorption kinetics of amino acids, peptides, and intact proteins. *International Journal of Sport Nutrition and Metabolism, 17,* S23-S36.

The Look AHEAD Research Group. (2010). Long Term Effects of a Lifestyle Intervention on Weight and Cardiovascular Risk Factors in Individuals with Type 2 Diabetes: Four Year Results of the Look AHEAD Trial. *Archives of Internal Medicine,170*, 1566-1575.

Thorp, A. A., Dunstan, D. W., Clark, B., Gardiner, P., Healy, G. N., Keegel, T., Winkler, E. (2009). Stand up Australia: sedentary behavior in workers. *Medibank Private Limited.* Retrieved from http://www.medibank.com.au/Client/Documents/Pdfs/Stand_Up_Australia.pdf

Thorp, A. A., Healy, G. N., Owen, N., Salmon, J., Ball, K., Shaw, J. E., . . . Dunstan, D. W. (2010). Deleterious associations of sitting time and television viewing time with

cardiometabolic risk biomarkers: Australian Diabetes, Obesity and Lifestyle (AusDiab) study. *Diabetes Care, 33*(2), 327-334.

Thorp, A. A., Healy, G. N., Winkler, E., Clark, B. K., Gardiner, P. A., Owen, N., & Dunstan, D. W. (2012). Prolonged sedentary time and physical activity in workplace and non-work contexts: a cross-sectional study of office, customer service and call centre employees. *International Journal of Behavioral Nutrition and Physical Activity, 9*(128), 1-9.

Tran, T. T., Gupta, N., Goh, T., Naigamwalla, D., Chia, M. C., Koohestani, N., . . . Bruce, W. R. (2003). Direct measure of insulin sensitivity with the hyperinsulinemic-euglycemic clamp and surrogate measures of insulin sensitivity with the oral glucose tolerance test: correlations with aberrant crypt foci promotion in rats. *Cancer, Epidemiology, Biomarkers & Prevention, 12,* 47-56.

Troiano, R.P., Berrigan, D., Dodd, K.W., Masse, L.C., Tilert, T., & McDowell, M. (2008). Physical activity in the United States measured by accelerometer. *Medicine Science Sports and Exercise, 40,* 181-188.

Trost, S. G., McIver, K. L., & Pate, R. R. (2005). Conducting accelerometer-based activity assessments in field-based research. *Medicine and Science in Sports and Exercise, 37*(11), S531-43.

Tuomilehto, J., Lindstrom, J., Eriksson, J. G., Valle, T. T., Hamalainen, H., Ilanne-Parikka, P., . . . Uusitupa, M. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among participants with impaired glucose tolerance. *The New England Journal of Medicine, 344,* 1343-1350.

Unwin, N., Shaw, J., Zimmet, P., & Alberti, K. G. (2002). Impaired glucose tolerance and impaired fasting glycemia: the current status on definition and intervention. *Diabetes and Metabolism,19*(9), 708-723.

Unwin, D. & Unwin, J. (2014). Low carbohydrate diet to achieve weight loss and improve HbA1c in type 2 diabetes and pre-diabetes: experience from one general practice. *Practical Diabetes, 31*(2), 1-4.

van der Ploeg, H. P., Chey, T., Korda, R. J., Banks, E., & Bauman, A. (2012). Sitting Time and All-Cause Mortality Risk in 222,497 Australian Adults. *Archives of Internal Medicine, 172*, 494-500.

Volgyi, E., Tylaysky, F. A., Lyytikainen, A., Suominen, H., Alen, M., & Cheng, S. (2008). Assessing body composition with DXA and bioimpedance: effects of obesity, physical activity, and age. *Obesity, 16,* 700-705.

Ware, J. E. & Sherbourne, C. D. (1992). The MOS 36-item short-from health survey (SF-36): I. conceptual framework and item selection. *Medical Care, 30,* 473-483.

Wei, M., Gibbons, L. W., Mitchell, T. L., Kampert, J. B., Lee, C. D., & Blair, S. N. (1999). The association between cardiorespiratory fitness and impaired fasting glucose and type 2 diabetes mellitus in men. *Annals of Internal Medicine, 130,* 89-96.

Wilmot, E. G., Edwardson, C. L., Achana, F. A., Davies, M. J., Gorely, T., Gray, L. J., . . . Biddle, S. J. (2012). Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. *Diabetologia, 55*(11), 2895-2905. doi: 10.1007/s00125-012-2677-z

World Health Organization. (August, 2011). Diabetes. Fact Sheet N°312. Available at: http://www.who.int/mediacentre/factsheets/fs312/en/index.html.

World Health Organization. (2008). Physical Inactivity: A Global Public Health Problem. Available online at http://www.who.int/dietphysicalactivity/factsheet_inactivity/en/. Retrieved 4/21/2012.