Journal of Diabetes and Its Complications 28 (2014) 767–771

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Influence of flavonoid-rich fruit and vegetable intake on diabetic retinopathy and diabetes-related biomarkers

Sara E. Mahoney *, Paul D. Loprinzi

Bellarmine University, Department of Exercise Science, Donna & Allan Lansing School of Nursing & Health Sciences, Louisville, KY

ARTICLE INFO

Article history:
Received 31 January 2014
Received in revised form 9 June 2014
Accepted 16 June 2014
Available online 21 June 2014

Keywords:
Inflammation
Diabetic retinopathy
Flavonoid
Fruit and vegetable consumption
Glycemic control

ABSTRACT

Objective: (1) Determine the relationship between dietary flavonoid-rich fruit and vegetable consumption on diabetes-related biomarkers (e.g., HgbA1c) and diabetic retinopathy.
Methods: Data from 381 participants with diabetes from the NHANES 2003–2006 were analyzed. Blood samples were taken to measure C-reactive protein (CRP), HgbA1C, and fasting glucose and insulin. Diabetic retinopathy was assessed from a retinal imaging exam. A high-flavonoid fruit and vegetable consumption (HFVC) index variable was created from a food frequency questionnaire (FFQ).
Results: After adjustments, greater HFVC was associated ($p < 0.05$) with lower levels of CRP ($\beta = -0.005$), HgbA1C ($\beta = -0.005$) and glucose ($\beta = -0.59$), with greater HFVC reducing the odds of having diabetic retinopathy by 30%.
Conclusion: Adults with diabetes consuming more flavonoid-rich fruits and vegetables had lower degrees of inflammation, better glycemic control, and reduced odds of diabetic retinopathy.

1. Introduction

Diabetes is a metabolic disease that has markedly increased over the last two decades, from 6.6 million in 1990 to 20.1 million in 2011 (Centers for Disease Control, Prevention, 2011; Massey, Moore, Parson, & Tadros, 1989). This condition, often caused by uncontrolled hyperglycemia, inflammation, and oxidative stress, may result in microvasculature damage, ultimately leading to neuropathy, nephropathy, chronic kidney disease and retinopathy (Romeo, Liu, Asnaghi, Kern, & Lorenzi, 2002; Wada & Makino, 2013). Further, these secondary conditions may reduce quality of life and premature mortality (Jung, Kim, Hwang, & Ha, 2007).

While pharmaceuticals are commonly prescribed to those with diabetes, dietary modification, specifically increasing consumption of phytochemicals commonly found in fruits and vegetables, may be an effective strategy in reducing inflammation and maintaining glycemic control. This strategy is appealing because those with diabetic complications may be burdened with high medical costs, whereas fruit and vegetable consumption is relatively inexpensive as compared to drug therapy and without side effects seen in many pharmaceuticals. Several epidemiological studies have found an inverse relationship between flavonoid consumption, a polyphenolic compound found in fruits and vegetables, and risk of developing type 2 diabetes (Bahadoran, Mirmiran, & Azizi, 2013; Jacques et al., 2013); however, the effects of high-flavonoid fruit and vegetable consumption on factors influencing the progression and severity of diabetes have been underexplored among adults with diabetes.

Flavonoids found in a variety of fruits and vegetables may attenuate the severity and progression of diabetes through two primary mechanisms: improved glycemic control and reduction in systemic inflammation (Donath & Shoelson, 2011; Jung, Lee, Jeong, & Choi, 2004; Park et al., 2007; Zhang et al., 2011). Supplementation of flavonoids in diabetic rats led to improved hepatic glycogen content and improved glycemic control (Park et al., 2007; Zhang et al., 2011). *In vitro* models demonstrated that flavonoids such as quercetin exerted a beneficial effect of muscle cell glucose uptake mediated through GLUT-4 translocation (Park et al., 2007; Zhang et al., 2011). Additionally, there is mounting evidence that inflammatory cytokines play a prodegenerative role in diabetic complications, including non-proliferative diabetic retinopathy (Donath & Shoelson, 2011). Given the anti-inflammatory properties of flavonoids, it is plausible to suggest that adequate consumption of foods rich in flavonoids may be an effective strategy in attenuating secondary complications associated with diabetes.

Given that few studies have examined the effect of flavonoid consumption on biomarkers associated with diabetes severity and diabetes-induced end-organ damage among those with diabetes, the aim of this study was to, among a national sample of U.S. adults with diabetes, examine the association of high-flavonoid fruit and vegetable

Conflict of Interest Statement: All authors declare no conflict of interest.

* Corresponding author at: Bellarmine University, Department of Exercise Science, Donna & Allan Lansing School of Nursing. Tel.: +1 502 272 7607; fax: +1 502 272 7602.
E-mail address: smahoney@bellarmine.edu (S.E. Mahoney).

http://dx.doi.org/10.1016/j.jdiacomp.2014.06.011
1056-8727/

consumption (HFVC) on intermediate biomarkers associated with diabetes (e.g., HgbA1C, glucose, and insulin) and diabetic retinopathy.

2. Material and methods

2.1. Study design

Data from the 2003–2006 National Health and Nutrition Examination Survey (NHANES) were used. NHANES is an ongoing survey conducted by the National Center for Health Statistics (NCHS) which evaluates a representative sample of non-institutionalized U.S. civilians, selected by a complex, multistage probability design. All procedures for data collection were approved by the NCHS ethics review board, and all participants provided written informed consent prior to data collection.

2.2. Assessment of diabetes status

Participants were considered to have evidence of diabetes if they self-reported a previous diagnosis of the disease (excluding gestational diabetes mellitus), were taking insulin or diabetic pills to lower blood sugar, had an HgbA1C of 6.5% or greater (Anonymous, 2010b), or had a fasting glucose level of 126 mg/dL or higher (Anonymous, 2010a).

2.3. Assessment of high-flavonoid fruit and vegetable consumption (HFVC) index

On the basis of the National Cancer Institute Diet History Questionnaire (DHQ) that is widely used in nutritional epidemiology research (Subar, Thompson, Kipnis, et al., 2001), participants completed the NHANES Food Frequency Questionnaire (FFQ) (Subar, Dodd, Guenther, et al., 2006). Briefly, participants were asked to report the proportion of time certain types of foods were eaten over the past 12 months. For the present study, fruits and vegetables rich in flavonoids were identified by using the USDA flavonoid content of foods (USDA, 2007), and selection of these foods was similar to analyses completed by Cassidy et al. (2011) and Jacques et al. (2013). This index variable has demonstrated evidence of construct validity as the individual sub-classes of flavonoids selected to create this index variable have been shown to predict various outcomes such as hypertension and incidence of type 2 diabetes (Cassidy et al., 2011; Jacques et al., 2013). Fruit and vegetable juices were not included; analyses were limited to whole fruits and vegetables. For each food item, response options ranged from 1 to 11, and included never (Ali, McKeever Bullard, Impertore, Barker, & Gregg, 2012), 1–6 times/year (American Diabetes Association, 2012), 7–11 times/year (Babu, Liu, & Gilbert, 2013), 1 time/month (Bahadoran et al., 2013), 2–3 times/month (Cassidy et al., 2011), 1 time/week (Centers for Disease Control, Prevention, 2011), 2 times/week (Coskun, Kanter, Korkmaz, & Oter, 2005), 3–4 times/week (Anonymous, 2010a), 5–6 times/week (Donath & Shoelson, 2011), 1 time/day (Dubowitz et al., 2008), and 2 or more times/day (Ghanim et al., 2007). Responses were summed, with higher values indicating more frequent consumption of flavonoid-rich foods. With 15 items, the possible range for the HFVC index variable is 15–165.

2.4. Assessment of diabetes-related biomarkers

Evaluated diabetes-related biomarkers included HgbA1C, high-sensitivity CRP, blood pressure, fasting glucose and fasting insulin. HgbA1C was measured using the Primus instrument, which is a fully automated glycohemoglobin analyzer using high performance liquid chromatography. High sensitivity CRP concentration was quantified using latex-enhanced nephelometry. Blood pressure was measured 3 or 4 times, and the average mean arterial pressure (MAP) ([diastolic blood pressure × 2) + systolic blood pressure]) was calculated. Fasting glucose and insulin were measured enzymatically from a serum blood sample.

2.5. Assessment of diabetic retinopathy

Participants 40 years and older were eligible for the retinal imaging exam unless they were unable to see light with both eyes open or had an eye infection. Detailed procedures of the retinal imaging exam performed in the NHANES 2005–2006 cycle can be found elsewhere (National Health & Nutrition Examination Survey; Zhang, Saaddine, Chou, et al., 2010). Briefly, retinal imaging was performed using the Canon Non-Mydratic Retinal Camera CR6-45NM (Canon, Tokyo, Japan). Two forty-five degree non-mydriatic digital images were obtained on both eyes. Diabetic retinopathy was defined as the presence of 1 or more retinal microaneurysms or retinal blot hemorrhages using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading criteria (Anonymous, 1991), and was further classified as *no retinopathy*, *mild non-proliferative retinopathy*, *moderate-to-severe non-proliferative retinopathy*, *or proliferative retinopathy* according to ETDRS standards applied to the worse eye.

2.6. Assessment of covariates

Covariates included age, gender, poverty-to-income ratio (PIR), race–ethnicity, cotinine, homocysteine, body mass index (BMI), moderate-to-vigorous physical activity (MVPA), and various physician-diagnosed comorbidities, including coronary heart disease, stroke, cancer, kidney disease, and chronic obstructive pulmonary disease. Information about age, gender, PIR race/ethnicity, and the comorbidities were obtained from questionnaires. The PIR is calculated by dividing the family income by the poverty guidelines, which is specific to the family size, year assessed, and state of residence. Serum cotinine was included as a marker of active smoking status or environmental exposure to tobacco (i.e., passive smoking). Serum cotinine was measured by an isotope dilution high performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry. Homocysteine, a marker of endothelial function, was measured using the fluorescence polarization immunoassay. BMI was calculated from measured weight and height (weight in kilograms divided by the square of height in meters). Lastly, MVPA was assessed using the ActiGraph 7164 accelerometer. The accelerometer measured the frequency, intensity, and duration of physical activity by generating an activity count proportional to the measured acceleration. Estimates are reported in 1-minute time intervals. Activity counts ≥2020 were used to classify time spent in MVPA. Only those participants with at least 4 days of 10 or more hours/day of accelerometer wear time were included in the analyses in order to make sure that data adequately captured habitual physical activity patterns (Troiano et al., 2008). To monitor the amount of time the device was worn, nonwear was defined by a period of a minimum of 60 consecutive minutes of zero activity counts, with the allowance of 1–2 minutes of activity counts between 0 and 100 (Troiano et al., 2008).

2.7. Data analysis

All statistical analyses were performed using procedures from sample survey data using STATA (version 12.0, College Station, TX) to account for the complex survey design used in NHANES.

To provide descriptive characteristics of the study variables, means and proportions, respectively, were calculated for continuous and categorical variables (Table 1). To examine the independent association of flavonoid-rich foods (independent variable) on diabetes-related biomarkers, multivariable linear regression analysis was employed. Separate models were computed for CRP, MAP, HgbA1C, glucose, and insulin (Table 2). All models were adjusted for age, gender, PIR, race–ethnicity, comorbidity index, cotinine,