

Effects of Low-Carbohydrate Diet in Individuals Medicated for Type 2 Diabetes on Long-Term Glycemic Control and Medication Usage in Context of Workplace-Sponsored Wellness Program

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ABSTRACT

Purpose Examine effectiveness of adding structured low-carbohydrate diet to low-intensity aerobic exercise on long-term glycemic control in individuals medicated for type 2 diabetes within context of workplace-sponsored wellness program.

Methods Forty-three individuals medicated for type 2 diabetes participated in workplace-sponsored wellness program. Participants analyzed according to group (exercise-only or diet plus exercise). Longitudinal data analysis conducted using multilevel growth modeling with 4 waves of data collected from baseline through 3-months. Primary outcome measure was changes in laboratory measured glycosylated hemoglobin (HbA1c) levels.

Results Participants in diet plus exercise group (n = 30) had statistically significant and clinically meaningful reductions in HbA1c levels while reducing usage of anti-glycemic medication compared to exercise-only group at 3 months. Final multilevel growth model revealed reductions in HbA1c levels in participants in diet plus exercise group of -1.19 points (95 % CI -1.92 to -0.47; P = 0.002) compared to exercise-only group. Interaction between treatment group, medication effect score, and time revealed faster monthly reductions in HbA1c values while reducing usage of anti-glycemic medication for participants in diet plus exercise group of -0.13 points (95 % CI -0.19 to -0.07; P = 0.000) compared to exercise-only group. Participants in diet plus exercise group experienced significant reductions in body mass index, percentage of weight loss, body fat percentage, waist circumference, resting heart rate, and blood pressure compared to exercise-only group. Higher proportion of participants in diet plus exercise group achieved successful clinical outcome based on Global Rating of Change scores (X2 = 9.9; P = 0.000) compared to exercise-only group.

Conclusions Combining structured low-carbohydrate diet with low-intensity aerobic exercise in individuals medicated for type 2 diabetes provides statistically significant and clinically meaningful improvements in long-term glycemic control while reducing need for anti-glycemic medication within context of workplace-sponsored wellness program.

keywords : diabetes; workplace wellness; ketosis; exercise

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INTRODUCTION

By 2025 an estimated 380 million individuals worldwide will have diabetes - increasing 65 % over the next decade¹ - and largely attributable to rise in obesity among adults.² In the United States, 30 % of an estimated \$250 billion spent on diabetes-related care is on medications.³ For employers, diabetes and diabetes-related care ranks among the most costly concerns, including direct and indirect healthcare expenditures.^{4, 5} With regard to the workplace, diabetes-associated complications (eg, cardiovascular disease, retinopathy, neuropathy, and nephropathy) have a negative impact on worker productivity.⁴⁻⁷ In a workplace-based study by Burton et al² (2015), the annual medical and pharmacy costs for an employee with diabetes averaged \$9,340 compared to just \$4,447 for those without diabetes. These expenses did not include costs associated with worker absenteeism, disability, and decreased productivity.

Treatment of diabetes is multifaceted but typically centers around anti-glycemic medications, particularly when lifestyle changes of diet modification and exercise prescription fail to adequately control blood sugar. The most commonly prescribed medication for type 2 diabetes is metformin, which has been shown to lower glycosylated hemoglobin (HbA1c) levels by 0.5 % - 1.5 % when maximum or near maximum doses are used as a monotherapy.⁸⁻¹¹ Individuals with mild hyperglycemia (ie, HbA1c < 7.5 %) typically achieve good glycemic control with doses of 1,500 - 2,000 mg/day. Only marginal improvements in glycemic control are seen with doses > 2,000 mg/day.⁵ More severe cases of hyperglycemia (ie, HbA1c 7.5 % - 9.0 %) typically require additional medications and sometimes insulin therapy.⁸ Despite routine and widespread use of prescription medications to treat type 2 diabetes, research has provided compelling evidence that specific diet, exercise, and patient education-based interventions can effectively treat type 2 diabetes, including reduction or elimination of anti-glycemic medications.¹²⁻¹⁶ Good glycemic control is essential for proper diabetes care and contributes to reduced future medical complications.⁹ For those with type 2 diabetes, an energy-reduced, high-carbohydrate, low-protein, low-fat diet has been recommended to improve glycemic control, whether or not they use anti-glycemic medications.¹¹ However, more recent evidence provides support for use of low-carbohydrate diets (i.e., 20 - 70 g/day) as a powerful tool in glycemic control.¹⁵ Tay et al¹³ (2014), investigating an energy-reduced low-carbohydrate versus high-carbohydrate diet in patients with type 2 diabetes, found a two-fold greater reduction in anti-glycemic medication use in the low-carbohydrate group at 6 months. Additionally, 35 % of patients consuming a low-carbohydrate diet reduced their Medication Effect Score¹⁷ by ≥ 50 % and nearly two-thirds ≥ 20 %. Importantly, the low-carbohydrate group achieved better long-term glycemic control (ie, HbA1c levels) and spent significantly more time in normal glycemic ranges while significantly reducing anti-glycemic medication use.

Little research has been done within the context of workplace-sponsored wellness programs to examine value of a low-carbohydrate dietary approach on glycemic control and medication usage in employees with type 2 diabetes.² To our knowledge, no published studies have investigated the

effectiveness of a structured low-carbohydrate diet on glycemic control within the context of a workplace-sponsored wellness program directed at employees with type 2 diabetes. Burton et al² (2015), investigating a 12-month workplace diabetes management program, showed that while their education-based approach resulted in statistically significant improvements in knowledge of diabetes, the program did not result in any meaningful changes in diabetes control, medication use, or biometrics associated with diabetes.

The purpose of this investigation was to examine the effectiveness of adding a structured low-carbohydrate diet to a low-intensity aerobic exercise prescription on long-term glycemic control and medication usage in employees with type 2 diabetes. This study took place within the context of a workplace-sponsored wellness program offered to employees and their dependents at two large manufacturing facilities located in norther Utah. These facilities are self-insured and bear the financial burden of direct healthcare costs as well as indirect costs associated with treating chronic disease, including lost time and reduced productivity. This investigation addresses the goals of a workplace-sponsored wellness program, namely improved employee health and quality of life, improved employee work performance and productivity, and reduction of direct and indirect costs associated with chronic disease.

MATERIALS AND METHODS

Participants

Employees and dependents of Autoliv North America (Brigham City, UT and Ogden, UT, USA) medicated for type 2 diabetes recruited for this investigation from May 2017 through January of 2019. Employees meeting selection criteria (Table 1) and consenting to participate provided written informed consent. Institutional Review Board approval obtained through Ideal Protein® (Gatineau, Quebec; www.idealprotein.com) prior to study enrollment.

Study Design and Procedures

Participant enrollment and study flow outlined in Figure 1. Study began as randomized clinical trial design. Participants randomized to treatment groups (low-intensity aerobic exercise-only^{18, 19} or structured low-carbohydrate diet combined with low-intensity aerobic exercise). Laboratory outcomes included measurement of fasting glucose, HbA1c, complete lipid panel, and measures of liver and kidney function at baseline, 1 month, 2 months, and 3 months. Anti-glycemic medication usage including dose and frequency collected weekly. Other outcomes included measurement of body weight, body mass index, body composition, waist circumference, resting heart rate and blood pressure collected weekly.

Prior to enrollment, random number table computer-generated for treatment group assignment (www.randomizer.org). Odd-numbered envelopes assigned participants to exercise-only group and even-numbered envelopes assigned participants diet plus exercise group. Randomization envelopes prepared by Dr. Savage.

Employees and dependents of Autoliv North America (Brigham City, UT and Ogden, UT facilities) medicated for type 2 diabetes were informed of study by staff of on-site First Choice Healthcare clinics. Interested individuals referred to study coordinator and screened for eligibility. Eligible individuals asked to provide written informed consent prior to participation. Consented participants completed baseline data collection performed by staff blinded to participants' group assignment.

Following baseline data collection, participants randomly assigned to treatment groups and scheduled for initial meeting with certified personal trainer familiar with all study-related procedures. Participants in both treatment groups attended weekly supervised exercise sessions lasting 45 - 60 minutes throughout 3-month study period. In addition to weekly exercise sessions, participants instructed to perform low-intensity aerobic exercise as prescribed by their trainer an additional 2 days/week for a total of 36 exercise sessions. Participants in diet plus exercise group received additional education and instruction for structured low-carbohydrate dietary protocol they were expected to follow and provided food and supplements at each weekly visit. Participants in both groups provided with a journal and instructed to track exercise compliance, blood sugar measurements, anti-glycemic medication use, as well as food and beverage consumption. Journals collected weekly and select physical examination measurements repeated by the trainer at each follow-up visit. Blood draw and laboratory analysis repeated monthly throughout study. For this investigation, participants grouped and analyzed according to treatment group and medication effect score with primary outcome measure being HbA1c values.

Exercise-Only Group

Participants performed low-intensity aerobic exercise of their choice (typically walking or cycling) for minimum of 10 minutes and maximum of 60 minutes each session. Exercise intensity and duration monitored and adjusted by trainer as needed throughout study. Exercise intensity based on Rating of Perceived Exertion scale¹⁹, which was provided in each participant's journal for reference. Participants instructed to maintain "Light" exercise intensity each session and throughout study, which is considered an appropriate exercise intensity for those with type 2 diabetes.¹⁸

Participants instructed to contact their primary care provider if they experienced any adverse symptoms associated with exercising or with glycemic control. Weekly supervised exercise sessions took place at on-site fitness centers located near First Choice Healthcare clinics if medical assistance was required. All security personnel employed by Autoliv North America are trained emergency medical technicians and available whenever facilities are open.

Diet Plus Exercise Group

Participants performed same low-intensity aerobic exercise protocol described above plus consumed structured low-carbohydrate diet. Participants instructed in diet program (Ideal

Protein®, Gatineau, Quebec; www.idealprotein.com) including consumption of pre-packaged foods, beverages, and supplements throughout study in addition to preparing meals based on program recommendations. Diet was formulated to be energy-reduced (~1,200 calories/day), low-carbohydrate (~30 - 50 g/day), low-fat (~40-50 g/day), and provide adequate protein (~80 - 100 g/day). Dieters were instructed to eat at least 4 times daily including 2 - 3 pre-packaged foods (depending on individual weight loss goals) and 1 - 2 self-prepared meals from an approved list of foods. Dieters instructed to eat 4 cups of approved vegetables and drink at least 64 ounces of water daily. Nutritional supplements included and taken with each meal according to diet program guidelines. Participants instructed to consume only foods and beverages outlined in diet program but encouraged to record everything eaten or drunk during study in their journal along with blood sugar measurements, anti-glycemic medication use, and exercise compliance throughout study.

Self-Report Measures

Participants reported use of anti-glycemic medications including dose and frequency at baseline for purpose of calculating medication effect score.¹⁴ Participants tracked anti-glycemic medication use including dose and frequency in their journal throughout study. Participants completed a 5-item quality of life survey (EuroQol EQ-5D-3L)²⁰ at baseline and then monthly throughout study. At conclusion of the study, participants completed a 15-point Global Rating of Change questionnaire²¹ to determine clinical outcome.

Laboratory Analysis

Participants provided blood-draws to measure fasting glucose, HbA1c, complete lipid panel, estimated glomerular filtration rate (eGFR), aspartate aminotransferase, and alanine aminotransferase at baseline and monthly throughout study. Finger-stick β -hydroxybutyrate testing conducted by trainers monthly throughout study to evaluate dietary ketosis.

Physical Examination

Participants underwent the following measurements at baseline and weekly throughout study: body weight (clothed, no shoes), body mass index, body composition measured with handheld bioimpedance device, waist circumference, and resting heart rate and blood pressure.

Statistical Analysis

PASW Statistics for Windows, Version 20.0 (SPSS Inc., Chicago, IL) used for all analyses. Data screening ensured statistical assumptions for inferential analyses met. All inferential statistical analyses performed using HbA1c values as dependent variable and treatment group and medication effect score as independent predictor variables. A 2-level growth model with time as a level-1 random coefficient and predictor variables of treatment group and medication effect score as level-2 fixed coefficients used to compare differences within and between participants across time.²²⁻²⁷

For all longitudinal data analyses, between-participants factors were dichotomous variable treatment group with 2 levels (exercise-only and diet plus exercise) and continuous variable medication effect score. Within-participants factor was time with 4 levels (baseline, 1, 2, and 3 months). Results examined using 2-level growth model to test for between-group differences in growth-curves with repeated measurements being nested within participants and participants being nested within groups. Level-1 predictor variable time was treated as random slope and level-2 predictor variables treatment group and medication effect score treated as fixed slopes. Level-1 model describes variance in individual HbA1c values within participants by fitting growth curve to each participant describing time-course, slope, and curvature of change. Level-2 model describes variance among participants and attempts to predict an individual's HbA1c value and deviation from grand mean.²²⁻²⁷

Hypothesized growth model used to assess changes in HbA1c values over time detailed in Figure 2. Multilevel growth model fit to investigate linear and quadratic components of change along with treatment group and medication effect score as level-2 predictors. Cross-level interaction terms investigated to explore 2-way interaction between treatment group and time, medication effect score and time, and treatment group and medication effect score, as well as 3-way interaction between treatment group, medication effect score, and time. In absence of significant interactions, main effects for treatment group and medication effect score explored.²²⁻²⁷

Fitting an accurate growth model describing and quantifying change in HbA1c values over time involved numerous steps, interim models, and model comparisons. Our final model includes a level-1 model describing each participant's change over time, and a level-2 model describing inter-participant differences in change based on treatment group and medication effect score. All level-1 and level-2 predictor variables grand mean centered to improve model interpretation.²⁷ Growth modeling does not require extrapolation or imputation methods to account for missing data points, because participants with single data point can be included in final model. Intention-to-treat principles observed analyzing all participants regardless of compliance. Additionally, proportion of participants rating overall condition at final 3-month follow-up as at least "Quite a bit better" on 15-point Global Rating of Change scale²¹ examined.

Sample Size and Power

Sample size estimation based on examining presence of two-way interaction between treatment group and time by measuring difference in HbA1c values between groups at 3 months. Previously published studies have found a treatment effect following low-carbohydrate diet of 0.60 using HbA1c values as primary outcome measure. Effect size based on mean between-group difference in HbA1c values of 0.7 % with a standard deviation 1.1%.¹³ Minimal clinically important difference of HbA1c values is 0.5 %.^{10, 28}

Ordinary sample size calculation assumes all data points are independent. With multi-level modeling, ordinary sample size estimates need to be inflated by design effect, $1+(n-1)p$, where n

is average cluster size and p estimated intra-cluster correlation coefficient.²⁹ Intra-cluster correlation coefficient values for participant outcomes typically below 0.05 because participant response to treatment is variable.²⁹ Based on 4 observations per participant (baseline, 1, 2, and 3 month) a sample size of 30 participants per group sufficient to provide 80 % power to detect between-group difference in HbA1c values of ≥ 0.5 %, ³⁰ using two-sided hypothesis and α -level of 0.05.

To examine potential clinical impact of treatment interventions and overall patient satisfaction, Global Rating of Change scores calculated for each participant and examined using X² tests of association. An α -level of 0.05 used for all analyses.

RESULTS

Fifty-five individuals screened for study inclusion (Table 2). Forty-three participants analyzed in final growth model (Figure 2). Thirty participants (70 %) included in diet plus exercise group and 13 participants (30 %) included in exercise-only group. Randomization suspended during trial due to lack of recruitment in order to obtain enough participants in diet plus exercise group. No adverse events reported by any participants as a result of study participation. Figure 1 details number of participants completing blood draws and laboratory testing for HbA1c values at each follow-up occasion.

Results of this investigation revealed that in individuals medicated for type 2 diabetes participating in workplace-sponsored wellness program consuming a low-carbohydrate diet combined with low-intensity aerobic exercise demonstrated statistically significant and clinically meaningful reductions in HbA1c values while reducing use of anti-glycemic medication. Results of final growth model revealed reduction of HbA1c values for participants in diet plus exercise group of -1.2 points (95 % CI -1.9 to -0.47; $P = 0.002$) at 3 months compared to exercise-only group. Medication effect score not predictive of changes in HbA1c values at 3 months. Interaction between treatment group, medication effect score, and time revealed faster weekly improvements in HbA1c values in participants in diet plus exercise group of -0.13 points (95 % CI -0.19 to -0.07; $P = 0.000$) compared to exercise-only group. Findings demonstrate better magnitude and rate of improvement in average HbA1c values throughout study in participants in diet plus exercise group compared to exercise-only group.

Additional analyses revealed larger proportion of participants in diet plus exercise group (15 of 24) achieved ≥ 8 % weight loss ($X^2 = 12.9$; $P = 0.00$) compared to exercise-only group (0 of 12). Larger proportion of participants in diet plus exercise group (19 of 23) achieved successful clinical outcome ($X^2 = 9.9$; $P = 0.00$) compared to exercise-only group (3 of 11). Additionally, approaching significance was proportion of participants in diet plus exercise group (12 of 24) achieving clinically meaningful reductions of ≥ 0.5 % in HbA1c values ($X^2 = 2.1$; $P = 0.15$) compared to exercise-only group (3 of 12). Also, approaching significance was proportion of participants in diet plus exercise group (4 of 22) achieving ≥ 50 % reduction in anti-glycemic medication usage ($X^2 = 2.3$; $P = 0.13$) compared to exercise-only group (0 of 11). Finally, participants in diet plus exercise group

compared to exercise-only group had statistically significant improvements in body mass index (-2.8; $P = 0.00$), weight loss percentage (8.6; $P = 0.00$), body fat percentage (-1.4; $P = 0.04$), waist circumference (-5.6; $P = 0.01$), systolic blood pressure (-13.4; $P = 0.01$), diastolic blood pressure (-9.4; $P = 0.02$), Global Rating of Change scores (3.6; $P = 0.00$), and eGFR values (-12.7; $P = 0.00$).

DISCUSSION

Results of this investigation suggest that within context of a workplace sponsored wellness program individuals medicated for type 2 diabetes consuming a structured low-carbohydrate diet combined with low-intensity aerobic exercise achieve significantly better long-term glycemic control while reducing use of anti-glycemic medication. Participants in diet plus exercise group achieved statistically significant and clinically meaningful reductions in body mass index, total weight loss, percentage of weight loss, waist circumference, and blood pressure compared to exercise-only group. Additionally, a higher proportion of participants in the diet plus exercise group achieved significantly better patient outcomes and treatment satisfaction compared to those in the exercise-only group despite the exercise-only group averaging more weekly minutes of exercise throughout the study. No evidence was found in this study that consuming a structured low-carbohydrate diet resulted in any adverse changes in liver or kidney function; in fact, improvement was observed in some of these metrics including improved eGFR values.

Little research has been done within context of workplace-sponsored wellness programs examining value of managing individuals medicated for type 2 diabetes utilizing a structured low-carbohydrate dietary approach.² To our knowledge, no published studies have investigated effectiveness of a structured low-carbohydrate diet (with or without exercise) within context of a workplace-sponsored wellness program in individuals medicated for type 2 diabetes. Burton et al² (2015), investigating a 12-month workplace diabetes management program, showed that while their education-based approach resulted in statistically significant improvements in knowledge of diabetes, their program did not result in any meaningful changes in diabetes control, medication use, or biometrics associated with diabetes.

In this investigation, participants were recruited from a production facility which is self-insured and bears the direct and indirect costs associated with employees and dependents medicated for type 2 diabetes. Our results provide evidence that adding a structured low-carbohydrate diet to existing workplace-sponsored wellness program recommendations will improve the health and wellness of employees with type 2 diabetes. These findings should inform the design and implementation of future workplace-sponsored wellness programs, which traditionally focus on education and low-intensity aerobic exercise prescription, by providing additional tools directed at preventing and treating chronic disease and seek to improve employee health and productivity while also reducing direct and indirect health and productivity-related expenses.

Our final growth model revealed that treatment group interacted with medication usage to predict improvements in

HbA1c values in individuals medicated for type 2 diabetes participating in a workplace-sponsored wellness program. These findings are clinically relevant and should help inform the management of these individuals in the context of a workplace-sponsored wellness program. If individuals medicated for type 2 diabetes consuming a structured low-carbohydrate diet combined with low-intensity aerobic exercise are more likely to improve their long-term glycemic control while also reducing their use of anti-glycemic medication, then workplace-sponsored wellness programs can more effectively provide recommendations and interventions to their employees medicated for type 2 diabetes. Although the addition of a structured low-carbohydrate diet may require initial financial investment by employers, the benefits in long-term health and wellness will more than offset those costs through improved employee productivity and reduced lost-time expenses. Providing evidence-based and cost-effective recommendations to employees for improved long-term glycemic control while reducing need for anti-glycemic medications will help reduce both direct and indirect costs while improving employee quality of life and job satisfaction.

A case-series of 3 participants were allowed to participate in this investigation having elevated HbA1c values but not using anti-glycemic medication. The purpose of including these participants was to evaluate the effect of a structured low-carbohydrate diet combined with low-intensity aerobic exercise on normalizing HbA1c levels proactively eliminating need for anti-glycemic medication. Two of these participants were included in the diet plus exercise group and one in the exercise-only group. Both participants in the diet plus exercise group achieved significant and clinically meaningful reductions in HbA1c levels thus eliminating their need for anti-glycemic medication despite exercising significantly less than the participant in the exercise only group. The participant in the exercise-only group did not achieve a reduction in HbA1c levels and therefore remained at risk for requiring anti-glycemic medication. Additionally, similar to the results of the main study, the participants in the diet plus exercise group achieved significant improvements in weight loss, waist circumference, blood pressure, and lipid profile compared to the participant in the exercise-only group. This provides further evidence of the cost-effectiveness of a structured low-carbohydrate dietary approach in the context of a workplace-sponsored wellness program in individuals with type 2 diabetes.

Some limitations of this investigation have been identified. First, the original randomized design was abandoned in order to recruit enough patients to complete the diet plus exercise group. The original design would have resulted in a balanced study of 30 participants in each group and would have likely resulted in a larger treatment effect toward the diet plus exercise group and unlikely to have changed the overall conclusions of this investigation. Another potential limitation was the use of self-reported medication use and exercise compliance. While this could have resulted in inaccurate measures of medication use minutes of exercise completed, the results still favored the diet plus exercise group despite the exercise-only group reporting significantly more minutes of exercise on average.

This study demonstrated that in individuals medicated for type 2 diabetes participating in a workplace-sponsored wellness program utilizing a structured low-carbohydrate diet combined with low-intensity aerobic exercise is more effective for long-term glycemic control while reducing need for anti-glycemic medication than exercise alone at 3 months. Participants utilizing a structured low-carbohydrate diet combined with low-intensity aerobic exercise achieved better improvements in clinical and laboratory-based outcomes compared to exercise alone. These observed improvements were statistically significant and clinically meaningful. More individuals in the diet plus exercise group achieved a successful clinical outcome and rated their overall health and quality of life as improved at 3 months compared to the exercise-only group. These results are consistent with other published reports investigating the effects of low-carbohydrate dietary approaches in individuals medicated for type 2 diabetes.

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