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Diet and Nutrition Reverse Type 3 Diabetes and Accelerated Aging Linked to Global Chronic Diseases

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Abstract

The acceleration in the rate of chronic diseases that involve insulin resistance has become of global concern. The rate of the most prevalent chronic disease such as cardiovascular disease is linked to the metabolic syndrome, non alcoholic fatty liver disease (NAFLD) and other chronic diseases that include obesity, diabetes and neurodegenerative diseases. The gene-environment interaction in Western countries indicates that with urbanization access to food and its content may lead to induction of epigenetic alterations and identify the gene Sirtuin 1 (Sirt 1) to be responsible for the increased risk for insulin resistance and NAFLD relevant to Type 1, Type 2 and Type 3 diabetes in these countries. Nutrigenomics is linked to neuron and liver telomere maintenance, cell division and tissue growth and has become important with essential nutrients that regulate Sirt 1 function important to prevent NAFLD in individuals with diabetes. Nutrigenomic diets, exercise, drugs and lifestyle changes regulate Type 3 diabetes with neuron Sirt 1 transcriptional responses associated with DNA modifications that regulate brain insulin resistance relevant to NAFLD and diabetes.

Keywords: Nutrigenomics; Obesity; Diabetes; Accelerated Aging; Endocrine; Chronic Diseases; Diet

Background

In Western countries and third world countries the global obesity epidemic has been reported to effect at least 10% of the global population with projected health care costs to obesity related medical expenses reported to be 344 billion dollars to the year 2018 and may account for 21% of health costs in the United States. The acceleration in the rate of chronic diseases that involve insulin resistance has also become of global concern. The rate of the most prevalent chronic disease such as cardiovascular disease [1-4] is linked to the metabolic syndrome and non alcoholic fatty liver disease (NAFLD) and environmental factors such as stress, anxiety and depression are important to consider with the global increase in other chronic diseases that include diabetes and neurodegenerative diseases.

In 2013 the world health organization (WHO 2013) indicated that the number of global deaths (63%) included cardiovascular disease (48%), cancer (21%) and chronic respiratory conditions (12%). Nutritional and anti-aging therapies may prevent accelerated aging involved in the global obesity epidemic that currently involves various endocrine and chronic diseases in Western populations. Obesity and diabetes are defined as endocrine disorders with the medical conditions such as hyperinsulinemia involved with hormonal imbalance with various inflammatory complications of organs such as the liver, brain, thyroid, parathyroid, adrenal gland and pancreas [5,6]. Stress, fatigue, anxiety and depression are closely linked to chronic diseases and the molecular mechanisms that involve the apelinergic pathway have become important to Type 3 diabetes and neuroendocrine disease with theinduction of insulin resistance that lead to obesity and diabetes [7-12]. Metabolic diseases such as cardiovascular disease and neurodegeneration are associated with accelerated aging process and involve alteration in blood lipids such as cholesterol and triglyceride with a decrease in high density lipoprotein (HDL) [13-16]. Anxiety disorders effect mental health and induce changes in the brain associated with plasma hormone dysregulation and alterations in the biological clock especially in tissues such as the liver, adipose tissue and brain.

The gene-environment interaction in Western countries indicates that with urbanization [17] and access to food and its content may lead to induction of epigenetic alterations that are associated with lipid and glucose dyshomeostasis with increased risk for insulin resistance relevant to Type 1, Type 2 and Type 3 diabetes and obesity in these countries. Diets that contain various organic pollutants with overnutrition lead to abnormal xenobiotic metabolism [18-22] with marked effects on DNA strand breakage with cell apoptosis. High calorie diets, exercise and lifestyle changes regulate transcriptional responses with DNA modifications that include DNA methylation, histone tails, chromatin and micro RNA (short ribonucleic acid gene regulators)that regulate DNA expression and promote chronic disease susceptibility (Figure1). The gene environment interaction now identify the nuclear receptor Sirtuin 1 (Sirt 1)that regulates appetite [23] to be involved in the induction of insulin resistance and Type 3 diabetes and involve alterations in nuclear receptors, micro RNA with chromatin remodelling [24] that are now closely associated with obesity, diabetes and neurodegenerative disease.

Sirtuin 1 contributes to the Post-Transcriptional Dysregulation in Type 1, Type 2 and Type 3 Diabetes

Nutritional research has concentrated on the identification of nutrient sensing diets that provide regulation of histone deacetylases (HDAC) that are involved in epigenetic control of gene expression that controls

metabolic and tissue glucose and cholesterol homeostasis [7,14,17]. Sirt 1 is a NAD+ dependent protein deacetylase and is involved in the deacetylation of the nuclear receptors (Figure 1) with its critical involvement in insulin resistance [25]. The anti-aging protein Sirt 1 and cell senescence has been closely linked to telomere biology and global DNA repair which provides mechanistic explanations for Sirt 1 functions in the protection of DNA damage, and thus genomic stability [26,27] with relevance to Type 1, Type 2 and Type 3 diabetes. Anti-aging strategies that target telomere shortening and brain glucose dysfunction in obesity and diabetes are of particular interest to biological aging since telomere shortening has been associated as an early risk for dementia and Type 3 diabetes.

In calorie restriction regulation of the Sirt 1 gene involved in lifespan and aging has now become essential therapy for glucose and cholesterol maintenance with reversal of chronic diseases such as obesity, diabetes and neurodegenerative diseases in global communities [24]. Considerable interest in chronic diseases of the central nervous system that include neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) may provide a useful model for the prevention and management of various chronic diseases. Risk factors such as diet and lifestyle indicate that Sirt 1 dysregulation is important to liver and metabolic health [24] and central to Type 3 diabetes since Sirt 1 is involved in neuron loss [28] associated with insulin resistance and neurodegenerative disease.

In Figure 2 a summary is shown of the relevance of Sirt 1 in the genetic regulation of diabetes. HLA class I, II genes and genes of the HLA region of chromosome 6 have also been shown to be involved greatly with the risk for Type 1 diabetes (HLA-DR, DQ and DP). In caucasian populations contribution by DQA1and DQB1 haplotypes, linkages to DRB1*03 and DRB1*04 haplotypes have been associated with Type 1 diabetes. Other ethnic groups such as African, Americans, Japanese and Chinese specific haplotypes have also been associated with Type 1 diabetes [29]. An interest in global chronic diseases has identified Sirt 1 dysregulation to involve Type 1 diabetes with nutritional regulation of Sirt 1 important to assist with glucose homeostasis in these Type 1individuals. Sirt 1 regulation of the MODY gene *via* transcription factors hepatocyte nuclear factor 1(HNF-1) and HNF-4 or HNF1/HNF4 complex [30-32] has been shown with evidence of Sirt1/HNF-4genetic regulation of liver and pancreas in Type 1 diabetes.

In Type 2 diabetes more than 150 genetic loci are associated with the development of diabetes and 50 candidate genes have shown to play a major part in the development of the disease and include genes such as peroxisome proliferator-activated receptors, ATP-binding cassette transporter sub-family C member 8, KATP mutations and Calpain 10 [29]. These genes are involved in pancreatic β cell function, insulin action and glucose metabolism in metabolic conditions (Figure 2). In Type 2 diabetes the relevance of stress to defective apelinergic pathways that involve the pancreas, liver, kidney and brain have been identified [7] with severity of diabetes associated with poor insulin actions and glucose regulation. Sirt 1 plays an important role in the regulation of the apelinergic pathway relevant to Type 2 diabetes with connections to brain insulin resistance (stroke, dementia, AD) and Type 3 diabetes [7]. Individuals with Type 1 and Type 2 diabetes involve early and accelerated organ diseases of the brain when associated with Type 3 diabetes and the liver with Sirt 1 repression closely involved with insulin resistance in these individuals.

A single gene effect associated with Sirt 1 repression versus multiple diabetic genes effect may indicate either the interaction of the diabetic individual is sensitive to gene-environments events that involve diet and lifestyle changes. Cellular miRNA have become important since they may be regulated by diet, drugs, xenobiotics, stress and anxiety (environment) that may be relevant to the stress sensitive Sirt 1 [7]. Nutritional intervention is now critical early in life to maintain normal Sirt 1/ fibroblast growth factor 1 regulation of circadian rhythm that maintain brain-liver pathways and glucose homeostasis [32,33]. Sirt 1 regulation

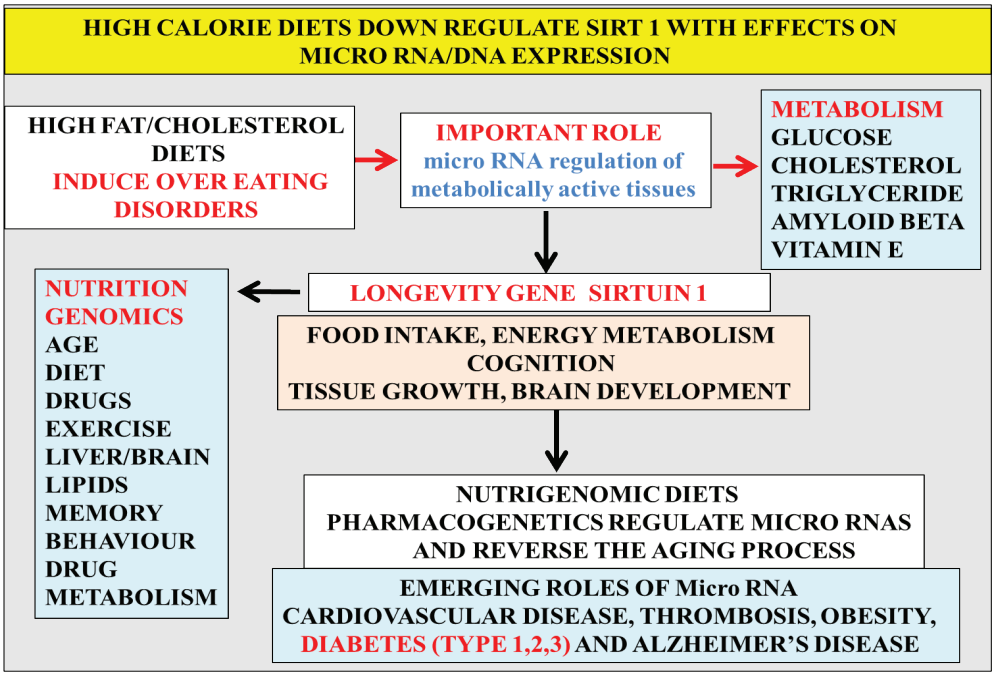

Figure 1: High calorie diets, stress, exercise and lifestyle changes regulate transcriptional responses with DNA modifications that regulate neuron micro RNA and DNA expression and promote chronic diseases associated with obesity, diabetes (Type 1,2,3) and neurodegenerative disease. The gene environment interaction indicates that the stress sensitive anti-aging gene Sirtuin 1 is downregulated with effects on drug therapy linked to the induction of Type 3 diabetes.

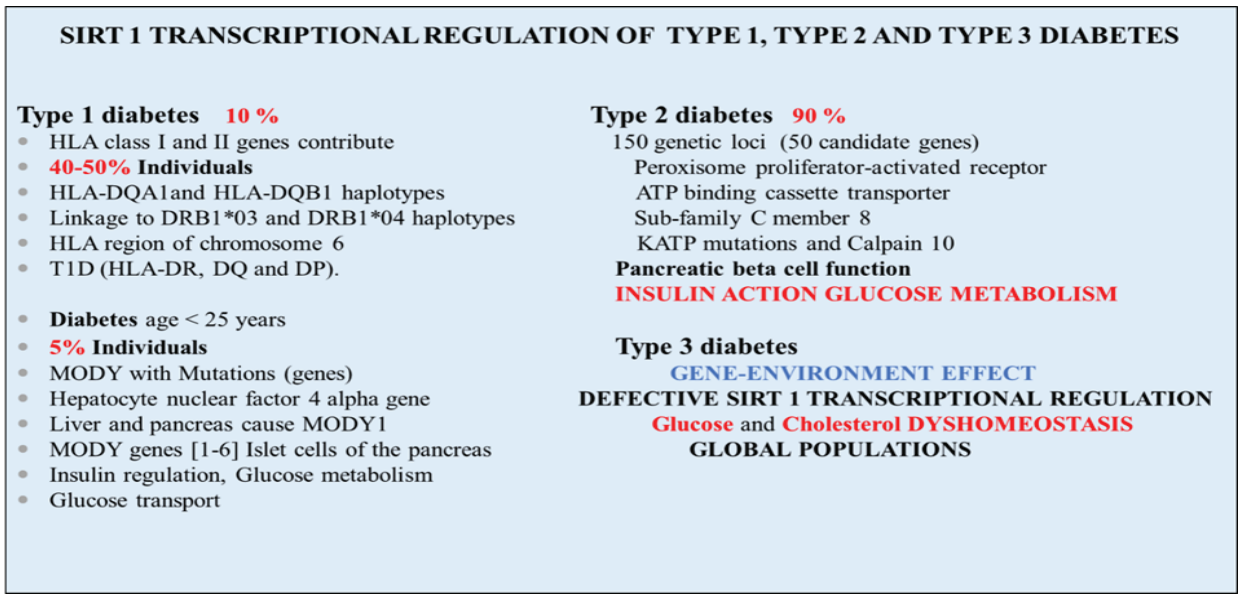

Figure 2: The genetic regulation of Type 1 and Type 2 diabetes is associated with the gene expression of Sirt 1 in global populations. A single gene effect associated with the repression of the anti-aging gene Sirt 1 versus multiple diabetic genes may indicate the interaction of the diabetic individual to gene-environments events such as unhealthy diets and stress that involves Sirt 1 dysregulation of glucose and cholesterol in the brain and peripheral tissues.

targets various transcription factors peroxisome proliferator-activated receptor-gamma co-activator (PGC-1 alpha), p53 tumour suppressor protein, pregnane x receptor (PXR) to adapt gene expression to metabolic activity, insulin resistance and inflammation [24]. Effects of feeding on Sirt 1and p53 interactions are involved in nuclear-mitochondria interactions, mutations, cell death (apoptosis) or permanent cellular senescence [24] with relevance to Sirt 1 deacetylation of p53 that determine DNA repair critical for maintenance of cell glucose homeostasis [34,35].

Effects of p53 on gene regulators include micro RNA (miRNAs) [36,37] and their role in the induction of obesity [38] and diabetes [39-41] indicates altered expression of multiple miRNAs in metabolic tissues [42] Furthermore miRNAs such as miR-34a [43] and miR-122, miR-132 [44,45] that directly inhibit Sirt 1 are associated with poor activation of hepatic genes involved in glucose and lipid metabolism [46] with an increase in acetylated p53 involved with cell apoptosis and NAFLD [47,48]. The p53 effects on miR-34a transactivation involve Sirt1 expression associated with insulin resistance and the development of metabolic disease [49,50].

Nutrigenomics diets maintain Drug and Insulin Therapy with the Prevention of Type 3 Diabetes

Interest in the nature of food intake has increased since the nature of fat consumption (low or high) may require further evaluation and may contain xenobiotics with marked effects on neuronal apoptosis and neuroendocrine disease [17].The effects from environments in developing countries (urban inhabitants) contain xenobiotics (soil, water, air) that may contribute to Type 3 diabetes. High fibre diets [51] that contain fruit and vegetables have become important for the treatment of NAFLD with the reduction in the absorption of lipophilic xenobitics with the prevention of Type 3 diabetes. Activation of hepatic nuclear receptors such as the Sirt1/pregnane X receptor (PXR) by calorie restriction (low glycemic index/fatty acid consumption) are important to the science of nutrigenomics [17] with relevance to activation of hepatic xenobiotic metabolism connected to the prevention of neuronal apoptosis.

The consumption of fruits such as apples that contain pyruvic acid (450 mg/apple) an antioxidant and an activator of Sirt1 [52-54] is essential for diabetes treatment. Other brain nutrients to prevent Type 3 diabetes to maintain brain glucose homeostasis include phosphatidyl inositol and leucine both important for the maintenance of Sirt 1 related neuron function. Exercise and heavy work activities may rapidly deplete brain pyruvic acid, leucine and phosphatidyl inositol with the acceleration of brain insulin resistance [55]. Excessive ingestion of vegetables not more than (1-2 gm/day) may cause suprachiasmatic disorders with accumulation of brain phytosterols with aging [51]. The nature of phytosterols that regulate liver cholesterol metabolism are critical to prevent and reverse NAFLD with HDL cholesterol metabolism closely linked to phytosterol ingestion [51]. Specific polyphenols found in vegetables and fruits need careful evaluation since high doses may cause increased oxidative stress with toxicity to the liver and induction of NAFLD and chronic disease [13]. Nutritional science that involves the maintenance of Sirt 1 regulation of DNA repair require effective function of neuronal telomeres and ingestion of therapeutic foods is essential to prevent Type 3 diabetes [29]. Nutrigenomic diets have become important to prevent Sirt 1 inhibition with diets rich in palmitic acid and alcohol discouraged and both are inhibitors of Sirt 1 [29]. Butyric acid is a histone deacetylase inhibitor used in the treatment of diet induced insulin resistance [56,57] with doses required to reduce amyloid beta protein aggregation in AD but butyric acid may completely inhibit the Sirt 1 deacetylase activity essential for cell telomere growth and mitochondria survival [24].

Sirt 1 is essential for maintenance of insulin therapy in diabetes and aging [58-60]. In diabetes interest in the hepatic drug transport has accelerated with toxic effects of drugs on insulin therapy. More than 600 drugs (eg: Asprin, Warfarin, Furosemide, Atrorvastatin, Clopidogrel, Levothyroxin Acetaminophen, Cholecalciferol, Simvastatin) have been listed that corrupt insulin therapy with drug-drug interactions involved in diabetes [61]. Interests in nutrigenomic diets and drug transport indicate the importance of Sirt 1 in brain to liver drug transport pathways *via* the blood brain barrier [62-66] and require hepatic Sirt 1 regulation of glucose, drug, cholesterol and bile acid metabolism [24]. Diabetes and hepatic and brain amyloid beta metabolism [29] are connected to drug metabolism (Figure 3) and defective hepatic drug metabolism may be

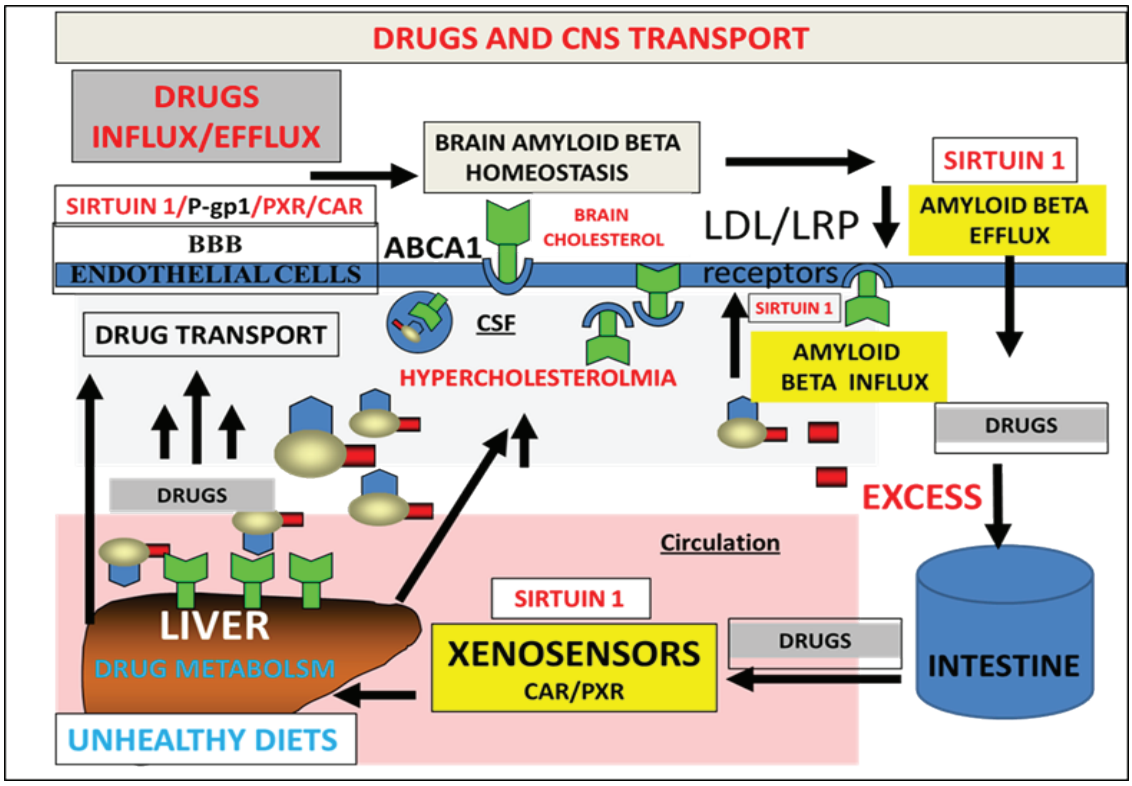

Figure 3: Unhealthy diets such as high fat diets downregulate hepatic drug metabolism with the corruption of insulin therapy in diabetes and aging. Amyloid beta metabolism in the brain and liver are connected to drug metabolism and defective hepatic drug metabolism may be the primary defect in Type 3 diabetes with acceleration of neuronal apoptosis by abnormal brain amyloid beta metabolism associated with Type 1 or Type 2 diabetes. Abbreviations: P-gp1, P glycoprotein, PXR, pregnane X receptor, CAR, constitutive androstane receptor, ABCA1, ATP binding cassette transporter 1, BBB, blood brain barrier, LDLr, low density lipoprotein receptor, LRP, LDL receptor related protein.

the primary defect in diabetes with acceleration of neuronal apoptosis by toxic brain amyloid beta metabolism secondary to Type 3 complications associated with Type 1 or Type 2 diabetic disease [29].

In recent finding approximately 40 miRNAs have been shown to be dysregulated [67-69] in diabetic individuals. The identification of specific dietary supplements that may regulate DNA or microRNA metabolism has become important with nutritional interventions essential for rapid reversal for the severity of diabetes. Diets that do not contain therapeutic food supplements promote Sirt 1 downregulation and disturb p53/mi RNA metabolism [70] with relevance to toxic effects of drugs on insulin therapy in diabetes. Several miRNA have been shown to effect drug metabolism with nuclear receptors involved in the regulation of drug and xenobiotic metabolism [71]. Elevated xenobiotic cell levels have been shown to interfere with miRNA expression [72] with relevance to nuclear Sirt 1 activity.

Nutrigenomic diets activate Sirt 1 and accelerate the hepatic metabolism of toxins such as bacterial lipopolysaccharides (LPS) and mycotoxins that inhibit Sirt 1 and promote insulin resistance with relevance to brain, liver and pancreatic disease [73]. Nutrigenomic diets that do not contain LPS have become important since LPS effects on membrane asymmetry [74,75] involve membrane calcium levels/flux that determine severity of insulin resistance, abnormal drug transport with amyloid beta dyshomeostasis [13] connected to Type 3 diabetes.

Conclusion

Nutritional interventions have become important for the reversal of Type 3 diabetes associated with accelerated aging and linked to Type 1 and Type 2 diabetes. Therapeutic foods that contain anti-aging dietary components activate the anti-aging gene Sirt 1 with relevance to cell glucose dyshomeostasis linked to heart, pancreas, liver and brain diseases. Nutrigenomic diets that activate hepatic Sirt 1 improve drug metabolism with relevance to insulin therapy in diabetes. Lifestyle changes such as drug, environment, diet and stress are involved with the metabolism of therapeutic nutrients that are depleted from the brain with extended workload/exercise treatment periods associated with the downregulation of brain nuclear receptors with relevance to Type 3 diabetes and the severity of insulin resistance in various global communities.

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