Role of Bioactive Food Components in Diabetes Prevention: Effects on Beta-Cell Function and Preservation

Yoon Sin Oh¹,² and Hee-Sook Jun¹–³

¹Lee Gil Ya Cancer and Diabetes Institute, Gachon University, Incheon, Korea. ²Gachon Medical Research Institute, Gil Hospital, Incheon, Korea. ³College of Pharmacy and Gachon Institute of Pharmaceutical Science, Gachon University, Incheon, Korea.

ABSTRACT: Bioactive compounds found in fruits and vegetables can have anti-oxidant, anti-inflammatory, and anti-carcinogenic effects and can be protective against various diseases and metabolic disorders. These beneficial effects make them good candidates for the development of new functional foods with potential protective and preventive properties for type 1 and type 2 diabetes. This review summarizes the most relevant results concerning the effects of various bioactive compounds such as flavonoids, vitamins, and carotenoids on several aspects of beta-cell functionality. Studies using animal models with induced diabetes and diabetic patients support the hypothesis that bioactive compounds could ameliorate diabetic phenotypes. Published data suggest that there might be direct effects of bioactive compounds on enhancing insulin secretion and preventing beta-cell apoptosis, and some compounds might modulate beta-cell proliferation. Further research is needed to establish any clinical effects of these compounds.

KEYWORDS: nutritional bioactive compound, pancreatic beta-cell, insulin secretion, beta-cell preservation

CITATION: Oh and Jun. Role of Bioactive Food Components in Diabetes Prevention: Effects on Beta-Cell Function and Preservation. Nutrition and Metabolic Insights 2014:7 51–59 doi:10.4137/NMi.s13589.

Received: November 6, 2013. Resubmitted: April 21, 2014. Accepted for Publication: April 22, 2014.

Academic Editor: Joseph Zhou, Editor in Chief

Type: Review

Funding: This study was supported by grants from the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science, and Technology (No. 2010-0009378) and RAD program of MOTIE/KUIT.

Competing Interests: Authors disclose no potential conflicts of interest.

Copyright: © the authors, publisher and licensee Libertas Academica Limited. This is an open-access article distributed under the terms of the Creative Commons CC-BY-NC 3.0 License.

Correspondence: with72@gachon.ac.kr; hsjun@gachon.ac.kr

This paper was subject to independent, expert peer review by a minimum of two blind peer reviewers. All editorial decisions were made by the independent academic editor. All authors have provided signed confirmation of their compliance with ethical and legal obligations including (but not limited to) use of any copyrighted material, compliance with ICMJE authorship and competing interests disclosure guidelines and, where applicable, compliance with legal and ethical guidelines on human and animal research participants.

Introduction

It is generally accepted that food can have health-promoting properties that go beyond its traditional nutritional value. Bioactive compounds are defined as components of food that influence physiological or cellular activities in the animals or humans that consume them. For example, flavonoids, vitamins, and carotenoids are bioactive compounds found in fruits and vegetables that act as anti-oxidants, anti-inflammatory, anti-carcinogens, and protective agents against metabolic syndromes such as diabetes and coronary disease.¹,² Recently, much attention has been given to bioactive food components that may be beneficial for the prevention of diabetes.

The prevalence of type 2 diabetes and metabolic disease is rapidly increasing worldwide³ and is becoming an important health problem. In type 2 diabetes, pancreatic beta-cells fail to compensate for insulin resistance, resulting in the development of hyperglycemia, loss of functional beta-cell mass, and subsequently deficiency of insulin.⁴ In type 1 diabetes, destruction of pancreatic beta-cells mediated by autoimmune responses results in absolute insulin deficiency and development of hyperglycemia (Fig. 1). Thus, research to discover novel and cost-effective preventative agents that can enhance beta-cell function is important to decrease the development of both type 1 and type 2 diabetes and their related complications.

As the pancreas is located first in line after enteric absorption, the pancreas could be exposed to high concentrations of absorbed bioactive compounds. Therefore, pancreatic beta-cells might be one of the major targets for the effects of bioactive compounds. This review discusses the most relevant results concerning the effects of flavonoids, vitamins, and...
carotenoids on prevention of diabetes, focusing on beta-cell function and beta-cell preservation (Tables 1 and 2).

**Methods**
A computerized search of the “MEDLINE/Pubmed” database from January 1995 to January 2014 for English-language publications was conducted using the following combinations of key word: “bioactive component or food compound or nutrients (genistein, resveratrol, anthocyanins, quercetin, EGCG, vitamin D, vitamin A, vitamin C, lycopene)” and “insulin secretion or beta-cell function or beta-cell preservation, diabetes (type 1 & 2) or metabolic syndrome, or insulin resistance. We excluded letters, abstracts, and conference proceedings that were not published in full in peer-reviewed journals. Their titles and abstracts were then reviewed to select those papers dealing with the association between food component and beta-cell preservation.

For questions correlating diabetes with responses to food components, we included any articles that pertained to the effect of bioactive food components on beta-cell function using cell culture, and presented research on diabetic animal models. We also identified studies that assessed the effect of bioactive food component on beta-cell preservation, ie proliferative and anti-apoptotic effects. To evaluate the effect on humans, we summarize all relevant reviews such as cohort/case–control studies, randomized clinical trials, controlled clinical trials, and systemic reviews.

**Effect of Flavonoids on Beta-Cells**
Flavonoids and isoflavonoids are polyphenolic compounds commonly found in fruits and plants. They fulfill many roles in plant physiology, including nitrogen fixation and flower pigmentation. Because of their abundance, they make up a significant proportion of the human diet. Flavonoids are antioxidants and have anti-inflammatory and protective effects on metabolic diseases.

**Genistein.** Genistein is the most studied isoflavone with respect to diabetes. Genistein is found in a number of plants including lupine, fava beans, soybeans, and soybean products.

**In vitro studies.** Ohno et al demonstrated that genistein increased glucose-stimulated insulin secretion in MIN-6 cells, a mouse pancreatic beta-cell line, as well as in cultured islets from mice and rats. Although a high concentration (100 μmol/L) of genistein inhibited insulin secretion in rat islets, acute genistein treatment at a physiological concentration (5 μmol/L) potentiated glucose-stimulated insulin secretion in both beta-cell lines and isolated mouse islets.
Several flavonoids including genistein are known to modulate cell proliferation as well as beta-cell apoptosis. Although chronic treatment (four days) with a high concentration (100 µmol/L) of genistein reduced proliferation of cultured islet cells, acute treatment (24 hours) with a lower concentration (5 µmol/L) induced proliferation of both INS-1 cells, a rat beta-cell line, and human islets. Similarly, a low dose of genistein reduced sodium fluoride-induced beta-cell apoptosis, whereas a high dose of genistein caused apoptosis. Genistein has well-known weak estrogenic effects by binding to estrogen receptors. However, in pancreatic cell lines and mouse islets, the insulin-secreting activity and proliferative effect of genistein is mediated at least in part via cAMP accumulation and protein kinase A activation and is independent of estrogen receptor mechanisms, protein tyrosine kinase, or nitric oxide-signaling pathways.

Animal studies. Consistent with in vitro results, soy protein containing genistein and daidzein, another isoflavone present in soy, suppressed blood glucose levels in non-obese diabetic mice by inducing plasma insulin levels. Another study showed that chronic consumption of high fat increased insulin secretion with an increase in pancreatic islet area and consumption of soy protein ameliorated this situation in rats. The study also demonstrated that soy isoflavones decreased peroxisome proliferator-activated receptor-γ and sterol regulatory element binding protein-1 expression, which are markers of lipogenesis, and ameliorated the hyperinsulinemia observed during obesity. Consumption of a genistein-supplemented
diet (250 mg/kg diet) before the induction of diabetes by streptozotocin (STZ) preserved the islet mass because of enhanced proliferation and reduced apoptosis relative to the control mice.11 This study showed that genistein prevented STZ-induced rises in fasting blood glucose and improved glucose tolerance and circulating insulin levels. Elmarakby et al also demonstrated that administration of genistein at 10 mg/kg/body weight for 10 weeks in STZ-induced diabetic mice resulted in significant reductions in fasting blood glucose levels.14

Human studies. As human studies using genistein alone to test its anti-diabetic efficacy are scarce, whether it can be used to prevent or ameliorate type 2 diabetes in humans is largely unknown. However, data from a recent human study examining the effect of genistein administration in postmenopausal women showed that genistein administration at 54 mg/day decreased fasting glucose and increased glucose tolerance and insulin sensitivity.15 As discussed above, data from animal models and in vitro studies suggest that genistein may be a novel anti-diabetic compound.

Resveratrol. Resveratrol (3,5,4’-trihydroxystilbene) is a polyphenolic compound found in grape skins and red wine that has been shown to increase lifespan in various organisms.16 In vitro studies. Resveratrol shows beneficial effects for the prevention of diabetes and diabetic complications, but its effect on insulin secretion in vitro is controversial. Zhang et al reported that a range of concentrations (3–100 µmol/L) of resveratrol had no effect on insulin secretion in RINm5F cells.17 On the other hand, resveratrol induced insulin secretion at the tested concentrations (10–100 µmol/L) in other cell lines (hamster-derived HIT-T15 cells and rat-derived RINm5F cells) as well as in INS-1 cells.18 In contrast, treatment with resveratrol (1–100 µmol/L) inhibited glucose-stimulated insulin secretion in pancreatic islets from normal rats.19 A protective action of resveratrol on the pancreas has also been reported. Exposure of isolated rat islets to cytokines resulted in deleterious effects, such as increased nitric oxide production and increased DNA binding of nuclear factor-κB, and these effects were suppressed by resveratrol.20 The effect of resveratrol on insulin secretion was dependent on concentration, tested cell lines, and experimental designs. However, the anti-oxidant effect on various toxic agents was consistent; resveratrol was able to attenuate cytokine-induced toxicity and effectively reduce oxidative damage of the pancreas, and thereby may protect beta-cell function.

Animal studies. In animal studies, the effect of resveratrol on modifying insulin secretion is different depending on the animal model. In normal mice and rats, administration of resveratrol (3 mg/kg) increased plasma insulin levels and reduced blood glucose.21 On the other hand, in STZ/ nicotinamide-treated diabetic mice, an animal model with moderate hyperglycemia, resveratrol was shown to reduce plasma insulin levels, likely as a result of the reduction of hyperglycemia. Therefore, the researchers suggested that the anti-hyperglycemic effect of resveratrol may be because of its anti-oxidant effects on other tissues, not to a direct effect on insulin secretion.21 Although the exact mechanism of resveratrol action is still poorly understood, there is no doubt that this compound is able to improve insulin action in different animal models of insulin resistance.

Human studies. Most human studies demonstrate that resveratrol improves glucose tolerance and insulin sensitivity.

---

Table 2. List of bioactive food components that may influence insulin secretion and diabetes.

| CLASS     | BIOACTIVE COMPONENT | DIETARY SOURCES | EFFECT OBSERVED |
|-----------|---------------------|-----------------|-----------------|
| Flavonoids| Genistein           | Soybean, soy products | Insulin secretion ↑ |
|           |                     |                  | Beta-cell proliferation ↑ |
|           |                     |                  | Beta-cell apoptosis ↓ |
|           | Resveratrol         | Grapes, red wine | Insulin secretion ↔ |
|           |                     |                  | Beta-cell apoptosis ↓ |
|           | Anthocyanins & Anthocyanidins | Fruit, vegetables | Insulin secretion ↑ |
|           |                     |                  | Beta-cell apoptosis ↓ |
|           | Quercetin           | Fruit, vegetables | Insulin secretion ↑ |
|           |                     |                  | Beta-cell apoptosis ↓ |
|           | Epigallocatechin-3-gallate (EGCG) | Green tea | Insulin secretion ↑ |
|           |                     |                  | Beta-cell apoptosis ↓ |
| Vitamins  | Vitamin D           | Dairy products, fish | Insulin secretion ↑ |
|           |                     |                  | Beta-cell apoptosis ↔ |
|           | Vitamin A           | Vegetables       | Insulin secretion ↔ |
|           | Vitamin C           | Vegetables, fruits | Insulin secretion ↑ |
| Carotenoids| Lycopene           | Tomatoes         | –                |
In a pilot study in obese insulin-resistant adults, Crandall et al found that after four weeks of resveratrol treatment, peak postprandial glucose decreased and glucose tolerance improved, but the effects were not dose-dependent. Bhatt et al conducted a randomized trial with type 2 diabetic subjects and found significant improvements in the resveratrol group for fasting blood glucose, HbA1c, total cholesterol, triglyceride, and low density lipoprotein concentrations. Another study of type 2 diabetic patients (according to the WHO diagnostic guidelines) also demonstrated that daily ingestion of 10 mg resveratrol decreased insulin resistance, and this effect was because of a decrease of oxidative stress and improvement of insulin signaling via the AKT pathway.

**Anthocyanins and anthocyanidins.** Anthocyanins and anthocyanidins are responsible for a variety of colors, including red, blue, and purple, in fruits, vegetables, and flowers and are prevalent in the human diet.

**In vitro studies.** Studies have shown that anthocyanins and anthocyanidins stimulate insulin secretion and have protective effects on beta-cells in vitro. Several of these molecules were shown to be effective insulin secretagogues when tested in pancreatic cell lines. Among the anthocyanidins tested, pelargonidin was the most effective. As well, the anthocyanidin cyanidin-3-glucoside stimulated insulin secretion in INS-1 cells and pancreatic and duodenal homeobox-1 and insulin-like growth factor-II gene transcript levels, which are important factors for insulin gene transcription. Zhang et al reported that pre-incubation of INS-1 cells with anthocyanins decreased the generation of oxidative-stress-induced intracellular reactive oxygen species and reduced reactive oxygen species-mediated apoptosis and necrosis. As well, pretreatment with anthocyanins attenuated autophagic cell death caused by H2O2 exposure.

**Animal studies.** Administration of cyanidin-3-glucoside-rich bayberry fruit extract reduced blood glucose levels in STZ-induced diabetic ICR mice and improved impaired glucose tolerance. As well, the administration of ethanolic extract of cherry fruit resulted in a significant reduction in blood glucose in alloxan-induced diabetic rats. In a study using male STZ-induced diabetic Wistar rats, intraperitoneal injection of pelargonidin, an anthocyanin, normalized elevated glycemia and improved serum insulin levels. In a type 2 diabetes mutant mouse (KK-Ay) model, intake of anthocyanins was found to inhibit elevation of blood glucose levels and improve insulin sensitivity via down-regulation of retinol-binding protein.

**Human studies.** Wedick and coworkers followed a total 3,645,585 women and men who were free from diabetes, cardiovascular disease, and cancer at the beginning of the study. They found 12,611 subsequent cases of type 2 diabetes, and consumption of anthocyanin-rich foods, particularly blueberries and apples or pears, was associated with a lower risk of type 2 diabetes. No significant associations were found for total flavonoid intake or other flavonoid subclasses. Diabetic patients who consumed pomegranate juice (384 mg/dL anthocyanins) exhibited anti-oxidative effects such as a significant reduction in their serum lipid peroxides and the oxidative state of their monocytes/macrophages by 56% and 28%, respectively. These findings indicate a substantial benefit to diabetes patients would be obtained by developing a functional food containing anthocyanin extracts.

**Quercetin.** Quercetin is a natural polyphenolic flavonoid found in a wide variety of plant-based foods, which displays anti-diabetic properties in vivo.

**In vitro studies.** Hii and Howell reported that quercetin stimulated insulin release and enhanced Ca2+ uptake from isolated islet cells. Youl et al also showed that 20 μmol/L of quercetin potentiated insulin secretion in INS-1 cells induced by various secretagogues such as glucose, glibenclamide, or KCl. In this study, quercetin also protected beta-cell function and viability from H2O2-induced oxidative damage, and both effects were mediated via phosphorylation of extracellular signal-regulated kinase (ERK)1/2, suggesting that ERK1/2 activation is involved in the actions of quercetin.

Cytokines such as interleukin (IL)-1β induce the expression of inducible nitric oxide synthase and production of nitric oxide in islet β-cells, which leads to β-cell injury and reduced insulin secretion. Quercetin (10 μM) reduced IL-1β-induced nitrite production, levels of inducible nitric oxide synthase protein, and IκBα phosphorylation. Additionally, quercetin significantly reversed the inhibition of insulin secretion by IL-1β.

**Animal studies.** Quercetin has beneficial effects in animal models of type 1 diabetes. Vessal et al reported that quercetin brought about the regeneration of pancreatic islets and increased insulin release in STZ-induced diabetic rats. A similar effect was observed by Coskun et al— injection of quercetin (15 mg/kg/day) before induction of diabetes by STZ-treatment reduced the detrimental effect of STZ on plasma insulin and glucose levels. Similarly, rutin, a glycosidic form of quercetin, ameliorated the decrease in fasting plasma insulin levels induced by STZ-treatment in rats, whereas it had no effect in normal rats when administered at 100 mg/kg for 45 days. It also reduced pancreatic concentrations of thiobarbituric acid-reactive substances and lipid hydroperoxides and increased the activities of anti-oxidant enzymes. These results suggest that the anti-oxidative activities of quercetin may protect pancreatic beta-cells from damage by decreasing oxidative stress induced by hyperglycemia, fatty acids, and cytokines.

**Human studies.** Little information has been reported concerning the anti-diabetic effect of quercetin in humans. In a randomized, blinded crossover study, a single oral dose of quercetin (400 mg) effectively suppressed postprandial hyperglycemia in patients with type 2 diabetes. Moreover, a pilot study showed that QR-333, a topical compound that contains quercetin, safely induced relief from symptoms of diabetic neuropathy and improved quality of life.
Epigallocatechin-3-gallate (EGCG). EGCG is a polyphenolic compound found mostly in green tea. EGCG may have health benefits as a nutritional supplement for various diseases. Although the biological effects of EGCG are generally attributed to its anti-oxidant activity of scavenging oxygen free radicals as well as its anti-tumor and anti-mutagenic activities, the anti-oxidant effect of EGCG is disputed.

In vitro studies. The addition of EGCG protects against cytokine- and glucose-induced toxicity. Han reported that EGCG protected against cytokine-induced cell death in RINm5F cells. This effect was dose-dependent and was mediated by the down-regulation of inducible nitric oxide synthase expression through the inhibition of nuclear factor-xB activation. EGCG also protected against the suppression of insulin secretion induced by exposure to a high glucose concentration in RINm5F cells. In contrast, Suh et al reported that treatment of HIT-T15 cells with EGCG (5–100 µM) decreased cell viability and increased apoptotic cell death concomitant with the production of H2O2 and reactive oxygen species.

Animal studies. Animal studies suggest that EGCG may help to prevent the development of diabetes, although the evidence is not unanimous. Song et al reported that EGCG prevented autoimmune diabetes in mice induced by multiple low doses of STZ. EGCG enhanced oral glucose tolerance in severely diabetic mice and in moderately diabetic rats, suggesting that an increase in glucose-induced insulin secretion contributes to the anti-diabetic effect of EGCG. In contrast, EGCG showed a pro-oxidant, rather than anti-oxidant, effect in STZ-induced diabetic rats as was the case in the HIT-T15 cell line. When administrated for four days (5 mg/kg/day), EGCG impaired insulin secretion provoked by high glucose loading. In normal rats, EGCG had no effect on insulin secretion.

Human studies. Whereas some studies have demonstrated a potential anti-diabetic effect of green tea in healthy subjects, other studies revealed that green tea or EGCG had no significant effect in diabetic patients. Tsuneki et al found that in healthy Japanese subjects, an acute, high dose of EGCG-concentrated green tea supplement could control postprandial hyperglycemia, thus potentially reducing the risk for diabetes. However, in a long-term study performed by Mackenzie et al, type 2 diabetic adults who consumed green tea extract did not exhibit a hypoglycemic effect.

Effect of Vitamins on Beta-Cells

Vitamins are organic compounds that cannot be synthesized by an organism and so must be obtained in the diet. They have diverse chemical structures and biochemical functions. Some vitamins such as vitamin A, vitamin D, and vitamin C are known to play a role in beta-cell function, growth, and development.

Vitamin D. Vitamin D is a group of essential steroid hormones that are synthesized from exposure to sunlight and are also absorbed from foods. The best food sources include fatty fish and their liver oils, and eggs, and fortified foods. Although vitamin D’s role in islet physiology has yet to be clarified, several studies have revealed a role for vitamin D in pancreatic beta-cell function.

In vitro studies. Although the exact mechanisms for the action of vitamin D on beta-cells are not yet fully understood, it is likely that vitamin D has beneficial roles for beta-cell function. Bourlon et al showed that the insulin response of rat islets to high glucose was decreased by vitamin D3 deficiency and improved by treatment with 1,25(OH)2D3. Administration of a high concentration of 1,25(OH)2D3 increased insulin synthesis and release in isolated neonatal islets from normal animals. The effect of vitamin D on protecting beta-cells from apoptosis is controversial. Induction of beta-cell apoptosis induced by IL-1β or interferon-γ in vitro was prevented by 1,25(OH)2D3 and its analogs, MC903, and KH1060. In contrast, Palomer et al observed no effects of 1,25(OH)2D3 on IL-1β-induced beta-cell dysfunction. Bouillon et al did not observe direct protection by 1,25(OH)2D3 against cytokine-induced beta-cell death in various cell systems (whole rat islet, FACS-purified beta-cells, and INS-1 cells), but demonstrated decreased expression of chemokines by beta-cells treated with 1,25(OH)2D3.

Animal studies. Cade and Norman reported that vitamin D3 improved impaired glucose tolerance and insulin secretion in the vitamin D-deficient rat. Moreover, studies using vitamin D receptor-null mice showed impaired insulin secretion and glucose intolerance. Pretreatment with calcitriol, a hormonally active form of vitamin D, significantly improved glucose challenge-induced insulin secretion in islets isolated from normal mice. These direct effect of vitamin D on insulin secretion may be mediated by binding of its circulating active form, 1,25-OHD, to the beta-cell vitamin D receptor. There are also studies regarding the indirect effects of vitamin D on beta-cell function via its well-recognized role in regulating extracellular calcium and calcium influx. Beaulieu et al showed that calcium repletion normalized glucose tolerance and insulin secretion in vitamin D-depleted rats.

Human studies. Several studies have described a correlation between vitamin D deficiency and the incidence of diabetes. A recent cohort study showed that higher baseline serum 25(OH)D levels are associated with better beta-cell function. A case–control study also showed an association between vitamin D supplementation in infancy and decreased risk of type 1 diabetes. Studies on the administration of vitamin D supplementation or higher doses of 1,25(OH)2D3 to vitamin D-deficient patient with type 2 diabetes improved glucose tolerance and beta-cell function.

Vitamin A. Vitamin A or retinol is an essential dietary nutrient that is required for normal growth, reproduction, and vision. Root vegetables and greens, such as squash, carrots, pumpkins, collards, and beet greens, are good sources of vitamin A. Intracellularly, vitamin A is converted to all-trans-retinoic acid, 9-cis-retinoic acid, and a variety of other active metabolites.

In vitro studies. The effects of vitamin A on insulin secretion are dependent on its metabolites. Chertow et al showed...
that all-trans-retinoic acid (1000 nM) increased insulin secretion and insulin content of RINm5F cells, while inhibiting growth and increasing apoptosis. 65 However, 9-cis-retinoic acid, another active metabolite of vitamin A, reduced glucose-stimulated insulin secretion in mouse islets and in a rat beta-cell line (832/13) by reducing glucose transporter-2 and glucokinase activities. 66

Animal studies. Vitamin A is essential for pancreas development, islet formation, and function. 67,68 Vitamin A restriction during development impairs islet development and promotes glucose intolerance in adult rodents. 68 On the other hand, restricting vitamin A in mature diabetes-prone rats reduced diabetes and insulin. 69 There is controversy about the effectiveness of vitamin A for treating diabetes. A diet rich in vitamin A lowered blood glucose levels in non-obese diabetic mice, but in STZ-induced diabetic rats, a 12-fold increase in vitamin A intake did not show any effect on the degree of hyperglycemia or glycosuria. 70

Vitamin C. Vitamin C (ascorbic acid), an anti-oxidant vitamin, is widely distributed in fresh fruits and vegetables and plays an important role in protecting against free radical-induced damage. Most plants and animals, with the exception of humans, synthesize vitamin C from D-glucose or D-galactose. As glucose and ascorbic acid are structurally similar, transport and accumulation of ascorbic acid in pancreatic beta-cells is considered to affect glucose-induced insulin secretion.

In vitro studies. Kaplan et al found that the number of alpha- and beta-cells was increased after vitamin C supplementation (500 mg/kg). 71 However, a high dose of vitamin C (>200 µM) inhibited insulin secretion in rat islets, and the inhibition was dose-dependent. 72 The role of ascorbic acid in pancreatic beta-cells is not clear yet, but appropriate concentrations of vitamin C may have beneficial effects on beta-cells.

Animal studies. Some reports indicate lower levels of ascorbic acid in the plasma of diabetic patients and experimental diabetic animal models. 73,74 Wells et al reported that insulin release was depressed in islets from vitamin C-deficient guinea pigs and enhanced by the addition of ascorbic acid 2-phosphate. 75

Human studies. In contrast to the results from in vitro studies, a high dose of vitamin C supplementation may have a beneficial effect in type 2 diabetic subjects. Paolisso et al reported that after infusion of a high dose of vitamin C (0.9 µmol/minute) in type 2 diabetic patients, there was an increase in plasma vitamin C levels and whole body glucose disposal was increased. 76 A randomized double-blind study also demonstrated that ascorbic acid supplementation improved glycemic control among type 2 diabetic subjects and both fasting blood glucose and HbA1c levels improved. 77

Effect of Carotenoids on Beta-Cells
Carotenoids are compounds found in the chloroplasts of plants and also in algae and some fungi and bacteria. They are responsible for the yellow or orange color of plants and are important for human health.

Lycopene. Lycopene, a powerful anti-oxidant carotenoid compound occurring naturally in tomatoes and pink grapefruit, is known for its health-promoting role in the prevention of chronic diseases such as cancer and cardiovascular disease. Although the effects of lycopene have been established in various disorders, little attention has been given to the possible anti-diabetic effects of lycopene on beta-cells.

Animal studies. Ali and Agha demonstrated that exogenous administration of 90 mg/kg lycopene to STZ-induced hyperglycemic rats caused a decrease in glucose levels with an increase in insulin concentration, and the effect was through lowering the free radical activity. 78

Human studies. An observational study showed that a high consumption of lycopene did not reduce the risk of developing type 2 diabetes. 79 However, very little is known about lycopene-rich diets and the incidence of diabetes; future research will be needed.

Summary
The great diversity of flavonoids, vitamins, and carotenoids makes it difficult to establish their effects on beta-cell function in the pancreas. Moreover, the effects depend on experimental design, tested concentrations, and the specific structure of the compound. Studies using animal models with induced diabetes support the hypothesis that bioactive compounds could ameliorate diabetic phenotypes. Published data suggest that there might be direct effects of bioactive compounds on enhancing insulin secretion and preventing beta-cell apoptosis, and some compounds might modulate beta-cell proliferation. For some compounds, the mechanisms of action involve their anti-oxidant properties, although other pathways might also be involved. Although many studies report beneficial effects on beta-cells, further studies are needed to confirm these effects in an actual clinical setting outside the laboratory.

Conclusion
Much evidence exists that flavonoids, such as genistein, anthocyanins, quercetin, and EGCG, and vitamins, such as vitamin D and C, enhance beta-cell function, lead to glucose tolerance in animal models and humans, and protect against diabetes. The availability of structural analogs of these components opens new perspectives for the exploitation of these interesting properties in humans. Carefully designed intervention studies using these components and their analogs, either alone or in combination, will determine their clinical potential in diabetes prevention.

Acknowledgments
We thank Dr. Ann Kyle for editorial assistance.

Author Contributions
Conceived and designed the experiments: YSO and HSJ. Analyzed the data: YSO and HSJ. Wrote the first draft of the manuscript: YSO. Contributed to the writing of the manuscript: YSO and HSJ. Agree with manuscript results

REFERENCES

1. Kris-Etherton PM, Heckler KD, Bonanome A, et al. Bioactive compounds in foods: their role in the prevention of cardiovascular disease and cancer. Am J Med. 2002;113(suppl 9B):71S–88S.

2. Kris-Etherton PM, Lefevre M, Beecher GR, Gross MD, Keen CL, Etherton TD. Bioactive compounds in nutrition and health-research methodologies for establishing biology, J. function: the antioxidant and anti-inflammatory effects of flavonoids on atherosclerosis. Annu Rev Nutr. 2004;24:511–538.

3. Kahn SE, Hull RL, Utschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006;444(7112):840–846.

4. Karaca M, Magnan C, Kargar C. Functional pancreatic beta-cell mass: involvement in type 2 diabetes and therapeutic intervention. Diabetes Metab. 2009;35(2):77–82.

5. Gilbert ER, Liu D. Anti-diabetic functions of soy isoflavone genistein: mechanisms underlying its effects on pancreatic beta-cell function. Food Funct. 2013;4(2):200–212.

6. Ohno T, Kato N, Ishii C, et al. Genistein augments cyclic adenosine 3′-5′-monophosphate (cAMP) accumulation and insulin release in MIN6 cells. Endocr Res. 1993;19(4):273–285.

7. Persaud SJ, Harris TE, Burns CJ, Jones PM. Tyrosine kinases play a permissive role in glucose-induced insulin secretion from adult islets. J Mol Endocrinol. 1999;22(3):19–28.

8. Liu D, Zhen W, Yang C, Zander JD, Huh RE, Reynolds KA. Genistein acutely stimulates insulin secretion in pancreatic beta-cells through a cAMP-dependent protein kinase pathway. Diabetes. 2006;55(5):1043–1050.

9. Sorensen RL, Bolel TC, Rohl C. Effect of tyrosine kinase inhibitors on islets of Langerhans: evidence for tyrosine kinases in the regulation of insulin secretion. Endocrinology. 1994;134(4):1975–1978.

10. Elliott J, Scarpello JH, Morgan NG. Differential effects of genistein on apoptosis induced by fluoroide and pepsin in islets and pancreatic islets and adipocytes. J Agric Food Chem. 2002;50(21):5367–5372.

11. Fu Z, Zhang W, Zhen W, et al. Genistein induces pancreatic beta-cell proliferation through activation of multiple signaling pathways and prevents insulin-deficient diabetes in mice. Endocrinology. 2010;151(7):3026–3037.

12. Choi MS, Jung YU, Jeo KM, Kim JM, Lee MK. Genistein and daidzein prevent diabetes onset by elevating insulin level and altering hepatic gluconeogenic and lipogenic enzyme activities in non-obese diabetic (NOD) mice. Diabetas Metab Res Rev. 2008;24(1):74–81.

13. Noriega-López I, Tovar AR, González-Granillo M, et al. Pancreatic insulin secretion in rat fed a soy protein high fat diet depends on the interaction between the soy isoflavonoid pattern and isoflavones. J Biol Chem. 2007;282(28):20657–20666.

14. Elmarakby AA, Ibrahim AS, Faulkner J, Mozaffari MS, Liou GI, Abdelsayed R. Anti-diabetic functions of soy isoflavone genistein: mechanisms underlying its effects on pancreatic beta-cell function. J Nutr Biochem. 2007;18(2):137–143.

15. Fu Y, Zhang W, Zhen W, et al. Genistein induces pancreatic beta-cell proliferation through activation of multiple signaling pathways and prevents insulin-deficient diabetes in mice. Endocrinology. 2010;151(7):3026–3037.

16. Choi MS, Jung YU, Jeo KM, Kim JM, Lee MK. Genistein and daidzein prevent diabetes onset by elevating insulin level and altering hepatic gluconeogenic and lipogenic enzyme activities in non-obese diabetic (NOD) mice. Diabetas Metab Res Rev. 2008;24(1):74–81.

17. Borra MT, Smith BC, Denu JM. Mechanism of human SIRT1 activation by resveratrol. J Biol Chem. 2005;280(17):17187–17195.

18. Zhang Y, Jayaprakasam B, Seeram NP, Olson LK, Nanjan MJ. Resveratrol supplementation improves glycemic control in type 2 diabetes mellitus. Nutr Res. 2012;32(7):537–541.
64. Kumar S, Davies M, Zakaria Y, et al. Improvement in glucose tolerance and
65. Chertow BS, Gokinger NQ, Driscoll HK, Primerano DA, Matthews KA. Effects of all-trans-retinoic acid (ATRA) and retinoic acid receptor (RAR) expression on secretion, growth, and apoptosis of insulin-secreting RINm5F cells. Pancreas. 1997;15(2):122–131.
66. Kane MA, Follas AE, Pingitore A, et al. Identification of 9-cis-retinoic acid as a pancreas-specific autacoid that attenuates glucose-stimulated insulin secretion. Proc Natl Acad Sci U S A. 2010;107(50):21884–21889.
67. McCarroll JA, Phillips PA, Santucci N, Piorala RC, Wilson JS, Apte MV. Vitamin A inhibits pancreatic stellate cell activation: implications for treatment of pancreatic fibrosis. Gut. 2006;55(1):79–89.
68. Matthews KA, Rhoten WB, Driscoll HK, Chertow BS. Vitamin A deficiency impairs fetal islet development and causes subsequent glucose intolerance in adult rats. J Nutr. 2004;134(8):1958–1963.
69. Driscoll HK, Chertow BS, Jelic TM, et al. Vitamin A status affects the development of diabetes and insulin in BB rats. Metabolism. 1996;45(2):248–253.
70. Seifert E, Rettura G, Padawer J, Stratford F, Kambosos D, Levenson SM. Impaired wound healing in streptozotocin diabetes. Prevention by supplemental vitamin A. Ann Surg. 1981;194(1):42–50.
71. Kaplan B, Gounl B, Erdogan D, Elbeg S. Effects of limited food intake and vitamin C supplementation on pancreatic glucagon and insulin in guinea pigs. Eur J Histochem. 2007;51(2):137–144.
72. Bergsten P, Moura AS, Atwater I, Levine M. Ascorbic acid and insulin secretion in pancreatic islets. J Biol Chem. 1994;269(2):1044–1045.
73. Chen MS, Hutchinson ML, Pecoraro RE, Lee WY, Labbe RF. Hyperglycemia-induced intracellular depletion of ascorbic acid in human mononuclear leukocytes. Diabetes. 1983;32(11):1078–1081.
74. McLennan S, Yue DK, Fisher E, et al. Deficiency of ascorbic acid in experimental diabetes. Relationship with collagen and polyol pathway abnormalities. Diabetes. 1988;37(3):359–361.
75. Wells WW, Dou C, Dybas LN, Jung CH, Kalbach HL, Xu DP. Ascorbic acid is essential for the release of insulin from scurbutic pig pancreatic islets. Proc Natl Acad Sci U S A. 1995;92(25):11869–11873.
76. Paolisso G, D’Amore A, Balbi V, et al. Plasma vitamin C affects glucose homeostasis in healthy subjects and in non-insulin-dependent diabetics. Am J Physiol. 1994;266(2 pr 1):E261–E268.
77. Eriksson J, Kohvakka A. Magnesium and ascorbic acid supplementation in diabetes mellitus. Ann Nutr Metab. 1995;39(4):217–223.
78. Ali MM, Agha FG. Amelioration of streptozotocin-induced diabetes mellitus, oxidative stress and dyslipidemia in rats by tomato extract lycopene. Scand J Clin Lab Invest. 2009;69(9):371–379.
79. Wang L, Liu S, Manson JE, Gaziano JM, Buring JE, Sesso HD. The consumption of lycopene and tomato-based food products is not associated with the risk of type 2 diabetes in women. J Nutr. 2006;136(3):620–625.