Polyphenols and flavonoids in the prevention and treatment of diabetes type 2

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ABSTRACT

The genetic basis of diabetes is associated with genes that predispose to obesity development. There are also variants of genes that change the metabolism and distribution of glucose in the body tissues. Others regulate the lipid profile or affect insulin resistance, directly or indirectly affecting the risk of developing diabetes. Polyphenols are a group of compounds that have a protective effect on pancreatic cells. Thanks to their antioxidant activity, they protect cells against apoptosis, improve glucose metabolism and reduce hyperglycemia. The aim of the review was to discuss the mechanisms of bioactive food compounds influence on the human genome and to demonstrate their relationship between diabetes prevention and treatment.

Keywords: Diabetes, diet, food, polyphenols, flavonoids, genes, alleles

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INTRODUCTION

The number of people with *diabetes mellitus* has been rising in the past three decades. Currently this disease is the ninth major cause of death, worldwide. About 1 in 11 adults suffer for diabetes and 90% of them is diagnosed as type 2 (T2DM). Asia is a major area of the rapidly emerging T2DM, with China and India as two top epicentres [1]. In contrast, the percentage of Polish people with recognized diabetes in the years 2010–2014 was found to be 4.47% (± 0.09%) [2]. Type 2 diabetes is characterized by hyperglycemia and tissue resistance to insulin. The mechanism underlining disease development is a gradual deterioration of insulin sensitivity through a decrease in the number of insulin receptors, which in consequence leads to excessive insulin production. Environmental factors seems to be a key stimulus that, along with the influence of the genome, initiates an inflammatory process leading to the loss of pancreatic function associated with carbohydrate metabolism [1].

Thus, the purpose of this article was to present modulate properties of polyphenols and flavonoids on genetic mechanism underlying diabetes development and treatment.

GENETIC MECHANISM OF DIABETES DEVELOPMENT

At the moment, there are two mechanisms known to provide changes in the genome: histone acetylation and DNA methylation.

Histone proteins (H2A, H2B, H3, H4) are responsible for the spatial configuration of the deoxyribonucleic acid molecule. Histone acetylation leads to a reduction in the affinity of histones to the DNA strands, which results in the relaxation of spatial density and increases the transcriptional activity.

DNA methylation is closely related to genomic regions where a significant concentration of CpG dinucleotides occurs (*Cytosine - Phosphate - Guanosine*). This is where the methylation process takes place and reaction is catalysed by DNA-methyltransferases (DNMT 1, DNMT 2, DNMT 3L, DNMT3a, DNMT3b). The most important donor of methyl groups in the human body is S - adenosylmethionine (SAM). The - CH3 group is attached to the 5th carbon of the cytosine ring to form 5-methylcytosine, which by attaching to the larger collapse of the helix inhibits the transcription factors. A significant part of the CpG clusters is located in the promoter regions or near the first exons of the given gene [3].

Micro-RNA is a molecule consisting of a single strand of RNA and its role is to modify the expression of other genes. miRNA regulates inflammatory and insulin signalling processes. Both phenomena are directly related to insulin tissue resistance. The role of miRNA in the development of insulin resistance and T2DM has been investigated on various tissues (liver, fat, muscle and pancreas) as well as in humans and mice. In addition, miRNA microbubble transport can be a mechanism by which miRNAs act as local and systemic insulin resistance mediators. Studies indicate that miRNA 143-145 groups induce insulin resistance initiated by obesity. Mice that did not posses an active miRNA group 143-145 were protected from IR (*Insulin Resistance*) indicated via high caloric intake. On the other hand, the conditioned miRNA overexpression worsened the sensitivity of tissues to insulin. The mi -NA-7 family let-7 (miRNA family regulate cell differentiation and death processes) also participate in the regulation of insulin resistance. Mice fed a high-fat diet (HFD) with overexpression of let-7 miRNA showed impaired glucose tolerance and insulin resistance despite normal insulin secretion [4,5,6]. miRNA 375 is particularly important when it comes to regulation of blood glucose. It is produced in β-pancreatic cells and contributes to maintaining their viability and enhances insulin synthesis in mouse models with developed insulin resistance. In this respect, mice show increased expression of miRNA 375, and for those that have low miRNA 375 expression, low insulin synthesis and hyperglycaemia are observed [7].

PPAR-γ is a suppressor gene (*Peroxisome Proliferator-Activated Receptor*) that regulates the activity of genes affecting lipid metabolism and adipocyte differentiation. The lower incidence of the *PPAR* variant γ Ala12 reduced the risk of diabetes development via increase in insulin sensitivity [8]. Adiponectin (encoded by the *ADIPOQ* gene) is an important adipocytokine that is secreted by fat cells and plays an important role in inflammatory process associated with insulin resistance, and T2DM. The studies of the Asian population showed a correlation between SNP (*Single Nucleotide Polymorphism*) of *ADIPOQ* and T2DM [9]. In a prospective study of 673 patients with T2DM, significant dose-related interactions were identified between *ADIPOQ*rs 1501299G>T polymorphism and carbohydrate intake. This study proved the relationship between rs1501299 G>T polymorphism and the level of carbohydrate absorption, fasting glycemia, blood glucose level and glycated hemoglobin [10].

The MARINA clinical trial evaluated influence of n-3 PUFA intake and the risk of T2DM [11]. The IRS1 gene encodes the insulin receptor 1 (IRS1) substrate - a protein of central importance for insulin signaling pathways. Two genetic variants (rs7578326 and rs2943641) near IRS1 were identified in GWAS studies as related to T2DM. The occurrence of IRS1 variants of the

rs7578326G allele and rs2943641T was associated with the estimated lower IR risk and lower fasting insulin levels in two independent populations with different ancestors. Allele expression has been shown to be modulated by dietary factors, in particular the SFA/MUFA (*Saturated Fatty Acids/Monounsaturated Fatty Acids*) dietary ratio to the amount and quality of carbohydrates. In another study, the relationship between IRS1 rs2943641 and vitamin D level was also analyzed. Homozygous Portuguese carried the smaller rs2943641T allele with serum higher levels of vitamin D exhibited lower risk of IR and T2DM compared to those who carried the main allele [12, 13].

The *CAV2* gene encodes the protein components of caveolae. These are the dentures of the plasma membrane. The caveolae are important in the performance of many cellular functions, such as signal transduction, lipid metabolism, cell proliferation, apoptosis and differentiation. The study showed a significant relationship between *CAV2* polymorphism rs2270188 G>T, fat and SFA intake with respect to T2DM. Homozygous individuals of the rare T allele had a 100% higher risk of T2DM when daily fat intake increased from 30% to 40% of energy. What is more, an increase in SFA consumption from 10% to 20% of energy caused an about 200% higher risk of T2DM. Homozygotes with the G allele and heterozygotes did not show an increased risk of T2DM in response to increased fat intake or SFA [14].

The Obesity-Related gene (*FTO*) is found on chromosome 16 and contains nine exons. In fact, several SNPs of this gene have been associated with the risk of obesity. A meta-analysis of 62 case-control studies from different regions (including Asia, Europe and North America) showed that SNPs rs9939609 T>A and rs8050136 C>A in FTO contributed to an increased risk of T2DM [15].

A case-control study involving 3430 patients with T2DM and 3622 healthy subjects showed gene-diet interactions while the Mediterranean diet was incorporated in people with the FTO-rs9939609 variant. In addition, when using a diet deviating from the principles of the Mediterranean one, people with the *FTO* variant rs9939609 showed a higher risk of developing T2DM, while strictly adhering to the Mediterranean diet, there was no similar relationship [16].

The Perilipin gene (*PLIN*) regulates fat metabolism and is associated with many risk factors for diabetes, including obesity, weight gain and insulin resistance. Analysis of the interaction between variants of this gene and diet showed a relationship between the polymorphisms *PLIN* 11482 G>A and *PLIN* 14995 A>T with dietary fat and carbohydrate intake. A cross-sectional study among Asian women explored that homozygotes with lower A allele were shown to have increased insulin resistance when SFA intake was high and carbohydrate intake was low. These gene-lipid interactions were observed only for SFA, but not for MUFA or PUFA [17].

As presented above, food bioactive ingredients do not only provide energy and build cell structures but also act like signal molecules that affect metabolism pathways and expression of specific gene alleles. What is more, by modulation of gene expression, they cause production of specific RNA matrix proteins.

POLYPHENOLS

Polyphenols are a wide group of chemical compounds that are found in fruits, vegetables, nuts, legume seeds or chocolate. The major representatives of polyphenols are stilbenes (e.g. resveratrol). These substances may exert a hypoglycemic effect by lowering glucose use, its absorption or release. They stimulate β-pancreatic cells to enhance secretion of insulin and protect them against glucotoxicity or the phenomenon of reduced insulin secretion [18].

FLAVONOIDS

The flavonoid family includes flavones, flavonols, flavanones, isoflavones and antho-cyanins. Studies have shown that these compounds regulate metabolic /carbohydrate/ immune management through increased insulin secretion, increased glucose transport, inhibition of proinflammatory cytokine synthesis, and formation of reactive oxygen species. What is more, flavonoids have the ability to inhibit the enzymes alpha - glucosidase and alpha - amylase responsible for the metabolism of carbohydrates. Research carried out by NHS nurses (*Nurses' Health Study*) showed a relationship between the presence of flavonoids, flavonols, phenolic acid and coffee in the urine and a reduced risk of type 2 diabetes incidence [19].

EPIGALLOCATECHIN GALLATE

One of the most common flavanones is EGCG (*Epigallocatechin Gallate*). In rat studies, the connection of EGCG with metabolic processes has been demonstrated. EGCG caused an improvement in β-pancreatic cells insulin secretion, increased cell ability to adapt in conditions of glucotoxicity, enhanced insulin sensitivity, reduced oxidative stress, inflammatory processes and regulated the mitochondria metabolism. These effects were the result of increased signaling of the insulin receptor 2 substrate (IRS2) (*Insulin Receptor Substrate 2*). In addition, EGCG demon-

strates the ability to protect β-pancreatic cells against the proinflammatory action of cytokines by altering the expression of antiapoptotic protein BCL-2 (*B-cell lymphoma 2*). In humans, the lowering effect of catechins on postprandial blood glucose was observed, however, long-term consumption of catechnis did not affect fasting concentrations of glycated hemoglobin [20].

QUERCETIN

Quercetin is found in red wine, fruits and vegetables. The protective effect of quercetin consumption is related to the reduction of oxidative stress, which translates into better survival of β-pancreatic cells through inhibition of cell membranes lipid peroxidation, synthesis of nitric oxide (NO) and increased activity of antioxidant enzymes. Studies have shown that quercetin supplementation over a 2 week period in mice with induced diabetes was resulted in: low blood glucose, increased insulin secretion, and increased cyclin dependent kinase inhibitor 1A (CDKN1A). In a further study in mice after quercetin supplementation, a reduction in oxidative stress levels as well as a decrease in the concentration of inflammatory markers such as interferon gamma (INF-γ), alpha (INF-α), and interleukin 4 (IL-4) were observed. Obese rats supplemented with quercetin were shown to have increased parameters of dyslipidemia, hypertension and hyperinsulinemia, interestingly similar to study carried out on mice, after higher doses of quercetin incorporation the reduction in oxidative stress parameters was noted [21,22].

FLAVONES

Other compounds classified as flavones (apigenin, luteoin) showed hypoglycemic effects, which is related to protective properties against glucotoxicity, increased tissues resistance caused by long-lasting high blood glucose levels. Moreover, quercetin along with apigenin and luteoin, protected pancreatic cells RINmF5 against cytokine-induced destruction. This mechanism was based on the nitric oxide II synthase gene inhibition, consequently eliminating the action of IL-1β and INF-γ (preventing the reduction of insulin secretion) [23].

Other flavones that have a significant gene impact are daidzein and genistein, which can be found in soybeans and other legumes. Rats with induced obesity, fed with a high content of daidzein and genistein were characterized by increased secretion of insulin, decreased expression of PPAR-γ, GLUT-2 (*Glucose Transporter 2*), SREBP-1 (*Sterol Regulatory Element-Binding Transcription Factor 1*) and hyperinsulinemia [24]. In diabetic-induced mice, increased genistein supply significantly improved glucose concentrations, glucose tolerance, and also retained the function of β-pancreatic Langerhans cells [25].

The narginine and hesperidin belongs to the flavonones and also have a preventive effect in the development of T2DM. These compounds were shown to decrease glucose and lipid levels, and thus improve the lipid profile by downregulation the expression of genes responsible for glucose metabolism. In the mouse study, a significant increase in the level of hepatic mRNA glucokinase, which catalyzes phosphorylation of glucose to glucose-6-phosphatase, through the PPAR-γ proliferator-activated receptor [26], has been demonstrated. Moreover, narginine reduced the hepatic expression of mRNA bound to phospho - pylpyruvate of carboxykinase and glucose phosphatase [27].

Studies on anthocyanins and anthocyanides indicate the effect of stimulating insulin secretion and protective effect on β-pancreatic cells through factors stimulating the transcription of insulin genes, as well as the reduction of oxidative processes leading to apoptosis [28]. It has been proved that anthocyanins contained in the diet of a mouse with type 2 diabetes prevented mouse from increasement of blood glucose and improved insulin sensitivity [29]. The antidiabetic activity of anthocyanins is correlated with the increased level of *SLC2A4* (*Solute Carrier Family 2 member 4*) - the glucose transporting protein gene, the factor which lower the retinol-binding protein and associated inflammatory adipocytokines [30]. These effects were observed when the mice received an extract of anthocyanin-rich blueberries. The mice were shown to enhance AMPK activity (adenosine-5'-monophosphate-activated kinase) and Slc2a4 in adipose tissue, while hepatic gluconeogenesis and lipid content were suppressed. Inactivation of acetyl-CoA carboxylase and increase in PPAR-α, acetyl-CoA oxidase and livers carnitine palmitylotransferase in T2DM mice fed with anthocyanins were also noted [31].

PHENOLIC ACIDS

The most common phenolic compounds are caffeic, chlorogenic and ferulic acids [32]. The studies showed a positive relationship related to the consumption of caffeine (from 1 to 6 cups per day) and the reduced course of T2DM [33].

Positive effects caused by phenolic acids include improved insulin sensitivity, while no increased insulin secretion or improvement in fasting or postmeal glucose results were observed [34]. The mechanism of phenolic acids protective influence is the inhibition of α-amylase and α-glucosidase enzymes [35]. In mouse preadipocytes, coffee reduced the accumulation of lipids during

their differentiation and inhibited the expression of PPAR-γ, adiponectin, Glut 4 (*Glucose Transporter 4*) and lipoprotein lipase [36]. In case of diabetes it has been shown that chlorogenic acid administered when fasting lowers plasma glucose concentration and reduces HbA1c levels through the adiponectin receptor signaling pathway, raising its level in adipose tissue and increasing the number of adiponectin receptors in the liver and muscles. In addition, chlorogenic acid has an inhibitory effect on gluconeogenesis by decreasing the activity of hepatic glucose-6-phosphatase (G6Pase), and increasing the transport of glucose to skeletal muscles by elevated AMPK concentration and improves lipid metabolism by increasing the hepatic PPAR-α concentration [37].

RESVERATROL AND CURCUMIN

The phenolic compounds present in grapes, peanuts, red wine and berries have been shown to demonstrate the ability to: improve carbohydrate metabolism, increase insulin sensitivity, protect β-pancreatic cells, improve insulin secretion and regulate metabolic processes. Resveratrol has anti-inflammatory properties. When diabetes and other metabolic diseases were analyzed, resveratrol inhibited the expression of IL-6 and IL-8 [38]. The results of clinical trials on resveratrol are inconclusive. In adult obese persons with insulin resistance after 4-week supplementation with resveratrol it was observed that post-prandial glucose concentration was reduced, while the effect of the dose was not demonstrated [39].

In T2DM, resveratrol supplementation significantly improved fasting glucose, glycated hemoglobin, total cholesterol, triglyceride, and low-density lipoprotein (LDL) results. In addition, the observed effect of supplementation was the increase in insulin sensitivity, decrease in oxidative stress and increased insulin signaling through the AKT pathway [40].

Curcumin exhibits a similar antidiabetic effect to resveratrol. Administration of resveratrol or curcumin improves pancreatic function and enhances insulin secretion in β-pancreatic cells. It is suspected that this is caused by suppression of cAMP and cGMP degradation and inhibition of phosphodiesterase activity [41]. In the study in which the anti-diabetic properties of curcumin were analyzed in the population of people with an increased risk of developing diabetes, improvement in the secretory function of the pancreas was observed. In the HOMA-β (*Homeostatic Model Assessment*) project - a study evaluating the functionality of β-pancreatic cells, after administration of curcumin, a decreased concentration of C-peptide and adiponectins in the course of T2DM was registered [42].

Other studies show the anti-inflammatory properties of curcumin. This compound has been shown to lower pro-inflammatory cytokines such as TNF-α (*Tumor Necrosis Factor α*), leptin, resistins via inhibiting the transcription factors NF-kB and Wnt/β - catenin, and activating proliferator-peroxisomal-γ receptors and cell signaling pathways of Nrf. Due to the properties described above, curcumin has the ability to regulate hyperglycaemia and hyperlipidemia [43].

CONCLUSIONS

As shown on *in vivo*, *in vitro* and population studies, polyphenols and flavonoids have properties that can affect the risk of developing diabetes and what is more could be a significant element of disease treatment due to the regulation of expression genes related to the diabetes, regulation of cell signalling pathways, modification of carbohydrate metabolism and in consequence indirectly affecting the transport, use and storage of glucose. Additionally polyphenols and flavonoids protect pancreatic cells from oxidative stress, thus preventing their damage and/or destruction.

Conflicts of interest

None declared.

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