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Review

Nutrigenomics and Diabetes Mellitus

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Abstract

Technical insight has linked the genetic buildup of an individual with the protective role of nutrients, thereby aiming to increase patients' quality of life. Because nutrition has been linked to several inflammatory diseases and conditions, such as Type 2 diabetes, cardiovascular disease, rheumatoid arthritis, and inflammatory bowel disease, recent studies have focussed on the combination of nutrition along with genetics paving the way to the development of the modality "Nutrigenomics". With the prevalence of Diabetes Mellitus [DM] increasing globally at an alarming rate, it has become a major health concern of the worldwide population. The predisposition of an individual to DM is partly contributed by genetics and, to a larger extent, is influenced by the changing dietary environment. Nutrigenomics has the potential to advance the prevention and therapy of diet-related disorders like DM by contributing to a genetic angle of view along with the nutritional counterpart. This review focuses on the genetic and nutrient microenvironment, bridging the two disciplines and forecasting its influence on DM.

Keywords: nutrigenomics, Diabetes Mellitus, nutrition, genetics.

Abbreviations: EGCG – Epigallocatechin gallate; MafA – v-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog A; NF-κB – Nuclear Factor kappa B; Pdx1 – Duodenal homeobox factor transcription factor; PI3K – Endothelial phosphatidylinositol 3-kinase; PPAR – Peroxisome proliferator-activated receptor.

Introduction

Diabetes Mellitus (DM) is a syndrome with numerous etiologies that is defined primarily by chronic hyperglycemia and dysfunctions in protein and lipid metabolism. The hyperglycemia manifested by DM patients results from the inability to manufacture, secrete or absorb insulin or a combination of all these. The abnormalities of carbohydrate, lipid and protein metabolism are brought on by insufficient insulin levels to produce an adequate response and/or insulin resistance of target tissues, primarily skeletal muscles, adipose tissue, and, to a lesser extent, the liver, at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes [1]. The American Diabetes Association (ADA) first recommended the traditional classification of diabetes in 1997 as Type 1, Type 2, and Gestational Diabetes Mellitus (GDM) and is the widely accepted classification till then. Insulin resistance is the center of the hypothesis that distinguishes between Type 1 and Type 2 DM [2]. The destruction of pancreatic ß-cells is the causative factor of Type 1 DM, which makes up about 5–10% of DM cases. It constitutes 80–90% of DM cases affecting children and adolescents. The factors that act as predictors for Type 1 DM are increased growth velocity and impaired glucose sensitivity of ß cells [3]. Reduced insulin response as a result of pancreatic cell dysfunction is the mainstay of Type 2 DM, which accounts for more than 90–95% of DM cases, with obesity and long periods of physical inactivity being the contributing factors. Most Type 2 DM patients have higher body fat percentages that are primarily concentrated in the abdominal region, which contributes to insulin resistance through mechanisms

like free fatty acids (FFA) being released increasingly and dysregulation of adipokine [4]. The data accumulated from the genomic-wide association study (GWAS) indicated a strong genetic background for DM, thereby necessitating the need to study the genetic architecture of the same. While our genetic makeup has largely remained intact, the nutritional environment has drastically changed throughout evolution, particularly after the advent of agriculture circa around 10,000 years ago. An individual's evolving nutritional and physical environment contributes to the increasing incidence of diet-related polygenic conditions. It is warranted that genomic interactions be combined with the nutritional/dietary lifestyle to facilitate nutrigenomic analysis of DM [5].

Diabetes Mellitus and genetics

National and international research networks and consortiums like the Type 1 Diabetes Genetic Consortium, TrialNet Pathway to Prevention study and Wellcome Trust Case Control Consortium (WTCCC) have carried out linkage and genome-wide association studies (GWAS) of both Type 1 and Type 2 DM [6]. One of the primary reasons for T1DM is genetic predisposition. According to numerous research, genetic factors can account for up to 50% of T1DM risk factors. The HLA complex highly influences the pathophysiology of T1DM. Using genomic screening, it has been identified that more than 50 HLA antigens and HLA genes are linked to Type 1 DM, particularly related to HLA-DR and HLA-DQ. The HLA class II haplotypes DR4-DQA1*03:01-DQB1*03:02, known as DR4-DQ8 and HLA-DRB1*03:01-DQA1*05:01-DQB1*02:01, known as DR3-DQ2 are the main HLA Class II halotypes associated with Type 1 DM that can either increase or decrease the binding ability of the related autoantigens [7]. The DR4-DQ8/DR3-DQ2 genotype, which results from the interaction between the two haplotypes mentioned above, has the highest risk for T1DM. The risk of developing T1DM is related to other alleles like DR3, DRB4, and DRB5. However, some haplotypes, such as DR2 or DQB1*06:02-DRB1*15:01-DQA1*01:02, have a protective effect. Studies have identified around 50 non-HLA genes associated with Type 1 DM, like insulin gene (INS), on chromosome 11p15.5 and tandem repeats (VNTR) within the 5'-untranslated regions of the coding sequence of INS known as INS-VNTR that regulate the insulin expression. T cell activation is suppressed by lymphoid-specific phosphatase, which is encoded by protein tyrosine phosphatase non-receptor type 22 (PTPN22), and its polymorphism negatively regulates the T cell activation, thereby increasing the susceptibility to Type 1 DM [8]. T-cell specific transmembrane co-receptor is encoded by Type 1 DM susceptible gene cytotoxic T-lymphocyte antigen (CTLA-4), located on chromosome 2q33 that binds to B7 ligand that down-regulates the expression of Interleukin-2 receptor thereby acting as a negative regulator of cytotoxic T cells. Interleukin-2 receptor subunit alpha (IL2RA), IL-4, IL-13,interferon-induced helicase (IFIH1), Gli-similar 3 protein (GLIS3) and ubiquitin-associated and SH3 domain-containing protein A (UBASH3A) are some of the genes that are also implicated in influencing the risk rate of Type 1 DM [9].

It is generally known that genetic factors play a significant role in the etiology of Type 2 diabetes. First-degree relatives of T2DM patients are around three times more likely to get the condition than people without a family history of the condition. When both parents have T2DM, the lifetime risk of having the disease increases to 70%. People with one parent who has the disease are at a 40% lifetime risk. Compared to dizygotic twins (20–30%), monozygotic twins (70%) have better concordance rates for T2DM.

Last but not least, variations in the prevalence of diabetes among ethnic groups strongly suggest hereditary disease predisposition [10]. The foundation of genetic predisposition in Type 2 DM is polygenicity. The genes calpain 10 (CAPN10) and transcription factor 7-like 2 (T-cell specific, HMG-box) (TCF7L2) were found to be related to Type 2 DM through linkage analysis studies. Cysteine protease is involved in functions like intracellular remodeling and post-receptor signaling and is enforced by CAPN10. TCF7L2, mapped to chromosome 10, is the type of DM gene most strongly replicated and associated with it. It codes for the transcription factor active in beta cells, which is also a member of the Wnt signaling pathway and is involved in impairing insulin secretion and enhancing the rate of hepatic glucose production [11]. The molecular target of thiazolidinediones, PPARG, is an implicated candidate gene that increases the susceptibility to develop Type 2 DM by 20%, following point mutation of proline to arginine in the amino acid skeleton [12]. In some populations, insulin sensitivity is decreased by polymorphism of genes IRS-1 and IRS-2 that codes for peptides involved in insulin signal transduction [13]. Missense mutation of the KCNJ11 gene that codes for ATP-sensitive potassium channels involved in regulating insulin secretion from beta cells is strongly implicated in the pathophysiology of Type 2 DM [14]. MODY genes

involved in the physiology of monogenic diabetes in young, like HNF1A, HNF1B, and HNF4A, regulate the functioning of pancreatic beta cells, and their role in the pathophysiology of Type DM is yet to be identified through WGAS [15]. WGAS in the Caucasian and Asian populations revealed a hematopoietically expressed homeobox (HHEX) gene mapped on chromosome 10q to be involved in coding for the transcription factor of the Wnt signaling pathway, thereby contributing to the underlying mechanism of Type 2 DM [16]. SLC30A8, i.e., Solute carrier family 30, member 8 codes for a protein that is expressed particularly in the islets of Langerhans and regulates the storage and secretion of insulin granules, thereby conferring a high risk of developing Type DM in susceptible individuals following mutation or polymorphism of the same [17].

The genes identified as a result of WGAS constitute those genes related to the activity of beta cells and the secretion of insulin with an extended spectrum of action, including sensitivity to insulin and activating insulin signaling pathway. Most of the implicated genes of DM are found to be associated with atherosclerotic heart disease, dyslipidemia, and microcoagulopathy, thereby strengthening the genetic background of DM and its complications [18].

Nutrition pattern and Diabetes Mellitus

Studies documented in the literature have indicated a strong association between diet and the incidence of DM. The drastic decline in the incidence of DM during the First World War in Germany and European countries due to food shortage and famine has strengthened this association. As a result of globalization, the dietary pattern shifted to high fat and high carbohydrate, which, being supplemented by a sedentary lifestyle, heightened the risk of contracting DM in the susceptible population. Diet consumed by an individual will cause alteration in the homeostatic loop of the organism by inducing multiple metabolic processes [19].

The metabolic homeostasis of the body is furnished by precisely controlling the glucose metabolism. This maintenance is established through two events, namely metabolites-induced enzyme transcription and hormonal regulation. Insulin-induced protein kinase B activation (PKB/AKT) regulates glucose uptake by various tissues such as the liver, adipose tissue, and skeletal muscle, decreases the hepatic output of glucose, and enhances glycogen synthesis and glycogen decomposition. The regulation of glucose homeostasis is monitored by insulin via activating the mTOR/S6K1 signaling pathway. The carbohydrate-rich diet consumed by an individual releases glucose that enhances the protein recruitment to endosomal membranes, and as a result, production of P13P is stimulated, and finally, the mTOR/S6K1 signaling pathway is activated. The expression of enzymes like pyruvate kinase, glucokinase, ATP citrate lyase, and acetyl CoA carboxylase is regulated through generic regulation of carbohydrate-responsive-element binding protein (ChREBP), which functions as a helix-loop-helix leucine zipper transcription factor. Studies have emphasized that a nutritional diet that releases carbohydrates at a slow pace can lower the insulin and glucose responses, enhancing the fibrinolytic capacity of the body and, henceforth, therapeutically targeting DM [20].

Lipid metabolites like stearic acid and deoxysphingolipids, along with the fatty acids chain length and saturation level, act as biomarkers of insulin resistance. The increased rate of accumulation of lipids in cells, mainly adipocytes, upregulates the expression level of proinflammatory cytokines that, in turn, regulate insulin resistance. The free fatty acids-induced inhibition of Akt/PKB activation impairs the insulin signaling pathway of the body. Alongside the mechanism mentioned above, the free radicals generated by mitochondria exert their influence on glucose homeostasis [21]. Dietary fatty acids and their derivatives activate the Peroxisome proliferator-activated receptors (PPARs) that function as lipid sensors that regulate fatty acid oxidation, indirectly improving glucose metabolism. Insulin sensitivity is impaired by the inhibition of the Akt signaling pathway brought about by the activation of tribbles pseudokinase 3 (TRB3) by PPAR. The data put forward by various studies indicated the influence of fatty acids on regulating insulin and glucose homeostasis, and further replacement of saturated fats by mono or poly saturated fatty acids enhances the body's tolerance level towards glucose and insulin [22].

Proteins have showcased various methods of influencing glucose homeostasis by upregulating insulin secretion and its action, thereby reducing hyperglycemia and increasing insulin sensitivity. A diet that targets a long-term release of high protein causes the whole body to manifest insulin resistance by enhancing the mTOR/S6K1 signaling pathway, which further results in an elevated gluconeogenesis rate and a high glucagon turnover rate [23]. On the other hand, diabetic people benefit from a low-protein diet that enhances insulin sensitivity through control over the ATF4/FGF21 signaling pathway. Soy protein enhances insulin

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sensitivity in the liver by upregulating INSR mRNA expression [24]. With the activation of the P13K/AKT signaling pathway, cod/fish protein selectively improvised the translocation of GLUT4 to T tubules, thereby improving the transport of glucose as secondary to insulin response [25]. The synthesis and breakdown of protein causes changes in the skeletal backbone composed of amino acids that regulate gene expression, such as CHOP, which is involved in glucose metabolism. The main mechanism by which they enhance insulin resistance and glucose control is via inhibition of P13K as a result of activation of mTOR/S6K1 signaling pathway as well as the release of hormones like leptin, GLP-1 and Ghrelin along with activation of mTORC1/PKC signaling pathway via GCN2/eIF2α/ATF4/FGF21 transduction pathway, insulin sensitivity, energy expenditure and thermogenesis is improved by leucine deprivation or methionine deficiency [26].

Micronutrients also play a role in maintaining the body's insulin resistance and glucose homeostasis. Selenium, whose main sources are cereals, black tea, milk, soybeans, and mushrooms, can attenuate diabetes by mimicking insulin and, therefore, prevent hepatic insulin resistance by downregulating glucose and insulin tolerance. At high concentrations, selenium can induce high rates of gluconeogenesis and fasting blood glucose levels, further adding to the risk of diabetes [27]. Chromium influences glucose metabolism by increasing the expression of GLUT2 and activating the PI3K/AKT signaling pathway in skeletal muscles, thereby favoring insulin binding to INSR [28]. Sodium and Magnesium regulate glucose metabolism and glycaemic control in diabetic patients by enhancing natriuresis via the PPARδ/SGLT2 pathway [29].

Among the vitamins, Vitamin D and E play a crucial role in the modulation of insulin resistance and the functioning of pancreatic beta cells. Pancreatic beta cells, adipose tissues and skeletal muscle host the Vitamin D receptor (VDR) and vitamin D through this receptor, along with the activation of transcription factor PPAR, which is involved in fatty acid metabolism, affects the glucose utilization in the body. It directly enhances the sensitivity and action of insulin by upregulating INSR gene expression as well as altering the influx of calcium to the beta cells, thereby controlling the insulin release from them. Vitamin D also negatively downregulates TNF-alpha and IL-6, proinflammatory cytokines that are closely associated with the insulin resistance manifested by the system [30]. Besides the role played by Vitamin E in the maintenance of cell function, cell signaling and lipid metabolism, it also exerts its role in the regulation of insulin sensitivity by affecting the signaling pathway via the alteration of the INSR phosphorylation cascade along with the altered generic expression of PPAR gene [31].

Gene nutrient interactions in Diabetes Mellitus

Keeping in mind the crucial role played by dietary nutrition in the pathophysiology of DM, nutrient-gene interactions become a necessary step in understanding the mechanisms of DM. With the advent of molecular tools, the influence nutrition has over the genome was identified, and the various mechanisms by which it either upregulates or downregulates the generic expression and the combination of both led to the concept of "Nutrigenomics". The gene expression may be modulated by nutrient-gene interaction directly, through metabolite action or activation of various signaling pathways [32]. Fruits, vegetables, legumes and cereals harbor polyphenols within them, the plant product classified into stilbenes, lignans, flavonoids and phenolic compounds. These compounds showcase hypoglycemic effects through various mechanisms ranging from their antioxidant activity, ability to curb glucose release, protection of the beta cells of the pancreas from glucotoxicity, modulation of intracellular signaling pathways to enhance the utilization of glucose from peripheral tissues to the advanced glycated end products formation being inhibited [33]. The enzymes responsible for carbohydrate digestion- alpha-glucosidase and alpha-amylase- are inhibited by tannins, phenolic compounds and flavonoids.

These compounds also influence different stages of intracellular signaling pathways, such as upregulating mitochondrial status and suppressing the production of inflammatory cytokines and reactive oxygen species. The flavanols thatpresent in green tea catechins decrease the elevated serum glucose levels, preventing vascular endothelial dysfunction via activation of the P13K signaling pathway, which subsequently activates eNOS pathway systems [34]. The epigallocatechin gallate (EGCG) inhibits the activities exhibited by the lipogenic enzymes and ameliorates mitochondrial action, thereby exhibiting its reductive glucolipotoxic effect. By increasing the viability of beta cells in conditions of oxidative stress, inflammation, and glucotoxicity, EGCG enhances the insulin secretory function and also protects the pancreatic beta cells from cytotoxicity induced by pro-inflammatory cytokine by modulating the expression of BCL-2 [35]. Naringin and hesperidin,

present in citrus fruits, exert hypoglycemic action in DM by increasing the mRNA level of hepatic glucokinase via upregulating adipocyte GLUT-4 and PPAR. They also lowered the hepatic mRNA expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase [36]. Quercetin, the dietary flavanol found in red wine, fruits, nuts and vegetables, preserves the integrity of pancreatic beta cells by diminishing the rates of oxidative stress, lipid peroxidation, and nitric oxide production and elevating the activity of antioxidant enzymes via activation of Nrf-2/HO-1 activation and inhibition of Nuclear factor kappa B, It protects dorsal root ganglion against apoptosis induced by high glucose thereby being a therapeutic option for diabetic neuropathy [37]. Apigenin and luteolin present in celery, parsley and herbs, along with quercetin, protects the beta cells from damage caused as a result of glucotoxicity and by inhibiting the iNos gene expression by suppressing NF-κB activation, prevent the IL-1β and IFN-γ induced inhibition of insulin secretion [38]. The isoflavones, daidzein and genistein present in soyfood, legumes and soybean by activation of cAMP/PKA-dependentERK1/2 signaling pathway ameliorate hyperinsulinemia observed during obesity along with decreasing the generic expression of GLUT-2, PPAR and SREB-1 [39].

Anthocyanins and anthocyanidins found in blueberries have a protective effect on the pancreatic beta cells and exert antidiabetic action by upregulating the expression of gene coding for GLUT-4 transporter-solute carrier family 2 members 4(Slc2a4), inactivating acetyl CoA- carboxylase, elevating the expression of PPAR, acetyl-CoA oxidase and carnitine palmitoyltransferase-1A in the liver along with downregulating the expression of retinol-binding protein and the associated inflammatory cytokines [40]. Studies have showcased a lower risk of developing DM following habitual coffee consumption. Caffeine produces chlorogenic acid that enhances the expression of α-amylase and α-glucosidase. The expression of differentiation marker genes such as adiponectin, PPAR, lipoprotein lipase, and CCAAT-enhancer binding protein alpha is downregulated by caffeine. Chlorogenic acid downregulates gluconeogenesis by inhibiting hepatic glucose-6 phosphatase activity, upregulating hepatic PPAR-alpha activity, thereby improving lipid metabolism and enhancing glucose transport in skeletal muscles by regulating the expression of AMPK [41]. Ferulic acid improves insulin sensitivity, expression of insulin signaling inhibitor genes for enzymes PEPCK and G6Pase and restores glucose and insulin tolerance levels to normal range by downregulating the binding of SREBP1c, HNFIα and HNF3β factors with Slc2a2 promoter [42]. Blueberries, red wine, and grapes harbor resveratrol in them, which improves glucose homeostasis insulin resistance, protects the pancreatic beta cells and eventually regulates the synthesis and secretion of insulin. By augmenting brain-derived neurotrophic factor and enhancing the production of lipoxin A4, the anti-inflammatory lipid along with its anti-inflammatory action of blocking the NF-κB dependent expression of MCP-1, IL-6, IL-8, which are inflammatory cytokines, it reduces the occurrence of diabetes in the susceptible population [43].

With the usage of curcumin, insulin secretion by pancreatic cells is improved via inhibiting phosphodiesterase, which degrades cAMP and cGMP [44]. Its anti-diabetic effect is exerted as a result of anti-inflammatory action brought by down-regulating TNF-α, Wnt and Nrf-2 signaling pathway molecules, resistin, and leptin [45]. Vitamin D regulates the functioning of pancreatic beta cells by controlling the expression of various genotypes. Vitamin D improves insulin sensitivity by enhancing the expression of insulin receptors and PPAR. The expression and activity of cytokines IL-1, IL-6, and TNF are modulated by Vitamin D, thereby protecting the pancreatic beta cells from cytokines-induced apoptosis [46]. Vitamin A and retinoic acid, besides their antioxidant properties, are inducers of pancreatic cell differentiation and essential for maintaining beta and alpha cell masses in the pan. Itngside reguinsulining the se, which is stimulated due toesult of elevated glucose levels [47]. The proper functioning of carbohydrate metabolism genes like forkhead box A2, Hepatocyte nuclear factor 4 alpha, glucokinase and Calcium voltage-gated channel subunit alpha 1D is regulated by Biotin [48]. Pancreatic beta cell differentiation is promoted by Nicotinamide, which also induces insulin gene expression via enhancing v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog A expression [49]. Dietary amino acids and proteins regulate the expression of PI3K/PKB/mTOR pathway molecules in the pancreatic beta cells and downregulate the expression of Fbp1 and Pck1, which are glucogenic genes. Because of their potential effect on insulin signaling pathways and precursors involved in glucose synthesis in the liver, amino acids exert an insulinotropic effect on the pancreatic beta cells [50]. Arginine, leucine, isoleucine and valine cause slow cytosolic calcium oscillations in the pancreatic beta cells and function as inducers of glucose-stimulated insulin release. Accumulation of branched-chain amino acids, namely

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isoleucine, leucine and valine, which function as nutrient signals and metabolic regulators, causes mitochondrial dysfunction, apoptosis of beta cells and stimulation of stress kinases, thereby functioning as a reliable predictor of DM [51]. Glutamate dehydrogenase is allosterically activated by leucine, enhancing the synthesis and secretion of insulin by islet cell mass in the pancreas [52]. When plasma fatty acid levels get elevated along with the intracellular accumulation of fatty acyl CoA and diglycerol, inhibition of PI3Kinase activity occurs, resulting in diminished glucose-stimulated insulin transport activity. Insulin sensitivity and intake of saturated fatty acids show a negative correlation via downregulating glutathione peroxidase gene and MafA expression in pancreatic beta cells [53]. The expression of genes regulating insulin synthesis and secretion is downregulated by palmitate via inhibiting PDX1 nuclear translocation, curbing the MafA gene expression and reducing the activity of Scl2a2 and Gck genes. By activating the NLRP3-ASC inflammasome, the production of caspase-1, IL-1ß, and IL-18 is enhanced, causing a reduction in glucose tolerance and insulin sensitivity [54]. The survival of pancreatic beta cells, insulin secretion, response to insulin by skeletal muscles, insulin resistance, and the metabolism of adipocytes are influenced by cis-palmitoleic acid [55]. Omega-6 PUFA, mainly Linoleic acid, exerts anti-inflammatory action by inhibiting the activation of caspase-1 alongside reducing the secretion of IL-1ß, which improves the insulin sensitivity coupled with activation of NF-κB [56].

Conclusion

In this era of changing lifestyles, the incidence rate of chronic diseases like DM has increased. WGAS has revealed various genes associated with the pathophysiology of this condition, including the signaling pathway, differentiation of pancreatic cell population, insulin synthesis, and, subsequently, its secretion. Dietary modification is an exceptional part of the therapeutic approach to diabetic people, and with the advent of the modality Nutrigenomics, genetic and nutrient interactions are being studied, which has enhanced our understanding of the pathology, physiology as well as therapeutics of this globally evolving condition Diabetes Mellitus.

Conflict of interest

The authors declare no conflict of interest.

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