

Plant-Based Diets for Type 1 Diabetes

Hana Kahleova^{1*}, Brian Carlsen², Rickisha Berrien Lopez³, Neal D Barnard⁴

¹Clinical Research, Physicians Committee for Responsible Medicine, United States; ²Department of Surgery, Mayo Clinic, United States; ³School of Medicine, University of Maryland, United States; ⁴School of Medicine and Health Sciences, George Washington University, United States

ABSTRACT

Type 1 diabetes is a chronic autoimmune disease characterized by hyperglycemia resulting from the destruction of insulin-producing pancreatic beta-cells. The increasing incidence (at a worldwide rate of 3-5% a year) suggests that in addition to the genetic component, the risk may be influenced by environmental factors, including the diet. A plant-based diet has been shown to improve glycemic control in individuals with type 2 diabetes and to improve beta-cell function in overweight people but has not been thoroughly tested in type 1 diabetes due to its high carbohydrate content. We present two case studies of individuals with type 1 diabetes who adopted a plant-based diet and experienced a significant increase in insulin sensitivity, reductions in insulin dose, and improvements in cardiovascular risk factors.

Keywords: Diet; Nutrition; Type 1 diabetes; Plant-based diet

INTRODUCTION

Type 1 diabetes is a chronic autoimmune disease characterized by hyperglycemia resulting from the destruction of insulin-producing pancreatic beta-cells. While there is a genetic component to the risk of type 1 diabetes, the increasing incidence (at a worldwide rate of 3%-5% a year) suggests an environmental component, such as diet [1]. While it has been shown that a plant-based dietary intervention improves glycemic control in individuals with type 2 diabetes and may improve beta-cell function in overweight adult individuals [2], it is unclear whether such a diet could improve management of type 1 diabetes. Given the high carbohydrate content of plant-based diets, health professionals may be discouraged from recommending such a diet to patients with type 1 diabetes.

Dietary contributors to type 1 diabetes remain unclear. Some epidemiological and immunological studies have suggested that exposure to complex foreign proteins, particularly those in meat and dairy products, in early infancy may increase the risk of β -cell autoimmunity and type 1 diabetes in genetically susceptible individuals [3-6], although other studies have not supported this possibility [7]. An interventional pilot study suggested an early nutrition manipulation, including casein hydrolysate, compared

with conventional cow's milk formula, may decrease the risk of beta-cell autoimmunity over the course of more than 4 years [8]. Later findings from this study, however, contradicted this finding [9].

Dietary guidance for type 1 diabetes management typically includes careful attention to carbohydrate intake, consumption of processed and sugar-sweetened foods and drinks, and increased intake of whole grains, fruits, vegetables and legumes for both type 1 and type 2 diabetes, due to the beneficial effects on glycemic control [10,11]. Fiber-rich foods have been shown to reduce postprandial blood glucose levels in patients with either type 1 or type 2 diabetes [12].

We present two case studies of individuals with type 1 diabetes who adopted a plant-based diet and monitored changes in their glycemic control and cardiovascular risk factors. Both of them granted informed consent to publish the information.

Case study 1

In October 1996, a 25-year old male medical student began to experience acute polyuria, polydipsia, fatigue, and unexplained weight loss and, after appropriate testing, was diagnosed with type 1 diabetes. After diagnosis, he maintained good glycemic

*Correspondence to: Dr. Hana Kahleova, Physicians Committee for Responsible Medicine, 5100 Wisconsin Ave, 20016, Washington, DC, United States, Tel: +202-686-2210; Fax: + 202-686-2216; E-mail: hana.kahleova@gmail.com

Received date: April 20, 2020; Accepted date: July 09, 2020; Published date: July 16, 2020

Citation: Kahleova H, Carlsen B, Berrien Lopez R, Barnard ND (2020) Anti-Diabetic, Haematinic and Anti-Cholesterolic Effects of Wheat (*Triticum Aestivum* Linn.) Plant-Based Diets for Type 1 Diabetes. *J Diab Metab*. 11:847. doi: 10.35248/2155-6156.20.11.847

Copyright: © 2020 Kahleova H, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

control with normal HbA1c levels for many years, using an insulin pump or multiple daily insulin injections. His HbA1c was 6.2% in December 2012.

In 2013, at the age of 42, he decided to change his diet in hopes of improving his overall health, eliminating animal-derived products and processed foods. In the first several weeks after the diet change, he experienced unexpected and repeated episodes of hypoglycemia. At the time of his diagnosis, he was consuming about 150 g of carbohydrates per day and was taking 50-60 units total per day of insulin, about 60% of which was long-acting. The carbohydrate to insulin ratio was therefore around 1.25-3. After the diet change, he was consuming 400 g-450 g of carbohydrates per day in the form of whole, unprocessed fruits, vegetables, and grains and required 26 units total of insulin per day, for a carbohydrate to insulin ratio of 15-17. During this time, his weight dropped from 190 lbs to 180 lbs. His insulin requirements and weight have remained stable since then and his HbA1c has been ranging between 5.5%-5.8% over the last 2 years.

Case study 2

In February 2004, a 17-year old female was diagnosed with diabetes, initially thought to be type 2. Treatment with oral hypoglycemic medications was initiated. However, between November 2017 and February 2018, her HbA1c had risen from 5.4% to 8.7%. In February 2018, she was diagnosed with type 1 diabetes after testing positive for GAD-65 and IA-2 antibodies, and insulin therapy was initiated.

Aiming to improve her glycemic control, she adopted a low-carbohydrate (under 30 grams of carbohydrates a day), high-fat diet relying heavily on meats, full-fat dairy, avocados, and low-carbohydrate vegetables, such as green leafy vegetables and mushrooms. She avoided fruits and starchy vegetables. She noticed steadier blood sugar levels and an increased requirement for insulin per gram of consumed carbohydrate. Within several months, her HbA1c had decreased to 5.6%, but her total cholesterol concentration increased from 175 mg/dL in January 2018 to 221 mg/dL in the fall of 2018.

In January 2019, she decided to eliminate meat, dairy products, and egg products. Within the first few days after her diet change, she experienced repeated hypoglycemic episodes. In response, she reduced her insulin doses. The basal rate (units of insulin per hour) decreased by 24%. The correction factor (the blood glucose reduction produced per 1 unit of rapid-acting insulin) improved approximately 50%. Previously, one unit of insulin lowered her blood glucose by 43 mg/dL; after the diet change, one unit of insulin led to a decrease of 64 mg/dL. Similarly, the carbohydrate-to-insulin ratio (units of insulin per gram of carbohydrates consumed) improved by roughly 50%. 1 unit of insulin previously covered 10 grams of carbohydrates, but after the new diet, it covered 15 grams. After two months, despite a large reduction in insulin use, her HbA1c was unchanged at 5.4%. Her total cholesterol had dropped from 221 mg/dL to 158 mg/dL.

DISCUSSION

These case studies demonstrate increases in insulin sensitivity and reductions in insulin requirements after the adoption of a plant-based diet. Despite larger quantities of consumed carbohydrates, glycemic control improved significantly.

In type 2 diabetes, a robust body of research shows that a low-fat, vegan diet increases insulin sensitivity and improves glycemic control [13,14]. Insulin resistance is strongly related to fat accumulation within skeletal muscle (intramyocellular lipid) and liver cells (hepatocellular lipid) [15-17]. Reducing intramyocellular and hepatocellular lipid concentrations significantly improves insulin sensitivity. It is likely that some individuals with type 1 diabetes have a degree of insulin resistance (in addition to the absence of insulin production), complicating the management of their condition. If so, this provides a rationale for the use of a low-fat, vegan diet in individuals with type 1 diabetes. However, such a diet has not been tested in randomized trials in individuals with type 1 diabetes.

A small study in 10 people with type 1 diabetes showed that a high-carbohydrate (70%), high-fiber (70 g) diet increased insulin sensitivity and reduced insulin requirements and blood lipids, compared with a low-carbohydrate (39%), low-fiber (10 g) diet over the course of 4 weeks. The carbohydrate to insulin ratio was 6.22 ± 1.1 higher ($p < 0.001$) on the high-carbohydrate, high-fiber diet [18].

High-fat diets may inhibit glucose utilization [19], as the result of a downregulation of the genes required for mitochondrial oxidative phosphorylation in skeletal muscle [20] and by increasing serum endotoxin levels, thus leading to insulin resistance [21]. In contrast, a high-carbohydrate, high-fiber diet may increase postprandial metabolism [22-25] and improve glucose disposal through an increase in insulin signaling, resulting in GLUT4 translocation [26,27]. Therefore, a high-carbohydrate, high-fiber diet seems to increase insulin sensitivity and enhance glucose oxidation in type 1 diabetes.

In addition to improved glycemic control, plant-based diets have been shown to reduce other cardiovascular risk factors, particularly body weight, blood lipid concentrations, and blood pressure. In a meta-analysis of 15 clinical trials, including 17 intervention groups, vegetarian diets were consistently associated with weight loss. Overall mean weight loss among study completers was 4.6 kg [28]. A meta-analysis of 19 trials demonstrated that plant-based diets reduced total and LDL-cholesterol by 12.5 mg/dL (0.32 mmol/L) and 12.2 mg/dL (0.32 mmol/L), respectively [29]. In a meta-analysis of 7 clinical trials, plant-based diets reduced systolic pressure by 4.8 mm Hg and diastolic pressure by 2.2 mm Hg [30]. These observations are particularly relevant for type 1 diabetes, as cardiovascular disease is the primary cause of mortality and morbidity. Cardiovascular events occur more than a decade earlier in people with type 1 diabetes compared with non-diabetic individuals [31] and a recent meta-analysis estimated the standardized mortality ratio attributable to cardiovascular disease to be 5.7 for men and 11.3 for women with type 1 diabetes [32].

Blood glucose management is one of the cornerstones of diabetes care [33]. It has been well established that improved glycemic control reduces the risk of macrovascular and microvascular complications. Meta-analyses of large randomized controlled trials demonstrated that HbA1c reductions of approximately 1 absolute percentage point reduced the risk of both fatal and nonfatal myocardial infarction (15%) and cardiovascular disease (11-15%) [34-36]. A meta-analysis of six randomized controlled trials showed that plant-based diets reduced HbA1c by 0.4% compared with conventional diets in patients with type 2 diabetes [37]. This reduction in HbA1c alone (i.e., independently from the association with the decrease in body weight and the improvement in blood lipids, blood pressure, platelet aggregation and others) would be expected to decrease risks of myocardial infarction and cardiovascular disease by about 6% and 4.4-6%, respectively, based on estimates drawn from large prospective studies. Other healthful lifestyle factors add further reductions in risk.

Plant-based diets may decrease the risk of developing the microvascular complications. Mild impairment of renal function is present in about 40% of patients with diabetes [38]. Several studies have reported a reduction of microalbuminuria and proteinuria in patients with nephropathy when consuming a plant-based or a reduced-red-meat diet [39-41]. One study showed a 54% decrease of microalbuminuria in patients with type 1 diabetes after eight weeks of a largely plant-based diet [41]. Similarly, Azadbakht, et al. [42] performed a randomized controlled trial in adults with type 2 diabetes with nephropathy (urinary protein excretion between 300-1000 mg/day), substituting half of the animal protein for soy protein in the intervention group and following them for four years. They found that the soy protein intervention group had a significant improvement in proteinuria (-154 mg/day vs. +34 mg/day in the control group), along with significant decreases in total cholesterol (-23 mg/dL vs. +10 mg/dL, P=0.01), LDL cholesterol (-20 mg/dL vs. +6 mg/dL, P=0.01) and fasting glucose (-18 mg/dL vs. +11 mg/dL, P=0.03) [42].

Furthermore, more than 50% of diabetic patients suffer from neuropathy [43]. The most common clinical manifestations of diabetic neuropathy include pain, insensitivity to trauma, orthostatic hypotension, cardiac autonomic neuropathy, gastroparesis, and erectile dysfunction [44]. Diabetic neuropathy has a negative impact on quality of life and is associated with increased risk of sleep disturbances, depression and anxiety [45]. Diabetic neuropathy also increases the risk of amputations and cardiovascular disease [46]. A 20-week controlled pilot study demonstrated an improvement in diabetic neuropathy in response to a low-fat plant-based diet: Electrochemical skin conductance in the foot and perceived pain improved, compared with the control group [47]. These results are consistent with those of previous, smaller studies showing improvements in neuropathy in response to a plant-based diet combined with exercise [48,49], probably due to improved endoneurial microcirculatory perfusion [50].

Men and women with type 1 diabetes have 5 and 10 times, respectively, higher risk of coronary heart disease events [51]. In a large study, analyzing the data from the Swedish National

Diabetes Register, patients with type 1 diabetes were categorized according to the number of risk factors not at target: HbA1c, blood pressure, albuminuria, smoking, and low-density lipoprotein cholesterol. A steep-graded association has been demonstrated between cardiovascular risk factors and major adverse cardiovascular outcomes among patients with type 1 diabetes [52]. All of these risk factors except for smoking can be significantly improved with a plant-based diet.

A plant-based diet has been shown to reverse atherosclerosis in clinical trials [53-55], especially when combined with exercise and stress management [54,56,57]. In a systematic review and meta-analysis of 8 prospective studies among Seventh-day Adventists, plant-based diets were associated with a 40% reduced risk of coronary heart disease events and a 29% reduction in cerebral vascular disease events [58]. In addition to providing the substantial health benefits, plant-based eating may also reduce health care costs, particularly those related to insulin, hospital admissions and medical bills [59].

In research studies, the acceptability of plant-based diets appears to be similar to that of other therapeutic diets over both the short and long term, as indicated by rates of retention, diet adherence, and diet acceptance questionnaires [60-63].

In conclusion, the case studies presented here show dramatic increases in insulin sensitivity and reductions in insulin requirements on a high-carbohydrate, high-fiber plant-based diet. These studies are supported by a solid rationale for the use of such diets in type 1 diabetes management. However, randomized clinical trials are needed to verify these findings, assess their generalizability, and quantify the effectiveness of plant-based diets in the management of type 1 diabetes.

AUTHOR CONTRIBUTIONS

HK wrote most of the manuscript. BCC, RBL and NDB wrote parts of the manuscript and assisted with support, writing review and editing.

FUNDING

This research received no external funding.

CONFLICTS OF INTEREST

The authors declare no conflict of interest. Dr. Kahleova is Director of Clinical Research at the Physicians Committee for Responsible Medicine. Dr. Barnard serves without financial compensation as president of the Physicians Committee for Responsible Medicine and Barnard Medical Center, nonprofit organizations providing education, research, and medical care related to nutrition. He writes books and gives lectures related to nutrition and health and has received royalties and honoraria from these sources.

REFERENCES

1. Ziegler AG, Bonifacio E, Powers AC, Todd JA, Harrison LC, Atkinson MA. Type 1 Diabetes Prevention: A Goal Dependent on Accepting a Diagnosis of an Asymptomatic Disease. *Diabetes*. 2016;65:3233-3239.

2. Kahleova H, Tura A, Hill M, Holubkov R, Barnard ND. A Plant-Based Dietary Intervention Improves Beta-Cell Function and Insulin Resistance in Overweight Adults: A 16-Week Randomized Clinical Trial. *Nutrients*. 2018;9:10.
3. Akerblom HK, Knip M. Putative environmental factors in Type 1 diabetes. *Diabetes Metab Rev*. 1998;14:31-67.
4. Harrison LC, Honeyman MC. Cow's milk and type 1 diabetes: the real debate is about mucosal immune function. *Diabetes*. 1999;48:1501-1507.
5. Virtanen SM, Rasanen L, Ylonen K, Aro A, Clayton D, Langholz B, et al. Early introduction of dairy products associated with increased risk of IDDM in Finnish children. The Childhood in Diabetes in Finland Study Group. *Diabetes*. 1993;42:1786-1790.
6. Muntoni S, Cocco P, Aru G, Cucca F. Nutritional factors and worldwide incidence of childhood type 1 diabetes. *Am J Clin Nutr*. 2000;71:1525-1529.
7. Savilahti E, Saarinen KM. Early infant feeding and type 1 diabetes. *Eur J Nutr*. 2009;48:243-249.
8. Akerblom HK, Virtanen SM, Ilonen J, Savilahti E, Vaarala O, Reunanen A, et al. Dietary manipulation of beta cell autoimmunity in infants at increased risk of type 1 diabetes: a pilot study. *Diabetologia*. 2005;48:829-837.
9. Knip M, Åkerblom HK, Becker D, Dosch HM, Dupre J, Fraser W, et al. Hydrolyzed infant formula and early β -cell autoimmunity: a randomized clinical trial. *JAMA*. 2014;311:2279-2287.
10. Standards of Medical Care in Diabetes-2018 Abridged for Primary Care Providers. *Clin Diabetes Publ Am Diabetes Assoc*. 2018;36:14-37.
11. Pastors JG, Franz MJ, Warshaw H, Daly A, Arnold MS. How effective is medical nutrition therapy in diabetes care? *J Acad Nutr Diet*. 2003;103:827-831.
12. Riccardi G, Rivellese AA, Giacco R. Role of glycemic index and glycemic load in the healthy state, in prediabetes, and in diabetes. *Am J Clin Nutr*. 2008;87:269S-274S.
13. Barnard ND, Cohen J, Jenkins DJA, Turner McGrievy G, Gloede L, Jaster B, et al. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. *Diabetes Care*. 2006;29:1777-1783.
14. Kahleova H, Matoulek M, Malinska H, Oliyarnik O, Kazdova L, Neskudla T, et al. Vegetarian diet improves insulin resistance and oxidative stress markers more than conventional diet in subjects with Type 2 diabetes. *Diabet Med*. 2011;28:549-559.
15. Krssak M, Falk PK, Dresner A, DiPietro L, Vogel SM, Rothman DL, et al. Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a ¹H NMR spectroscopy study. *Diabetologia*. 1999;42:113-116.
16. Perseghin G, Scifo P, De Cobelli F, Pagliato E, Battezzati A, Arcelloni C, et al. Intramyocellular triglyceride content is a determinant of in vivo insulin resistance in humans: a ¹H-¹³C nuclear magnetic resonance spectroscopy assessment in offspring of type 2 diabetic parents. *Diabetes*. 1999;48:1600-1606.
17. Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. *N Engl J Med*. 2014;371:1131-1141.
18. Anderson JW, Zeigler JA, Deakins DA, Floore TL, Dillon DW, Wood CL, et al. Metabolic effects of high-carbohydrate, high-fiber diets for insulin-dependent diabetic individuals. *Am J Clin Nutr*. 1991;54:936-943.
19. Hue L, Taegtmeier H. The Randle cycle revisited: a new head for an old hat. *Am J Physiol Endocrinol Metab*. 2009;297:E578-E591.
20. Sparks LM, Xie H, Koza RA, Mynatt R, Hulver MW, Bray GA, et al. A high-fat diet coordinately downregulates genes required for mitochondrial oxidative phosphorylation in skeletal muscle. *Diabetes*. 2005;54:1926-1933.
21. Anderson AS, Haynie KR, McMillan RP, Osterberg KL, Boutagy NE, Frisard MI, et al. Early skeletal muscle adaptations to short-term high-fat diet in humans before changes in insulin sensitivity. *Obes Silver Spring Md*. 2015;23:720-724.
22. Bowden VL, McMurray RG. Effects of training status on the metabolic responses to high carbohydrate and high fat meals. *Int J Sport Nutr Exerc Metab*. 2000;10:16-27.
23. Nagai N, Sakane N, Moritani T. Metabolic responses to high-fat or low-fat meals and association with sympathetic nervous system activity in healthy young men. *J Nutr Sci Vitaminol (Tokyo)*. 2005;51:355-360.
24. Thyfault JP, Richmond SR, Carper MJ, Potteiger JA, Hulver MW. Postprandial metabolism in resistance-trained versus sedentary males. *Med Sci Sports Exerc*. 2004;36(4):709-716.
25. Barr SB, Wright JC. Postprandial energy expenditure in whole-food and processed-food meals: implications for daily energy expenditure. *Food Nutr Res*. 2010;54.
26. Jazet IM, Schaart G, Gastaldelli A, Ferrannini E, Hesselink MK, Schrauwen P, et al. Loss of 50% of excess weight using a very low energy diet improves insulin-stimulated glucose disposal and skeletal muscle insulin signalling in obese insulin-treated type 2 diabetic patients. *Diabetologia*. 2008;51(2):309-319.
27. Petersen KF, Dufour S, Morino K, Yoo PS, Cline GW, Shulman GI. Reversal of muscle insulin resistance by weight reduction in young, lean, insulin-resistant offspring of parents with type 2 diabetes. *Proc Natl Acad Sci*. 2012;109:8236-8240.
28. Barnard ND, Levin SM, Yokoyama Y. A systematic review and meta-analysis of changes in body weight in clinical trials of vegetarian diets. *J Acad Nutr Diet*. 2015;115:954-969.
29. Yokoyama Y, Levin SM, Barnard ND. Association between plant-based diets and plasma lipids: a systematic review and meta-analysis. *Nutr Rev*. 2017;75:683-698.
30. Yokoyama Y, Nishimura K, Barnard ND, Takegami M, Watanabe M, Sekikawa A, et al. Vegetarian Diets and Blood Pressure: A Meta-analysis. *JAMA Intern Med*. 2014;174:577-587.
31. Secrest AM, Becker DJ, Kelsey SF, LaPorte RE, Orchard TJ. Cause-Specific Mortality Trends in a Large Population-Based Cohort With Long-Standing Childhood-Onset Type 1 Diabetes. *Diabetes*. 2010;59:3216-3222.
32. Huxley RR, Peters SAE, Mishra GD, Woodward M. Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2015;3:198-206.
33. American Diabetes Association. Standards of medical care in diabetes-2014. *Diabetes Care*. 2014;37:S14-80.
34. Ray KK, Seshasai SRK, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet Lond Engl*. 2009;373:1765-1772.
35. Mannucci E, Monami M, Lamanna C, Gori F, Marchionni N. Prevention of cardiovascular disease through glycemic control in type 2 diabetes: a meta-analysis of randomized clinical trials. *Nutr Metab Cardiovasc Dis NMCD*. 2009;19:604-612.
36. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia*. 2009;52:2288-2298.
37. Yokoyama Y, Barnard ND, Levin SM, Watanabe M. Vegetarian diets and glycemic control in diabetes: a systematic review and meta-analysis. *Cardiovasc Diagn Ther*. 2014;4:373-382.

38. Soroka N, Silverberg DS, Gremland M, Birk Y, Blum M, Peer G, et al. Comparison of a vegetable-based (soya) and an animal-based low-protein diet in predialysis chronic renal failure patients. *Nephron*. 1998;79:173-180.
39. de Mello VDF, Zelmanovitz T, Perassolo MS, Azevedo MJ, Gross JL. Withdrawal of red meat from the usual diet reduces albuminuria and improves serum fatty acid profile in type 2 diabetes patients with macroalbuminuria. *Am J Clin Nutr*. 2006;83:1032-1038.
40. Barsotti G, Navalesi R, Giampietro O, Ciardella F, Morelli E, Cupisti A, et al. Effects of a vegetarian, supplemented diet on renal function, proteinuria, and glucose metabolism in patients with "overt" diabetic nephropathy and renal insufficiency. *Contrib Nephrol*. 1988;65:87-94.
41. Jibani MM, Bloodworth LL, Foden E, Griffiths KD, Galpin OP. Predominantly vegetarian diet in patients with incipient and early clinical diabetic nephropathy: effects on albumin excretion rate and nutritional status. *Diabet Med*. 1991;8:949-953.
42. Azadbakht L, Atabak S, Esmailzadeh A. Soy protein intake, cardiorenal indices, and C-reactive protein in type 2 diabetes with nephropathy: a longitudinal randomized clinical trial. *Diabetes Care*. 2008;31:648-654.
43. Deli G, Bosnyak E, Pusch G, Komoly S, Feher G. Diabetic neuropathies: diagnosis and management. *Neuroendocrinology*. 2013;98:267-280.
44. Boulton AJM, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care*. 2005;28:956-962.
45. Alleman CJM, Westerhout KY, Hensen M, Chambers C, Stoker M, Long S, et al. Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: A review of the literature. *Diabetes Res Clin Pract*. 2015;109:215-225.
46. Lam T, Burns K, Dennis M, Cheung NW, Gunton JE. Assessment of cardiovascular risk in diabetes: Risk scores and provocative testing. *World J Diabetes*. 2015;6:634-641.
47. Bunner AE, Wells CL, Gonzales J, Agarwal U, Bayat E, Barnard ND. A dietary intervention for chronic diabetic neuropathy pain: a randomized controlled pilot study. *Nutr Diabetes*. 2015;5:e158.
48. Crane MG. Regression of diabetic neuropathy with total vegetarian (vegan) diet. *J Nutr Med*. 1994;4:431-439.
49. Smith AG, Russell J, Feldman EL, Goldstein J, Peltier A, Smith S, et al. Lifestyle intervention for pre-diabetic neuropathy. *Diabetes Care*. 2006;29:1294-1299.
50. McCarty MF. Favorable impact of a vegan diet with exercise on hemorheology: implications for control of diabetic neuropathy. *Med Hypotheses*. 2002;58:476-486.
51. Livingstone SJ, Looker HC, Hothersall EJ, Wild SH, Lindsay RS, Chalmers J, et al. Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish registry linkage study. *PLoS Med*. 2012;9:e1001321.
52. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson AM, Miftaraj M, et al. Range of Risk Factor Levels: Control, Mortality, and Cardiovascular Outcomes in Type 1 Diabetes Mellitus. *Circulation*. 2017;135:1522-1531.
53. Ornish D, Scherwitz LW, Billings JH, Brown SE, Gould KL, Merritt TA, et al. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA J Am Med Assoc*. 1998;280:2001-2007.
54. Ornish D, Brown SE, Scherwitz LW, Billings JH, Armstrong WT, Ports TA, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. *Lancet*. 1990;336:129-133.
55. Esselstyn CB Jr. Updating a 12-year experience with arrest and reversal therapy for coronary heart disease (an overdue requiem for palliative cardiology). *Am J Cardiol*. 1999;84:339-341.
56. Daubenmier JJ, Weidner G, Sumner MD, Mendell N, Merritt-Worden T, Studley J, et al. The contribution of changes in diet, exercise, and stress management to changes in coronary risk in women and men in the multisite cardiac lifestyle intervention program. *Ann Behav Med Publ Soc Behav Med*. 2007;33:57-68.
57. Frattaroli J, Weidner G, Merritt-Worden TA, Frenda S, Ornish D. Angina pectoris and atherosclerotic risk factors in the multisite cardiac lifestyle intervention program. *Am J Cardiol*. 2008;101:911-918.
58. Kwok CS, Umar S, Myint PK, Mamas MA, Loke YK. Vegetarian diet, Seventh Day Adventists and risk of cardiovascular mortality: a systematic review and meta-analysis. *Int J Cardiol*. 2014;176:680-686.
59. Schepers J, Annemans L. The potential health and economic effects of plant-based food patterns in Belgium and the United Kingdom. *Nutrition*. 2018;48:24-32.
60. Barnard ND, Scherwitz LW, Ornish D. Adherence and Acceptability of a Low-Fat, Vegetarian Diet Among Patients With Cardiac Disease. *J Cardiopulm Rehabil Prev*. 1992;12:423.
61. Barnard N, Scialli AR, Bertron P, Hurlock D, Edmonds K. Acceptability of a Therapeutic Low-Fat, Vegan Diet in Premenopausal Women. *J Nutr Educ*. 2000;32:314-319.
62. Barnard ND, Scialli AR, Turner-McGrievy G, Lanou AJ. Acceptability of a low-fat vegan diet compares favorably to a step II diet in a randomized, controlled trial. *J Cardpulm Rehabil*. 2004;24:229-235.
63. Barnard ND, Gloede L, Cohen J, Jenkins DJA, Turner-McGrievy G, Green AA, et al. A low-fat vegan diet elicits greater macronutrient changes, but is comparable in adherence and acceptability, compared with a more conventional diabetes diet among individuals with type 2 diabetes. *J Am Diet Assoc*. 2009;109:263-272.