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TITLE: Reducing sitting time in type 1 diabetes: considerations and implications

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ABSTRACT

Sedentary behaviours are ubiquitous in modern society with western populations spending approximately ~50% of their waking hours expending low levels of energy expenditure. This behaviour is associated with cardiometabolic derangements and increased morbidity and mortality. In individuals living with, or at risk of developing type 2 diabetes (T2D), 'breaking up' sedentariness, by interrupting prolonged periods of sitting has been shown to acutely improve glucose control and cardiometabolic risk factors related to diabetes complications. As such, current guidelines recommend interrupting prolonged periods of sitting with short, frequent activity breaks. However, the evidence underpinning these recommendations remain preliminary and are focused on those with or at risk of developing T2D, with little information regarding whether and how reducing sedentariness may be effective and safe in those living with type 1 diabetes (T1D). In this review, we discuss the potential application of interventions that target prolonged sitting time in T2D within the context of T1D.

KEYWORDS

Type 1 diabetes, interrupted sitting, sedentary behaviour, vascular health, glycaemic control.

ABBREVIATIONS:

METs, Metabolic Equivalents; T1D, Type 1 Diabetes; T2D, Type 2 diabetes; HDL, High-density lipoprotein; MVPA, Moderate-to-vigorous physical activity; HbA1c, haemoglobin A1c

KEY MESSAGE

- In this review, we summarise research investigating interventions targeting prolonged sitting time for improving glucose management and risk factors associated with diabetes complications in individuals with T2D. We then discuss the potential applications of such a strategy in people living with T1D.

INTRODUCTION

Sedentary behaviour is defined as any waking, reclining or sitting behaviour with low-energy expenditure ≤1.5 metabolic equivalents (METs)[1]. This is distinct from physical inactivity which is defined as failing to achieve recommended amounts of physical activity[2]. The prevalence of sedentary behaviour is increasing worldwide with western populations spending approximately ~50% of their waking hours expending low levels of energy expenditure[3,4].

It is well-established that sedentary behaviour increases risk of morbidity and mortality[5,6]. For example, watching TV, a common proxy of sedentary behaviour, is associated with obesity and metabolic disturbances in a dose-dependent manner[7,8], and total sitting for more than 4-8 hours/day is significantly associated with a higher risk of mortality (i.e. 2% increase per 1-hour increase in sitting time per day)[6]. Further, *prolonged periods of sedentariness* (i.e. remaining sedentary for 2-hours or longer at a time, as opposed to total volume of sedentariness[9]) is also associated with obesity and cardiometabolic derangements[10].

In individuals with diabetes, sitting for a long periods of time has been shown to positively associate with worsening diabetes management, as determined by haemoglobin A1c (HbA1c) levels[11,12], which may contribute to an increased risk of diabetes-related complications. In people without Type 1 Diabetes (T1D), watching TV uninterrupted for more than 2-hours per day, is strongly associated with overweight and obesity in children and adolescents[13], a risk factor which has previously been shown to predict both macrovascular and microvascular complications in people with T1D independent of glucose control[14].

Conversely, the benefits of increased physical activity for individuals with diabetes, including those with T1D, are well-established and have been reviewed elsewhere[11,15]. Physical activity is widely promoted to all individuals with diabetes[16-20], with guidelines recommending at least 150-minutes or more of moderate-to-vigorous-physical activity (MVPA; 3.0 to 5.9 METs) for 3 days per week[20]. In addition, all individuals with diabetes are recommended to limit sedentary time and incorporate frequent episodes of low-intensity physical activity[21]. However, despite

physical activity being acknowledged as a critical element of diabetes care, most individuals with T1D do not meet recommended physical activity levels[22]. Indeed, research suggests that fewer than 20% of T1D individuals manage to achieve physical activity guidelines and ~60% of individuals remain inactive[23], with one study finding that 21% of the surveyed cohort exercised less than once per week[24].

Whilst many individuals with T1D do little-to-no exercise, individuals are often willing to increase participation in lower-intensity physical activity and are keen to learn how to reduce sedentary behaviours[25]. However, little information is available to individuals with T1D or the healthcare professionals who support them[26]. Historically, physical activity guidelines have been predominantly focused on *exercise* (e.g., a planned, structured, repetitive and purposeful physical activity in the sense of improving or enhancing physical fitness and overall health) rather than activities of everyday living (including sedentary behaviours) that contribute significantly to an individual's daily *physical activity* levels (e.g., any physical movement produced by skeletal muscles that leads to increased energy expenditure)[27]. It should be noted that exercise is not synonymous with physical activity, but rather a sub-category of physical activity. However, exercise-specific recommendations of MVPA translate poorly to general daily physical activity levels, including daily living and recreational activities, from which most individuals with T1D have most to gain[25]. Within the context of T1D, exercise is often viewed as daunting and unachievable by most and its promotion can often discourage individuals from becoming active[25]. For example, many people with T1D report fear of hypoglycaemia and an inability to manage their diabetes a major barrier to regular participation [28,29], yet few mention this fear when asked about general day-to-day physical activities.[25] In support of this notion, rather than promoting exercise *per se,* it seems logical and important for inactive T1D individuals to start with achievable and positive behavioural routines that can increase overall physical activity.

Recently, physical activity guidelines for individuals with diabetes have evolved to include recommendations specifically targeting prolonged periods of sitting time by 'breaking-up'

sedentary periods with bouts of standing and/or frequent, short low-intensity physical activity intervals, termed 'interrupted-sitting'[1,30]. This simple and acceptable approach may help to enable those inactive individuals to carry out physical activity across the day and may serve as an effective method for incorporating physical activity more easily into everyday life and improve health. Interrupting sitting with light activities could be particularly useful for those who are unable or unwilling to engage in structured exercise and this approach can be seen as an important 'stepping-stone' towards regular participation in physical activity or exercise[31]. Despite this, the evidence underpinning these recommendations remains preliminary and focused solely on individuals with or at risk of developing type 2 diabetes (T2D)[1,30-34]. Here we focus the spotlight on the potential utility and implications of applying interrupted sitting interventions within the context of adults with T1D.

COULD INTERRUPTING SITTING TIME BE AN EFFECTIVE HEALTH PROMOTING STRATEGY FOR T1D?

1. Interrupting sitting and glycaemic control

Emerging evidence in individuals with T2D suggests that interrupted prolonged periods of time spent sitting with short, frequent activity breaks may be a promising strategy for improving acute glycaemic control. Dempsey and colleagues[32] demonstrated that interrupting 7-hour prolonged sitting time with brief bouts of low-intensity walking for 3-minute every 30-minute significantly reduced the 22-hour glycaemia in T2D individuals, including nocturnal hyperglycaemia with glycaemic improvements continuing until the next morning. Time spent in nocturnal hyperglycaemia was approximately 60% greater under an uninterrupted sitting condition compared to an interrupted sitting condition[32]. This suggests that the acute metabolic improvements associated with interrupted sitting carry over into the evening and sleeping periods until the following morning. Further, interrupting prolonged sitting with frequent 3-minute bouts of walking every 15-minute has also been shown to improve fasting glucose and limit the *dawn phenomenon*[35].This is a particularly important consideration should a similar

glycaemic pattern be observed within the context of T1D in which the dawn phenomenon is a common issue.

The *dawn phenomenon* is defined as elevated blood glucose during early waking hours, and, to a large extent persists post-breakfast in T1D individuals[36]. The dawn phenomenon results from increased hormone-stimulated glucose output and impaired glucose utilisation[37], and represents a key feature of dysglycaemia and increased basal insulin requirements in T1D[38]. Results from Campbell and colleagues[39] indicated that nocturnal surges in growth hormone secretion drive the dawn phenomenon, whereas nocturnal increases in catecholamine levels do not appear to be sufficient by themselves to be responsible[37]. Resultantly, Clarke and colleagues[40] demonstrated that a two-to-threefold increase in the amount of insulin can be required to maintain euglycaemia overnight in some T1D individuals. Importantly, Zheng and colleagues[41] noted that moderate intensity of aerobic exercise prior to breakfast reduced the rate at which of blood glucose increases in T2D individuals, partially counteracting the dawn phenomenon. Although morning exercise is commonly recommended to people with diabetes improve early morning rises in glucose[42], it is unknown whether interrupted sitting may serve as an effective strategy to attenuate the dawn phenomenon, especially in individuals with T1D.

Interrupted sitting interventions can also improve meal-time glucose control. For example, Dempsey and colleagues[1] showed that 3-minute bouts of low-intensity walking on a treadmill every 30-minutes attenuated post-prandial glucose by 39% in T2D. Further, Paing and colleagues[43] demonstrated in 12 individuals with T2D that interrupting sitting time through performing 3-minute of low-intensity walking breaks after meals every 15-minute, resulted in a 48% reduction in the post-breakfast glucose (3.5±0.9mmol/L^{-1}), 62% reduction in cumulative 10.5-hour post-prandial glucose (5.6±2.4mmol/L^{-1}), and 34% reduction in 21-hour glucose (101.5±12.6mmol/L^{-1}) compared to interrupted sitting every 60-minutes. As such, the frequency of interrupting sitting maybe an important factor in achieving better glucose control, but the optimal time and frequency of these low intensity bouts remains unknown.

Short activity breaks from sitting have been shown to result in improvements in post-prandial glucose responses and daily glycaemic control, albeit with varying efficacy as compared to traditional forms of exercise[44,45]. For example, Peddie and colleagues[46] reported regular activity breaks to more effective than continuous physical activity at decreasing postprandial glycaemia and insulinaemia in normal-weight individuals without diabetes, whereas Blankenship et al[44] showed continuous walking be comparable to activity breaks at lowering postprandial glucose in people with T2D. Further, Blankenship et al[44] showed continuous physical activity was more effective at lowering daily hyperglycemia as compared to regular activity breaks in people with T2D, whereas Freire and colleagues[47] demonstrated lower daily glucose in response to breaks in sitting time as compared with low volume high-intensity interval exercise in overweight adults.

Given that different forms of physical activity, performed at different times of day induce divergent metabolic responses, it is likely that differences in study methodology, as well as the metabolic health of sampled participants were confounding factors and contribute to mixed study findings. For example, in a recent meta-analysis[45] exclusively in individuals without diabetes showed that interrupting sitting time with short, frequent bouts of walking activity was more effective in reducing post-prandial glucose than a single continuous session of isoenergetic exercise. A possible explanation for this difference could be that glucose counter-regulatory hormones increase during prolonged exercise, which promotes increased hepatic glucose production at a rate that can exceed glucose uptake, and affect which is further mediated by the fasted vs. postprandial state as shown by recent work in T1D[48]. Although yet untested, the net effect of interrupted sitting within a T1D setting may be an overall increase in blood glucose levels[45], especially for patients who are unaccustomed to physical activity and who would likely be performing activity breaks at a higher relative intensity, whereby the impacts of counterregulatory hormones are additive with short successive bouts of activity. The potential of exercise to induce transient hyperglycaemia in T1D has obvious negative consequences, however, manipulating activity type to diminish the counter-regulatory response

may consequently increase risk of hypoglycaemia, particularly late-onset hypoglycaemia[49,50]. As such, it is important that research establishes the impact of frequent, short bouts of activity on risk of hypo- and hyperglycaemia in T1D, and whether and what adjustments to treatment are necessary to maintain glucose control. For example, Campbell and colleagues[51] demonstrated that reducing pre- and post-exercise rapid acting insulin is an effective strategy in terms of preventing exercise induced hypoglycaemia and does not cause adverse hormonal disturbances in individuals with T1D, however whether insulin dosing adjustments will be necessary for lower intensity physical activity is not currently known. Furthermore, research is needed that investigates the glycaemic management requirements of reduced sitting interventions specifically in children and adolescents with T1D with and without technologies such as closed-loop systems which are likely to require greater input from healthcare professionals.

2. Interrupting sitting and cardiovascular risk

Interrupting prolonged sitting has also shown to improve cardiovascular risk factors in T2D.

Three minute bouts of light-intensity walking every 30-minutes in 24 inactive overweight and obese individuals with T2D has been shown to elicit a reduction in systolic blood pressure by 14 mmHg and diastolic blood pressure by 8 mmHg in T2D during the condition[33]. In one arm, participants replaced ~5 hours/day sitting with 2 hours of walking and 3 hours of standing; this was shown to improve plasma triacyclglycerols as compared with a sedentary condition, (1.46 [0.12] vs. 1.93 [0.17] mmol/L)[52]. Reducing sitting time by engaging in low-intensity activity breaks might be effective in improving features of metabolic syndrome in both T2D and T1D, given similarities in underlying disease pathology. Metabolic syndrome is a cluster of conditions that is defined as central obesity plus two additional factors[53], including increased triglyceride levels (>1.7 mmol/L), blood pressure (≥130/85 mmHg) and fasting plasma glucose (>5.6 mmol/L) and reduced high-density lipoproteins (HDL) cholesterol (<1.03 mmol/L in males and <1.29 mmol/L in females)[54]. Data from several studies suggest that excessive sitting

time was associated with reversible changes in components of the metabolic symptoms[55,56]. Given the high prevalence of insulin resistance and metabolic syndrome in T1D[57-60] interrupting prolonged sitting strategy may be a practical strategy that could contribute to reducing the risk of vascular complications in this cohort.

POTENTIAL MECHANISMS

Consistent with previous studies in people with and at risk of T2D, the improvement in glycaemic control in response to frequent sitting interruption interventions, is likely due to a combination of enhanced insulin sensitivity[61] and/or a greater dependence on insulin-independent contraction-mediated glucose uptake pathways. Acute exercise- or physical activity-induced insulin sensitivity has clear clinical significance in the prevention and treatment of chronic insulin resistance in peripheral tissue which has direct impacts on glucose control and vascular risk[61]. For example, skeletal muscle is a major site of glucose uptake in the post-absorpative state, and thus an improvement in peripheral insulin sensitivity results in improved glucose tolerance during and after mealtimes[62]. Indeed, recent investigations demonstrate that skeletal muscle contraction-mediated glucose uptake are associated with improved post-prandial glucose levels during one-day interventions employing frequent interruptions in sedentary time[63]. Although exercise is a known potent mediator of insulin-independent glucose uptake in T1D, there is no data assessing glucose kinetics in people with T1D in response to lower-intensity physical activity. Recent research has shown alterations in the mitochondrial ultrastructure and bioenergetics of skeletal muscle in active young adults with T1D [64]. For example, mitochondrial oxidative capacity was significantly lower, and the size and number of autophagic remnants in skeletal muscle higher, in individuals with T1D as compared to control subjects. As such, it may be that lower intensity physical activity may be insufficient to completely prevent or reverse skeletal muscle metabolic deficiencies and therefore more vigorous forms of activity are needed to achieve comparable glycaemic improvements. Furthermore, given that muscle mitochondrial impairments are implicated in

insulin resistance[65], it may be those individuals requiring intervention the most, who may respond the least.

FUTURE RESEARCH OPPORTUNITIES

There is currently no research on interrupting sitting with light intensity activity in T1D, and minimal evidence for longer-term effects on glucose control and complication risks in people with or at risk of T2D. Future research is required to assess the impact of interrupted sitting strategies that feature low-intensity physical activity on short and long-term glucose control in individuals with T1D, and whether such interventions yield beneficial effects on complication risk. Indeed, sedentary time is associated with premature mortality and cardiovascular risk factors for T2D, as well as cardiovascular disease and some types of cancer[66]. Therefore, interrupted sitting interventions in individuals with T1D are urgently needed. In particular, it would be beneficial to investigate the utility of such an intervention across a broad demographic of people with T1D, including individual characteristics such as the presence of insulin resistance which is known to mediate glucose control and vascular risk in T1D[60,67,68], and establish whether laboratory-based interventions can be translated to a remote, home-based environment.

CONCLUSION

Regular physical activity, including structured exercise provides numerous benefits for individuals with diabetes. In T2D individuals, these benefits are well-acknowledged, as frequently interrupting sitting time improves acute glycaemic control and reduces cardiovascular risks. To date, there are no published studies assessing the impact of interrupting sitting on glycaemic, metabolic, or vascular parameters in people with T1D. As such, it is unknown whether the benefits of such a strategy observed in T2D are comparable in T1D. Ongoing research should attempt to provide greater insight into the role of interrupted sitting interventions in T1D, with a particular focus on postprandial and nocturnal glucose control and the potential risk of provoking hypoglycaemic episodes. Should such an intervention yield positive results, this simple and acceptable approach may help enable individuals to incorporate

physical activity more easily into everyday life and improve health. In addition, similar interventions are needed with longer-term evidence and in free-living conditions.

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AUTHOR DISCLOSURES

A.M.A., M.D.C., M.H., M.A.Z., P.D., and M.F. have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

A.A performed searches, contributed to the selection of the references, and was involved in manuscript creation. M.H., M.A.Z., P.D., and M.F., critically appraised the work and was involved in editing of the final manuscript. All authors have reviewed and approved the final manuscript. M.D.C had overall oversight of the work, performed searches, contributed to the selection of the references, and formulated the hypothesis for investigation.

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