Change in Sedentary Time, Physical Activity, Bodyweight, and Hba1c in High-Risk Adults

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Abstract

Purpose—In recent years, there has been a migration towards the use of glycated hemoglobin (HbA1c) in determining glycemic control. This study aimed to quantify the associations between changes in body weight, sedentary time and moderate to vigorous physical activity (MVPA) time with HbA1c levels over a three year period among adults at high risk of type 2 diabetes.

Methods—This study reports baseline and three year follow-up data from the Walking Away from Type 2 Diabetes study. ActiGraph GT3X accelerometers captured sedentary time and MVPA. Linear regression examined the independent associations of changes in sedentary time, MVPA and body weight with HbA1c between baseline and three year follow-up.

Results—The sample comprised of 489 participants (mean age 64.2 ± 7.3 years, BMI 31.7 ± 5.1, 63.4% male) with valid baseline and follow-up accelerometer, body weight and HbA1c data. Following adjustment for known confounders, an increase in MVPA time (per 30mins/day) was associated with a decrease in HbA1c percentage (β = -0.11 (-0.18,-0.05), p=0.001) and an increase

in body weight (per 6 kg) was associated with an increase in HbA1c percentage (β = 0.08 (0.04,0.12), p<0.001). Presence of dysglycemia at baseline (HbA1c 6.0%) strengthened these associations (p<0.001 for interactions). Change in sedentary time was not significantly associated with change in HbA1c after adjustment for change in MVPA time.

Conclusion—Increases in MVPA and body weight were associated with a reduction and increase in HbA1c respectively, particularly in those with dysglycemia. Quantifying the impact that health behavior changes have on HbA1c can be used to inform prevention programs.

Keywords

Type 2 Diabetes; Primary Care; Sedentary Behavior; Dysglycemia

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic diseases and accounts for between 7 to 14% of health care expenditure globally (40). Both the prevalence and cost of T2DM in the United Kingdom (UK) are projected to rise in the future with 17% of the National Health Service (NHS) budget required for its treatment by 2035 (19). Given this current and projected increase in burden, health care policies and recommendations targeting prevention are gaining national and international traction with defined budgetary commitments (27, 29).

Lifestyle interventions have consistently been shown to reduce the risk of, and slow progression to T2DM in high risk populations, and form the cornerstone of diabetes prevention recommendations and programs (10, 26). There has been a wealth of good quality interventional and epidemiological evidence quantifying the combined and individual impact of lifestyle factors in improving glucose regulation and reducing the risk of T2DM based on outcomes from an oral glucose tolerance test (fasting and 2-hour post-challenge glucose levels) (11). However, such data no longer reflects clinical reality and decision making processes. Since the inclusion of HbA1c within the diagnostic framework for T2DM (36), there has been a migration towards HbA1c in the classification of diabetes risk and assessment of diabetes prevention programs run within routine care (20, 26, 27). This change is reflective of greater clinical utility of HbA1c compared to plasma glucose derived from an oral glucose tolerance test. For example, HbA1c does not need to be measured fasting, is a better indicator of chronic hyperglycemia, is less affected by any short term, illness related changes in plasma glucose levels and shows lower inter-test variability (20). Given the abundant shift in focus towards HbA1c in recent years, there is a requirement to extend prevention research by quantifying the impact of lifestyle change on this metabolic marker.

Increased physical activity and weight loss have consistently been shown to independently reduce the risk of T2DM and are key behavioral targets for prevention programs that have been translated into real world settings (6, 21). The importance of these factors on change in HbA1c needs further elucidation, although recent research is encouraging. For example, obese individuals with currently normal HbA1c levels (5.2-5.6%) have a greater chance of developing early onset T2DM than a lighter individual with currently higher levels (5.7 -

6.4%) (25). In addition to physical activity and body weight, high levels of sedentary time, defined as any sitting or reclining behaviors undertaken with low energy expenditure, have also been associated with poor metabolic health (8), increased risk of T2DM (4, 8, 34), cardiovascular disease (4, 34), and mortality (4, 34). Recent cross sectional links between sedentary time and insulin sensitivity have also emerged which further support the potentially detrimental impact of sedentary time upon glycemic control (5, 39).

The aim of this paper is to use a prospective dataset to quantify the association between changes in moderate to vigorous physical activity (MVPA), sedentary time and body weight with changes in HbA1c using a population at high risk of T2DM recruited from primary care over a three year period.

Methods

Research Design

This study performed an observational cohort analysis utilising baseline and three year follow up data from the Walking Away from Type 2 Diabetes trial, the design and results of which are described elsewhere (37, 38). In brief, this was a randomized controlled trial that evaluated the effectiveness of a pragmatic structured education program aimed at increasing physical activity and promoting healthy lifestyles over three years among those who were at high risk of T2DM.

Participants

Individuals taking part in the trial were recruited through 10 primary care practices in Leicestershire - United Kingdom (UK), in 2010. Individuals were recruited based on having a high risk of T2DM defined using the Leicester Practice Risk Score (13). The score calculates risk based on six variables (age, sex, ethnicity, BMI, family history of the disease and antihypertensive drug usage). Individuals ranked within the top 10% within their family practice were invited to take part in the study. Those with T2DM diagnosed at baseline, with established T2DM or currently taking steroids were excluded.

Informed consent was obtained from all eligible participants and full ethical approval from the local ethics committee was granted for the trial.

Demographic data

Information regarding medication, ethnicity, smoking status and home postcode (used to calculate index of multiple deprivation (IMD) score) was obtained following an interview administered protocol conducted by healthcare professionals. The IMD scores are publically available continuous measures of compound social and material deprivation which are calculated using a variety of data including current income, employment, health, education and housing.

Anthropometric data

Body weight, body fat percentage (Tanita TBE 611, Tanita, West Drayton, UK) and height were measured to the nearest 0.1 kg, 0.1% and 0.1cm respectively.

Bio-chemical data

Venous blood samples were obtained following a 12 hour overnight fast. All assays were measured in the same laboratory using stable methodologies and conducted by individuals blinded to the patients' identity. Glycated hemoglobin (HbA1c) was analysed using the Bio-Rad Variant II HPLC system (Bio-Rad Clinical Diagnostics, Hemel Hempstead, UK). All venepuncture was undertaken by trained phlebotomists. Data collection procedures between baseline and follow-up were standardized.

Accelerometer data

Participants were asked to wear an accelerometer (Actigraph GT3X, Pensacola, Florida, USA) on the right anterior axillary line above the hip for seven consecutive days during waking hours at both baseline and three year follow up. Data were collected in 60 second epochs. Freedson cut-points, using counts in the vertical axis only, were used to categorize sedentary time (<100 counts per minute) and MVPA time (1952 counts per minute) (9). In addition, MVPA time accumulated in bouts 10minutes (allowing for a two minute exception in the intensity threshold), was also derived. Non-wear time was defined as a minimum of 60 minutes of continuous zero counts and days with at least 600 minutes of wear time were considered valid (16). In order to be included in the analysis, a minimum of any four valid days was required (32). Accelerometer files were processed using KineSoft V3.3.76, a commercially available analytical software (KineSoft, Loughborough, UK).

Statistical analysis and data inclusion

From the 808 individuals randomized into the Walking Away from Type 2 Diabetes trial at baseline, 489 (61%) had valid measures of accelerometer data, bodyweight and HbA1c at both baseline and three years, and were subsequently included in this analysis. Of the 319 participants who were not included in this analysis, 289 were excluded on the basis of failing to meet the minimum accelerometer wear time requirements, while a further 30 did not provide biochemical data at both time points. The results of this intervention are reported elsewhere (38) with no significant changes to MVPA, sedentary time or bodyweight for the overall cohort. All analyses were conducted using IBM SPSS Statistics (version 22.0) and statistical significance was set to p<0.05. Only participants with valid measures of accelerometer data, bodyweight and HbA1c at both baseline and three years were included in the following analyses.

Linear regression models examined the independent associations between changes in; MVPA, sedentary time and body weight with a change in HbA1c over the three year period. Changes in all variables were calculated as three year follow-up data minus baseline data. Beta-coefficients representing changes in 'HbA1c %' reflect absolute changes in HbA1c units and not relative statistical percentage changes. Change data for MVPA and sedentary time were displayed in 30 minute/day unit increments for ease of interpretation. The lifestyle intervention arm of the Diabetes Prevention Program targeted a 7% reduction in body weight (2), change data for body weight in the current study was therefore displayed in 6 kg unit increments, as this represents a 7% difference in the average body weight of our cohort. Analyses were adjusted for the following variables: age, sex, ethnicity, beta-blocker use for hypertension, IMD score, change in accelerometer wear time and baseline measures of;

HbA1c, body weight, sedentary time and MVPA. Smoking status was also added as a measure of deprivation. Additional models simultaneously added change in all variables (MVPA, sedentary time and body weight) into the same model to establish the extent to which associations with HbA1c were independent of each other. A sensitivity analysis was conducted to see whether using MVPA time accumulated from bouts lasting 10minutes (in line with public health physical activity guidelines (35)) influenced the findings.

In addition, we also set out to investigate whether glycemic status at baseline independently modified associations through adding interaction terms to the model. Interaction significance was set to p<0.01. Glycemic status was defined as having dysglycemia (HbA1c 6.0% at baseline) or normal glycemia (<6% at baseline). Significant interactions were followed up with stratified analyses. A threshold of 6.0% was chosen to make the analysis consistent with recommendation for UK populations (26) and with international guidance (20).

Although commonly used, a cut-off value of <100 cpm to categorize sedentary time may be too high, particularly in older adults (1). We therefore ran a further sensitivity analysis to address whether similar results were yielded if sedentary time was categorized at a lower cut-off value of <50 cpm. Similarly, Freedson cut-points for MVPA (1952 counts per minute) may underestimate time spent in MVPA (12), therefore we conducted a sensitivity analysis to determine whether a lower cut-point (1041 cpm) influenced our findings.

Results

Those included in this analysis had a similar ethnic breakdown and baseline sedentary time compared with those who were excluded. There were also no significant differences in sex between those included and excluded. However, those excluded had a higher social deprivation score (22.7 vs. 17.6; p<0.001) were more likely to be; younger (61.8 ± 9.1 vs 64.2 ± 7.3 years, p<0.001) have a higher BMI (33.6 ± 6 vs. 31.7 ± 5.1 kg/m2, p<0.001) and engage in less MVPA at baseline (32.7 ± 25.1 vs 40.3 ± 27.6 mins/day, p<0.001). Table 1 reports the demographic, anthropometric, and cardiometabolic characteristics of those included in the study analysis.

Table 2 reports baseline and 3 year follow-up data for key anthropometric, cardio-metabolic and accelerometer derived measures.

Table 3 displays the adjusted associations of changes in; sedentary time, MVPA and body weight with HbA1c change.

Sedentary time: Following adjustment for known confounders, greater sedentary time (per 30mins/day) was associated with an increase in HbA1c (β = 0.02% (0.01, 0.03), p = 0.021). This association disappeared after further adjusting for a change in MVPA (β = 0.01% (-0.01, 0.02), p = 0.402).

MVPA time: An increase in MVPA time (per 30mins/day) was significantly associated with a decrease in HbA1c (β = -0.14% (-0.20, -0.08), p < 0.001) after adjustment for potential confounding variables. This remained significant after further adjustment for changes in both sedentary time and body weight (β = -0.11% (-0.18, -0.05), p = 0.001).

Body weight: When adjusting for all covariates, including change in MVPA, an increase in body weight (per 6kg) was associated with significantly greater HbA1c levels (β = 0.08% (0.04, 0.12), p<0.001).

Sensitivity analyses revealed that these results were largely unaffected when using MVPA accumulated in bouts 10 minutes (see Table, Supplemental Digital Content 1, Sensitivity analysis showing adjusted associations when using MVPA time accumulated in bouts 10 minutes), when using lower cut-points for sedentary time (see Table, Supplemental Digital Content 2, Sensitivity analysis showing adjusted associations when using lower sedentary time cut-points) or when utilising lower MVPA cut-points (see Table, Supplemental Digital Content 3, Sensitivity analysis showing adjusted associations when using lower MVPA time cut-points).

When interaction terms were added to the model, they revealed that glycemic status at baseline significantly modified the independent associations between a change in MVPA (p < 0.001) and a change in body weight (p < 0.001) with a change in HbA1c. Following-up on this interaction, stratification by glycemic status showed that those with dysglycemia had stronger associations compared to those with normal glycemia (Table 4). For individuals with dysglycemia, each 30 minute increase in MVPA per day was associated with a 0.17% (0.04, 0.29) decrease in HbA1c in the fully adjusted model (including change in sedentary time and body weight, p = 0.012), and each 6 kg increase in body weight was associated with a 0.19% (0.11, 0.27) increase in HbA1c (p < 0.001). Glycemic status did not significantly modify the association between sedentary time and HbA1c, and therefore did not warrant further stratification.

Discussion

Whilst the effect of physical activity and weight loss interventions on HbA1c have been well established in those with T2DM, (3, 33) the impact of individual lifestyle components on HbA1c in non-diabetic populations is not as well defined. This study helps to address this evidence gap by quantifying the relative importance of changes to; MVPA, sedentary time and body weight in the regulation of HbA1c levels in those at high risk of T2DM.

The current study demonstrated that both change in MVPA and body weight were independently associated with change in HbA1c whereby every 30 minute increase in MVPA per day was associated with a 0.11% (1.2mmol/mol) decrease in HbA1c and every 6 kg increase in body weight was associated with a 0.08% (0.9mmol/mol) increase. Of note, we found there was a significant interaction with glycemic status whereby those with dysglycemia at baseline had stronger associations of MVPA and body weight with HbA1c, further supporting the importance of lifestyle change in those with non-diabetic hyperglycemia.

Using linear scaling from data published for the large Atherosclerosis Risk in Communities (ARIC) study (30), it is suggested that each 0.1 absolute percentage increase in HbA1c (1.1mmol/mol), is associated with a 6.1% increased risk of diabetes, a 1.8% increased risk of coronary artery disease, a 3% increased risk of stroke and a 1.1% increased risk of all-cause

mortality in non-diabetic populations. Therefore the change in HbA1c associated with a 30 minute change in MVPA or a 6 kg change in bodyweight is likely to be clinically meaningful in a non-diabetic population.

Our findings are consistent with that of the Finnish Diabetes Prevention Study (FDPS), which achieved around a 0.2% reduction in HbA1c over three years with an intervention aimed at achieving a 5% body weight loss, at least 30 minutes of MVPA per day and a healthy diet in those with impaired glucose tolerance (22).

However, results from the Look Ahead study, which focused on achieving similar parameters to the FDPS, observed a reduction in HbA1c of 0.36% (3.9mmol/mol) over a four year period (23). This supersedes both the results of the FDPS mentioned above and the associations that attaining such parameters would have in the current study, however their use of overweight and obese diabetic participants may have steepened the gradient for improvement beyond that observed in non-diabetic populations.

Results of the current analysis are also consistent with cross sectional analyses from national surveys which have reported associations of MVPA, but not sedentary time, with HbA1c (14, 28, 31) and extend previous research that has demonstrated the effect of physical activity and body weight with risk of T2DM based on fasting or 2-h glucose values (11).

The current study supports MVPA and body weight as key targets for the prevention of T2DM when assessed by HbA1c. However, the results for change in sedentary time were more equivocal. Although sedentary time has been associated with an increased risk of T2DM (4, 34) and metabolic syndrome (8), the degree to which this is independent of MVPA or total physical activity levels has remained controversial (24). This study found that although change in sedentary time was associated with change in HbA1c, the findings were attenuated when adjusted for MVPA. This finding is in contrast to studies which have found associations between sedentary time and 2-h post challenge glucose and levels of insulin sensitivity (15, 18, 39), in addition to experimental interventions which have found improved postprandial glucose responses with reductions to sitting time (7, 17). This discrepancy in findings could result from the properties of HbA1c which reflect average glucose concentration and may therefore be less sensitive to the more subtle effects on postprandial responses and peripheral insulin sensitivity.

The 'Walking Away from Type 2 Diabetes' randomised control trial (37), from which the data in this analysis derived from, experienced no differences between control and lifestyle intervention groups, with a small decrease in activity levels for the entire cohort (38). A wide range of variation in both directions allowed the current analysis to be undertaken, but demonstrates the challenging nature of initiating and sustaining the amount of physical activity required to elicit clinically significant results.

The main strength of this study is that it provides novel prospective evidence in a high risk primary care population using objective measures of sedentary behavior, physical activity and body weight. Despite the prospective nature of this study, direct causality cannot be inferred and it is possible that unmeasured lifestyle factors were confounding relationships. In addition, whilst the study population is likely to be broadly representative of those

referred into diabetes prevention pathways within primary care, their high risk nature means the results are not be generalizable to the general population.

In conclusion, increasing MVPA and reducing body weight both have favorable influences on HbA1c levels in those identified as being at high risk of T2DM through a primary care setting. Through the use of regression modelling, this study is able to quantify the impact that manipulating important behavioral targets would have on HbA1c levels, this addresses an important limitation and can be used to inform future diabetes prevention interventions within primary care. Given the observational nature of this study, further research is needed to confirm these results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Table 1

Demographic, cardiometabolic and anthropometric characteristics of participants

Characteristics	Walking Away participants (n = 489)
Age (years)	64.2 ± 7.3
Male	310 (63.4)
Current smokers	30 (6.1)
Family history of diabetes (first degree)	169 (34.5)
B.M.I (kg/m^2)	31.7 ± 5.1
Cardiometabolic variables	
Total cholesterol (mmol/l)	5.2 (4.5 - 6)
HDL – cholesterol (mmol/l)	1.4 (1.2 - 1.6)
Ethnicity	
White European	441 (90.2)
South Asian	31 (6.3)
Other	17 (3.5)
Diagnosis	
Normal glycemic function (HbA1c <6%)	319 (65.2)
Dysglycemia (HbA1c 6%)	170 (34.8)

Continuous parametric results displayed as Mean ± SD, number (percentage) and continuous nonparametric results displayed as median (interquartile range)

Table 2

Body weight, physical activity and HbA1c characteristics at baseline and 3 years follow-up

Characteristics	Baseline	3 years
HbA1c (%)	5.8 (5.6 - 6.1)	5.7 (5.4 - 5.9)
HbA1c (mmol/mol)	39.9 (37.7 - 43.2)	38.8 (35.5 – 41.0)
Bodyweight	87.6 (79.3 - 98.9)	87.1 (78.1 - 98.1)
<u>Accelerometer variables</u>		
Wear time (h/day)	14.4 (13.5 – 15.2)	14.3 (13.5 – 15.1)
Sedentary time (mins/day)	542 (477 - 597)	566 (499 - 632)
Total MVPA (mins/day)	21 (12 – 41)	16 (7 - 33)
MVPA (mins/day accumulated in bouts ≥10mins)	4 (0 - 10)	3 (0 – 10)

Results displayed as median (interquartile range)

Table 3

Multiple linear regression models for changes in sedentary time, MVPA and body weight with HbA1c

	Sedentary time change (per 30mins/day) [a]	MVPA time change (per 30mins/day) [b]	Body weight change (per 6 kilograms) [c]
Model 1			
HbA1c Change (%)	0.02 (0.01, 0.03), p = 0.021	-0.14 (-0.2, -0.08), p < 0.001	0.09 (0.06, 0.13), p < 0.001
~HbA1c Change (mmol/mol)	0.2 (0.03, 0.38), p = 0.021	-1.5 (-2.2, -0.88), p < 0.001	1.0 (0.62, 1.4), p < 0.001
Model 2			
HbA1c Change (%)	0.01 (-0.01, 0.02), p = 0.402	-0.13 (-0.2, -0.07), p < 0.001	0.09 (0.05, 0.12), p < 0.001
~HbA1c Change (mmol/mol)	0.1 (-0.11, 0.26), p = 0.402	-1.4 (-2.15, -0.74), p < 0.001	1.0 (0.56, 1.34), p < 0.001
Model 3			
HbA1c Change (%)	0.004 (-0.01, 0.02), p = 0.615	-0.11 (-0.18, -0.05), p = 0.001	0.08 (0.04, 0.12), p < 0.001
~HbA1c Change (mmol/mol)	0.04 (-0.13, 0.22), p = 0.615	-1.2 (-1.93, -0.53), p = 0.001	0.9 (0.49, 1.26), p < 0.001

Data are unstandardized regression coefficients (95% CI), p-value.

Model 1: adjusted for age, sex, smoking status, ethnicity, beta-blocker use for hypertension, change in accelerometer wear time, IMD score, baseline HbA1c, baseline body weight, baseline sedentary time and baseline MVPA time.

Model 2: adjusted for all covariates in Model 1 and [a] MVPA time change, [b][c] sedentary time change

Model 3: adjusted for the same covariates as Model 2 and [a][b] body weight change [c] MVPA time change

Table 4

Associations between change in MVPA and body weight with a change in HbA1c stratified by glycemic status

	MVPA time change (per 30mins/day) [a]	Body weight change (per 6 kilograms) [b]
Impaired glycemic function (HbA1c 6%)		
HbA1c Change (%)	-0.17 (-0.29, -0.04), p = 0.012	0.19 (0.11, 0.27), p < 0.001
~ HbA1c Change (mmol/mol)	-1.8 (-3.19, -0.4), p = 0.012	2.1 (1.17, 2.98), p < 0.001
Normal glycemic function (HbA1c < 6%)		
HbA1c Change (%)	-0.07 (-0.13, -0.01), p = 0.031	0.04 (0.01, 0.08), p = 0.012
HbA1c Change (mmol/mol)	-0.8 (-1.47, -0.07), p = 0.031	0.5 (0.1, 0.82), p = 0.012

Adjusted for age, sex, smoking status, ethnicity, beta-blocker use for hypertension, baseline body weight, change in accelerometer wear time, IMD score, baseline HbA1c, baseline MVPA, baseline sedentary time, changes in sedentary time and [a] changes in body weight [b] changes in MVPA