


BRIEF REPORT

Behavioral Strategies to Lower Postprandial Glucose in Those with Type 2 Diabetes May Also Lower Risk of Coronary Heart Disease

Daniel J. Cox  · Kun Fang · Anthony L. McCall · Mark R. Conaway · Tom A. Banton · Matthew A. Moncrief · Anne M. Diamond · Ann G. Taylor

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ABSTRACT

Introduction: Efforts to lower glycosylated hemoglobin (A1c) in patients with type 2 diabetes (T2D) are intended to reduce the risk of diabetic complications, but A1c is not the only factor contributing to this risk. Consequently,

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D. J. Cox (✉) · T. A. Banton · M. A. Moncrief · A. M. Diamond
Department of Psychiatry and Neurobehavioral Sciences, Center for Behavioral Medicine Research, University of Virginia School of Medicine, PO Box 800223, Charlottesville, VA 22908, USA
e-mail: djc4f@virginia.edu;
djc4f@hscmail.mcc.virginia.edu

K. Fang
Department of Internal Medicine, Hospital of Xi'an Jiaotong University, Xi'an 710049, Shaan'xi, China

A. L. McCall
Department of Endocrinology and Metabolism, University of Virginia School of Medicine, Charlottesville, VA 22908, USA

M. R. Conaway
Department of Public Health Sciences, University of Virginia School of Medicine, Charlottesville, VA 22908, USA

A. G. Taylor
Department of Acute and Specialty Care, University of Virginia School of Nursing, Charlottesville, VA 22908, USA

we re-analyzed published data from a broad-spectrum lifestyle intervention that lowered A1c to assess its effectiveness in lowering the overall risk of two complications of T2D, namely, coronary heart disease (CHD) and stroke.

Methods: Data from 37 adults who participated in a randomized clinical trial of a lifestyle intervention intended to reduce postprandial glucose (PPG) were re-analyzed for their pre- and post-treatment risk of CHD and stroke using the T2D-specific UK Prospective Diabetes Study (UKPDS) v2.0 risk algorithm.

Results: Compared to participants who received routine care, those using the lifestyle intervention had a significantly greater reduction in 10-year risk for CHD, but not for stroke.

Conclusion: These secondary analyses suggest that broad-spectrum lifestyle interventions that focus on lowering PPG may lower the risk of future CHD, which could guide future research.

Trial Registration: ClinicalTrials.gov ID: NCT02432391.

Keywords: Behavioral medicine; Coronary disease; Postprandial hyperglycemia; Type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2D) is a risk factor for coronary heart disease (CHD) [1–6].

Conventional T2D lifestyle interventions that focus on weight loss with the intent to lower glycosylated hemoglobin (A1c) have been found not to reduce the occurrence of CHD events [7]. While gastric surgery among patients with T2D significantly reduces weight and the risk of future CHD, non-surgical weight reduction efforts do not reduce the risk of CHD [8]. Preliminary data suggest that an alternative lifestyle intervention that focuses on reducing postprandial glucose (PPG) instead of focusing on weight loss may lower A1c more than weight-loss-specific programs [9, 10]. This PPG-reducing intervention is named GEM (for Glycemic load, Exercise, and Monitoring blood glucose) and works by replacing high glycemic load foods with low ones, reducing sedentary behavior, increasing routine vigorous activity, and systematically monitoring blood glucose. Does such a broad-spectrum lifestyle intervention also reduce the risk of CHD?

In the analysis reported here, we re-analyzed data previously published by our group [9], with the aim to investigate the clinical significance of GEM in regard to reducing the risk of future CHD. Unlike our earlier study [9] in which risk was calculated using the generic American Heart Association Atherosclerotic Cardiovascular Disease (ASCVD) risk profile [11], in the present study we employed a T2D-specific risk engine, namely, the UK Prospective Diabetes Study (UKPDS) v2.0 algorithm [12], to calculate the probability that adults with T2D will have a CHD or stroke event in the next 10 years. The UKPDS v2.0 model uses five modifiable variables which a broad-spectrum lifestyle intervention could impact (A1c, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, and smoking) and five fixed variables (age, sex, diabetes duration, ethnicity, and presence of atrial fibrillation). While it is often assumed for those with T2D that the reduction of A1c is associated with a reduction in complications from diabetes, we investigated whether a broad-spectrum lifestyle intervention that focuses on changing diet and physical activity explicitly reduces the probability of developing CHD, the leading cause of death among adults with T2D [2].

METHODS

Thirty-seven participants from a previous study of 39 T2D adults [9] were analyzed for CHD and stroke risk using the UKPDS v2.0 algorithm. Two participants from the original study were not included because of insufficient data to complete the UKPDS v2.0 algorithm. Of the 37 participants analyzed, 54% were women. Seven were Black (18.9%), 29 were White (78.4%), and one was Hispanic (2.7%). Two participants were smokers. Seventeen had been randomized to Routine Care and 20 to Routine Care + GEM. All participants had to have been diagnosed with T2D in the past 5 years (mean disease duration 2.1 years), were required to be between 24 and 80 years of age (mean age 56 years), and had an A1c level of $\geq 7.0\%$ (53 mmol/mol) (mean A1c: 8.4%, or 68 mmol/mol). Exclusion criteria were: use of medications that directly lowered blood glucose (e.g., insulin, sulfonylureas, glinides) or impeded weight loss (e.g., prednisone); conditions that precluded increasing physical activity (e.g., severe neuropathy, active cardiovascular disease); or diagnosis of renal failure. Written informed consent was obtained from each participant prior to participation. The University of Virginia Institutional Review Board for Health Sciences Research approved the study, which conformed to the standards set by the Declaration of Helsinki.

All participants completed a physical examination and blood test at baseline and at month six (3 months after the conclusion of the treatment phase). The GEM intervention involved five individual treatment sessions during which the participants reviewed: (1) their motivation to manage T2D and to pursue the GEM intervention; (2) the use of systematic blood glucose monitoring to educate, activate, and motivate them in terms of self-management choices; (3) the replacement of high glycemic load foods with low ones; (4) becoming more physically active by reducing sedentary periods and increasing routine vigorous physical activity to 150 min/week or more; and (5) how to maintain the gains achieved with GEM. The intervention is described in detail in the original publication

[9]. The pre-treatment and follow-up data from that study were applied to the UKPDS v2.0 risk engine, which is one of the better prediction models of CHD occurrence among adults with T2D [16]. For each participant, the UKPDS v2.0 algorithm calculated the percentage risk for total and fatal CHD and stroke events. The total and fatal risks were then summed to provide an overall risk of CHD and stroke for each participant. The average overall risks are reported here. A one-tailed *t* test comparing pre-treatment versus post-treatment change in risk between groups was performed using SPSS v. 25 software (IBM Corp., Armonk, NY, USA) because the hypothesis—that GEM would lead to greater reduction in risk—was unidirectional.

RESULTS

The predicted risk of CHD was reduced more by GEM than by Routine Care ($t = 1.73$, $p < 0.05$, one-tailed *t* test). Specifically, the predicted risk of CHD events for those T2D participants in the Routine Care group changed negligibly from the pre-treatment to post-treatment assessment (21.6 vs. 21.4%, respectively). For those in the alternative lifestyle GEM group, the predicted risk of CHD events decreased from 20.9% (pre-treatment) to 17.0% (post-treatment).

In contrast to the CHD results, the predicted risk of stroke was not differentially reduced by the GEM intervention when compared to Routine Care (Fig. 1). The predicted risk for stroke decreased slightly from the pre-treatment to the post-treatment assessment in both the Routine Care (5.8 vs. 5.6%, respectively) and the GEM group (5.0 vs. 4.8%, respectively).

DISCUSSION

In agreement with our previously reported findings [9], the current broad-spectrum GEM lifestyle efficacy trial showed a significant reduction in A1c (8.4% [68 mmol/mol] to 7.4% [57 mmol/mol]), 2-h dinner PPG (+ 21.9 to – 11.1 mg/dl), and carbohydrate intake (223.3 to 131.1 g/day) and an increase in aerobic activity (25 to 39 min/day) and high-density

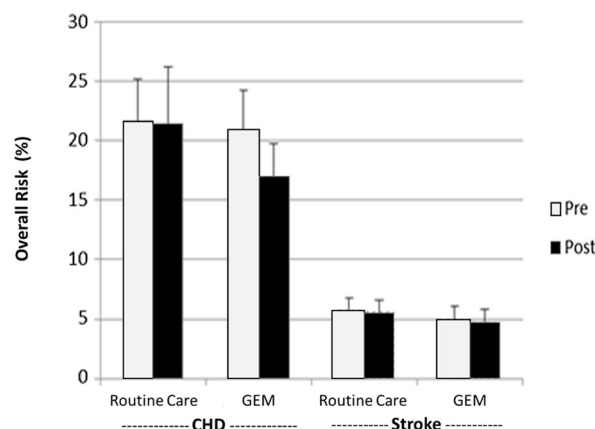


Fig. 1 Mean predicted risk of coronary heart disease (CHD) and stroke for the Routine Care and Glycemic load, Exercise, and Monitoring blood glucose (GEM) study groups, pre- and post-treatment. Error bars depict standard errors of the means

lipoprotein (HDL; 38.8 to 41.8 mg/dl), but it did not show a significant impact on total cholesterol, systolic blood pressure, or smoking status. The current analysis shows that GEM is also associated with a reduction in the predicted 10-year risk for CHD, primarily through an improvement in A1c and HDL. However, these preliminary data should be interpreted within the context of five factors. First, the baseline risk for CHD and stroke is not zero. When the GEM dataset is analyzed using the ASCVD risk profile and assuming no diabetes, the GEM group has a 2.3% risk of CHD in 10 years. Consequently, GEM reduced the elevated diabetic risk of future CHD by 21% ($1 - [17.0 - 2.3\%]/[20.9 - 2.3\%]$). Second, the risk of CHD increases with increases in the follow-up time because age and diabetes duration increase. Third, the UKPDS v2.0 algorithm does not take into account the impact of PPG on CHD risk, which is a potentially independent predictor of CHD [13–15] and a primary focus of the GEM intervention. This suggests that the GEM intervention may have had an even greater impact on CHD risk, given that it lowered PPG. Fourth, lifestyle weight loss interventions have been found not to reduce the occurrence [7] or risk of future CHD [8], while this focus on PPG did. Fifth, the sample analyzed here reflected people with relatively recent onset of T2D who were on few

medications. These preliminary findings may not extrapolate to people with diabetes of longer duration or who are on more intensive medication regimens.

In contrast, the risk for stroke was minimally lowered in those T2D patients on the GEM intervention, and the change was no different than that among T2D patients receiving Routine Care. This could be in part due to: (1) the baseline risk in the study sample was very low, leaving little room for improvement (floor effect), and (2) GEM [9] did not significantly lower systolic blood pressure, which is a primary risk factor for stroke.

CONCLUSION

Although this secondary analysis indicating a broad-spectrum lifestyle intervention designed to lower PPG also reduces risk of CHD should be interpreted cautiously, it can be used to guide future a priori research. The likelihood of it also reducing future risk of CHD may provide additional motivation for people with T2D to engage in this behavior change.

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Compliance with Ethics Guidelines. The authors received the approval of the University of Virginia Institutional Review Board for Health Sciences Research to conduct this work. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Springer's policy concerning informed consent has been followed.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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