Educational Administration: Theory and Practice
2024, 30(5), 2182-2188
ISSN:2148-2403
https://kuey.net/

Research Article

A Review On Nutrigenomics And Metabolic Diseases

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Citation: Luxita Sharma, et al (2024), A Review On Nutrigenomics And Metabolic Diseases, *Educational Administration: Theory and Practice*, *30*(5), 2182-2188
Doi: 10.53555/kuey.v30i5.3258

ARTICLE INFO

ABSTRACT

Nutrigenomics can be described as the science of tomorrow. It is a seminal field that can bring about the future of disease prevention and treatment. It would create advancements in nutrition and medicine. With the elaborate researches and substantial resources that future will be possible faster than you can imagine. This review article explores application of the concepts of nutrigenomics in etiological studies of metabolic diseases. While metabolic diseases have several causes such as age, lifestyle, overweight and disrupted insulin
metabolism; recessive genetic mutations are one of the prime causes. Many Genome-Wide Association studies have given insights into phenotypes, their biology and heritability and calculates their correlation to biomolecules absorbed from food. By isolating the factors that cause the genetic variation in an individual that makes them prone to develop metabolic diseases like obesity, cardiovascular diseases and type 2 diabetes, scientists can also formulate a counter mechanism that would account for the variability. Nutrients and bioactivemolecules can be both a catalyst that can cause certain mutations or the ones that instigate the health effect. The genetics of each disease originating from metabolic disorder is different. With accurate genetic information and biochemical analysis targeted dietary interventions can be formulated for individuals in order to prevent, treat or even eradicate these disorders.

Keywords: Nutrigenomics, nutrients, diet, metabolic disorders, genes, phenotype

INTRODUCTION

Food has several tasks in the body like providing energy that fuels its performance. This is not applicable to just to the functioning of the body. It applies to a more basic level like cellular or even genetic one. Nutrition research has had several break throughs in the past 30 years. According to the experts in this field, nutrigenomics is the 'next revolutionary wave in nutritional research' (Peregrin, 2001). Nutritional genomics aims to establish a correlation between nutrition and the genetic or cellular functions and thereby comprehend how it may affect the health of an individual. It aims to prove how dietary components can influence a person's genetic phenotype, changing its expression and phenotype. Nutrigenomics utilizes inputs from many other sciences and technologies including genomics, transcriptomics, proteomics, metabolomics etc. It would require population and sub population studies to study their diet, food habits, lifestyle and disease history. Nutrigenomics falls under a larger domain of systemic biology called nutritional genetics. Under this field also comes nutrigenetics which can be described as the opposite of nutrigenomics. It seeks to explain how the metabolic processing of certain nutrients differ among individuals based on their genetic makeup (Reen et al., 2015).

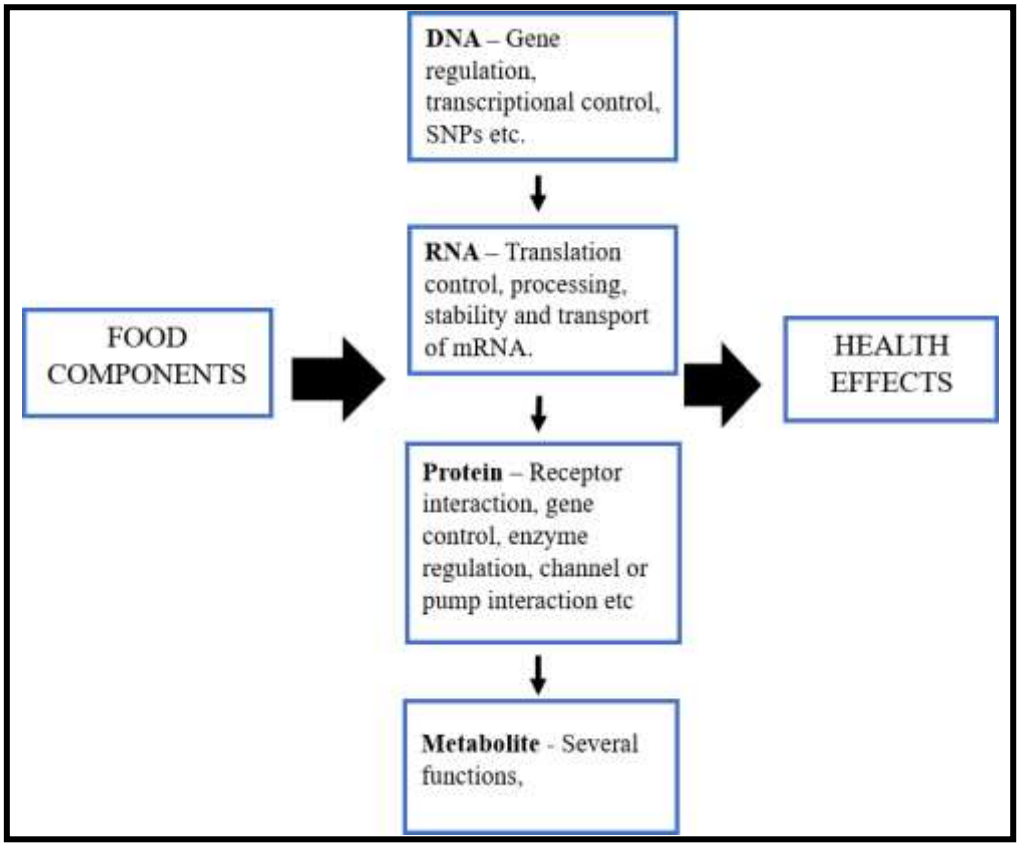

Fig.1. Specific molecular interactions caused by food that leads to health effects.

The biggest goal that nutrigenomics aims to achieve is increasing the practicality of creating personalized diet plans. This would be built on how the nutrients an individual ingests interactwith their genes and affect their metabolic pathways. Ayur nutrigenomics is a new area of research under this line of study (Vyas et al., 2018). It is a form of pre-emptive medicine combining Ayurveda and genomics. Here an individual's chances of developing diseases are analyzed based on his/her genetics, environment, lifestyle and pedigree (*prakriti*). It then formulates a customized ayurvedic treatment protocol than can preventive or curative depending on the homeostatic variation (Mukerji and Prasher, 2011). The role of genetic variations in the pathophysiology of diseases have already been proven. Pharmacogenomics orthe study of precision medicine, analyses a patient's genetic makeup and its response to specificdrugs in order to create personalized medicines that can help treat the diseases. Nutrigenomicscan help take this a step further by producing results that are more permanent and without the side effects that the drugs may cause. This could be through disease prevention by diet intervention. Currently this is possible only for a few nutrient related disorders like obesity, type 2 diabetes, cardiovascular diseases, some cancers etc. With a more comprehensive analysisof genetic variations using novel technology, prevention and treatment of polygenetic disorders could also become easier (Virgili & Perozzi, 2008). Even Hippocrates, father of medicine is believed to have said, "let food be thy medicine and medicine be thy food." Since the 1980s principles of nutrigenomics have been applied in the treating and managing IEM (Inborn Errors of Metabolism) like phenyl ketonuria, galactosaemia, tyrosinemia etc. Recent advancements have brought to light the exact nutritional implications of metabolic disorders. Typically, it would require to eliminate the nutrient involved in order to balance the enzymatic or metabolicdefect. Nutritional research and diet- gene interaction studies help provide nutrition support with other functional foods and dietary supplements that would ensure proper growth and development even in the absence of the restricted foods. (Kaur et al., 2018). Science has stipulated that all the answers to the human existence and evolution lies within our genes. In this regard nutrigenomic studies will able to reveal how dietary element act on human genomeand may cause structural changes, how diet can be risk factor or can be involved in the onset and progression of certain diseases (Srilakshmi, 2006).

Genetic studies conducted in order to study the causes of hereditary diseases has unraveled theheterogeneity and multifactorial heritability of Metabolic Syndrome (MetS). People with MetS suffer from high blood pressure, hypertriglyceridemia, low HDL cholesterol levels, insulin resistance and in most cases gynoid obesity. These risk factors make them susceptible to diabetes, obesity, cardiovascular diseases, inflammatory bowel disorder (IBD), PCOS etc.

Diabetes is one of the few metabolic disorders where the role of genetic factors in disease prevalence has been properly studied. Even type 1 diabetes or Insulin Dependent Diabetes (IDD), despite being an autoimmune disorder that is organ specific has a considerably solid genetic factor. Studies have shown genomic

connotations of HLA class II gene, insulin gene (INS), cytotoxic T-lymphocyte-associated protein 4 gene (CTLA4), protein tyrosine phosphatase, non- receptor type 22 gene (PTPN22) and interferon induced with helicase C domain 1 gene (Steck & Rewers, 2011). On the other hand, type 2 diabetes or Non-Insulin Dependent Diabetes (NIDD) has definitive genetic origins. Chlorpropamide alcohol flushing (CPAF) caused by the sensitivity to a neuropeptide called enkephalin is a strong genetic markerfor NIDD. Enkephalin is known to work a lot like morphine and morphine has proven hyperglycemic action. Hence by conjecture enkephalin in high amounts is believed to inhibit insulin secretion from islets of Langerhans in the pancreas. People with CPAF have 70 per centchance of developing type 2 diabetes in successful generations (Pyke, 1979).

Obesity being a metabolic disorder is caused by multitude of genetic mutations. Leptin, leptin receptor gene, melanocortin 4 receptor gene, pro-opiomelanocortin gene, carboxypeptidase E gene and prohormone convertase 1 gene have effects on glucose tolerance, leptin levels, satiety, food intake and energy expenditure (Loos & Bouchard, 2003). Cardiovascular diseases have considerable genetic etiological background. Epidemiological studies show cardiac defects that stem from single or multiple gene mutations. Currently 23 genetic markers associated to CVD have been detected. The mutations of cardiac sodium channel gene (SCN5A), sarcomere protein genes, elastin gene (ELN) and others can lead to haploinsufficiency, long QT syndrome,cardiomyopathy and arrythmia (Milewicz & Seidman, 2000).

With a clear genetic connection in the pathophysiology of a disease, applying the concepts of nutrigenomics to its management is easier and productive. Nutrigenomics aims to prevent disease and improve health status in the long run but presently its focused on finding the link between deviant phenotypes and genes that are affected by food components (Kaput, 2007). As a scarcely explored field nutrigenomics, along with nutrigenetics explores other important yet rarely discussed topics like personalized nutrition. Despite the proven connection between diet and diseases, the use of dietary interventions that are both disease centric and patient centric are limited. Through an individualized approach involving food and lifestyle, positive health outcomes can be observed (Ordovas et al., 2018).

BACKGROUND

The curiosity regarding nutritional genetics dates back decades, on how food affects the body on a molecular level and why some people respond to certain foods differently. Fortunately, theHuman Genome Project (1990 – 2003) sequenced the complete set of human genomes and made it accessible for detailed studies. Scientists were able to discover the evolutionary relationship between humans and food choices (Neeha and Kinth, 2013). For example, in 2002, Enattah and his colleagues discovered a heritable autosomal dominant trait called lactase persistence in some ethnic populations of Northern Europe, Middle East and Africa. Normallyin adults the lactase enzyme is not functional after the weaning period. Over time single nucleotide polymorphism (SNP) of the lactase gene allowed it to persistent and active through adulthood. This was a beneficial genetic adaptation that enabled these groups to consume milk and dairy products when the crop yields are not sufficient. Nutritional research has ever since tried to detect genes that have specific interactions with dietary elements (Fang et al., 2012).

Nutrition related diseases and disorders have been classically evaluated through human intervention studies and application of biomarkers to know the effect of essential nutrient deficiencies, micronutrient imbalance or even the toxic levels of other compounds. Using the knowledge obtained from the human genome sequence about gene function and interaction, biomedical analysis of disease mechanism has become more accurate. Nutritional genetics and genomics data is obtained from -omics disciplines like genomics, proteomics transcriptomics and metabolomics (Van Ommen, 2004).

Genomics studies the structure, function and mapping of genes. This information integrated with bio informatics can provide proof of phenotypic alterations caused by dietary elements and supplements. The effect of single nucleotide polymorphism on metabolic response to nutrients has already been proved. Developing a personalized and genotype- based diet based on the nutrigenomics model can valuable at individual and population levels (Ferguson et al., 2010). Genomic studies can explain food allergies, receptor-mediated nutrient sensing, enzymeinteractions and gut microbiome functions. The gene food interactions can be both negative and positive. Its effect on the expression of genetic makeup can be affected by evolutionary factors like polymorphism of the methylenetetrahydrofolate reductase gene (MTHFR) due reduced consumption folate rich vegetables and lifestyle variables like smoking or alcohol consumption (Mead, 2007). Proteomics is a discipline of biology that explains protein structure, composition and function. Although it provides a much better understanding of an organism's structure and function compared to genomics, proteomics is more intricate as protein expression is subject to time and environmental variations (Al- Amrani et al., 2021). Out of the 100,000 functional proteins in humans, a large number are involved in the digestion, absorption and metabolism of nutrients and others acts as biomarkers of health status. Proteomics essentially addresses the 'response to diet' part of nutrigenomics by identification and quantification of the bioactive proteins and peptides. This would extremely helpful in dealing with nutrition related problems and disorders

(Wang et al., 2006 & Kussmann, 2009). All the information contained in the genome (DNA) istoo vast and complicated to be studied. The process of transcription codes this information to RNA molecules that forms the proteins which then present as observable traits. In this context transcriptomics can be used for the biomarker profiling of the RNA transcripts altered by dietary components. This has extensive applications in precision nutrition (Habib et al., 2022).

Another important tool in nutrigenomics is metabolomics that studies endogenous and exogenous metabolites and their role in biological pathways and as disease risk indicators. Metabolomic technologies can provide valuable insights into the link between diet and disease(Clish, 2015).

NUTRIGENOMICS & DIABETES MELLITUS

Non -Insulin Dependent Diabetes (NIDD) although a primarily a lifestyle disorder, can also bedue to genetic mutations. As discussed earlier there more than 76 genetic variations associatedwith type 2 diabetes (T2DM). A majority of these gene expression is influenced by diet and nutrition. For instance, the substitution of proline with alanine in the peroxisome proliferator -activated receptor gamma (PPARG) can reduce the risk of NIDD. These Ala12 variants can upregulate PPARG gene by binding with unsaturated fatty acids and negate the negative action of saturated fats on glucose metabolism. The TCF7L2 variant gene's T2DM risk can be modified through a low glycaemic index diet. Additionally, SLC30A8 zinc transporter gene found in the Islets of Langerhans of the pancreas have an effect on insulin secretion. The individuals who have the SNP variants SLC30A8 can lower their fasting glucose levels throughzinc supplementation.

Recent research showed the elucidated the interaction between 14 dietary factors namely; glycaemic load, protein, total energy, carbohydrate, alcohol, total fat, SFA, MUFA, PUFA, n3fatty acids, n6 fatty acids, n3: n6 FA, trans fat and fibre and the 4 T2DM phenotype variant traits – fasting insulin, fasting glucose, insulin resistance and β cell function. Out of all the factors have tremendous effect on glucose homeostasis. Dietary flavonoids specifically epigallocatechin gallate (EGCG) found in fruits, tea and chocolate can stimulate insulin secretion from β cells affected by cytotoxicity due to BCL-2 modified expression. Other gradesof flavonoids like apigenin and luteolin (celery and herbs) and isoflavonoids like daidzein and genistein (soy foods) by regulating the genistein-induced cyclin D1 (Ccnd1) expression improving hyperglycaemia, glucose tolerance and β cell proliferation. Vitamins also play a major role in the modulation of genes involved in glucose homeostasis. Vitamin D adjusts chemokine expression, boosting β cell functions. Cytokine induced increase in IL-6 mRNA expression can be avoided through biotin intake. In the same way amino acids leucine, taurine, L-alanine and L-glutamine regulate class of genes like Sur-1, mTor complex, Glut-2 and theircorresponding phenotypic traits that might implicate diabetic symptoms (Berna et al., 2014).

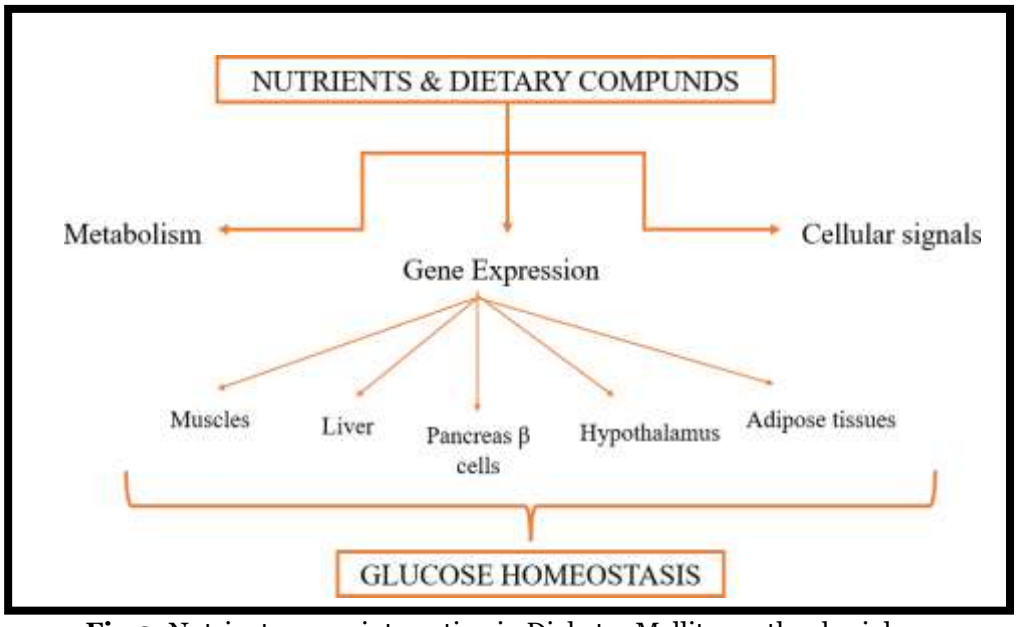

Fig.2. Nutrient – gene interaction in Diabetes Mellitus pathophysiology

NUTRIGENOMICS AND CARDIOVASCULAR DISEASES

Cardiovascular diseases (CVD) can be a ramification of gene- diet interaction along with several other environmental factors. However, the effect can be variable in different populations. Twin studies and epidemiological researches conducted in the past decade revealed single nucleotide polymorphism at the Peroxisome proliferator-activated receptor alpha (PPARA) and perilipin (PLIN) loci to be major risk factors. Both these genes have majorrole in energy homeostasis through lipid and glucose metabolism and adipocytes access for lipolysis respectively (Low & Tai, 2007). Biochemical evidence-based etiology of CVD like ischemic

strokes, coronary heart disease and peripheral aortic disease already proves the importance of maintaining an appropriate serum lipid profile. This involves HDL, LDL and total cholesterol levels, triglycerides, apolipoprotein obtained saturated, monounsaturated andpolyunsaturated fatty acids (Dong et al., 2021).

Numerous nutrition intervention studies were conducted by scientists to examine the interactivity of diet and the allelic variants of the genes that express CVD risk factors or relatedphenotypes. An abridged version of the results those studies produced is condensed here. The presence of the recessive allele A in APOA1 showed an elevation in postprandial LDL cholesterol after high MUFA intake (Lopez-Miranda et al.,1994). The reaction between vitamin B12 and folate decides the plasma homocysteine levels in MTHFR gene (D'Angelo et al., 2000). Similarly following a Mediterranean diet reduced the plasma homocysteine levels. Saturated fat causes high VLDL cholesterol and lower HDL cholesterol concentrations in E2 carriers of APOE genotype (Campos et al., 2001). In individuals who have Glu298Asp SNP ofthe endothelial nitric oxide synthase (eNOS) gene, showed good flow mediated brachial arterydilatation on Omega 3 interaction (Leeson et al., 2002). In the Angiotensin I- converting enzyme insertion-deletion polymorphism, the ID-II variants showed a linear response to dietarysalt consumption (Zhang et al., 2006). Salt intake has a similar relationship with M235T polymorphism in the gene that codes for the protein angiotensinogen. Some specific disease-based studies have also produced promising results. Serum folate amount controls ischaemic stroke and coronary artery disease chances in C677T SNP of the MTHFR gene (Markus, 1997& Yoo, 2000). Isothiocyanates, found in broccolis, cabbages etc generates modified Glutathione S-transferase (GST) genotypes that decreases the possibility of myocardial infarction (Cornelis et al., 2007). Despite these encouraging results these studies have significant limitations as the sample size of subjects is less. Recommending a standardised dietor nutrient intake based upon these results is not probable without considering other factors like age, sex, smoking, physical activity etc in cross study analysis. Fortunately, large scale Genome wide association studies and novel technologies can help bridge this gap in the near future (Corella & Ordovas, 2009).

OBESITY AND NUTRIGENOMICS

Obesity is one of the most prevalent diseases in the world today that account for morbidity andmortality. Apart from being a threat itself this excess and unhealthy body fat accumulation presents the risk of other chronic diseases. Like the previously discussed disorders obesity too has a plausible genetic background along with extrinsic causes (Elliot & Johnson, 2007). In terms of precision nutrition in obesity management the primary goal is weight management. Generally, it would involve calorie restriction from the macronutrient intake. Fashioning a dietary intervention to realise this goal is much easier if you can quantify the exact genetic and epigenetic biomarkers of the disease. Understanding how a specific nutrient interacts with the process of transcription and translation increases the efficiency of weight management by regulating the associated aspects such as food intake, lipid and glucose metabolism, insulin signalling and the circadian cycle.

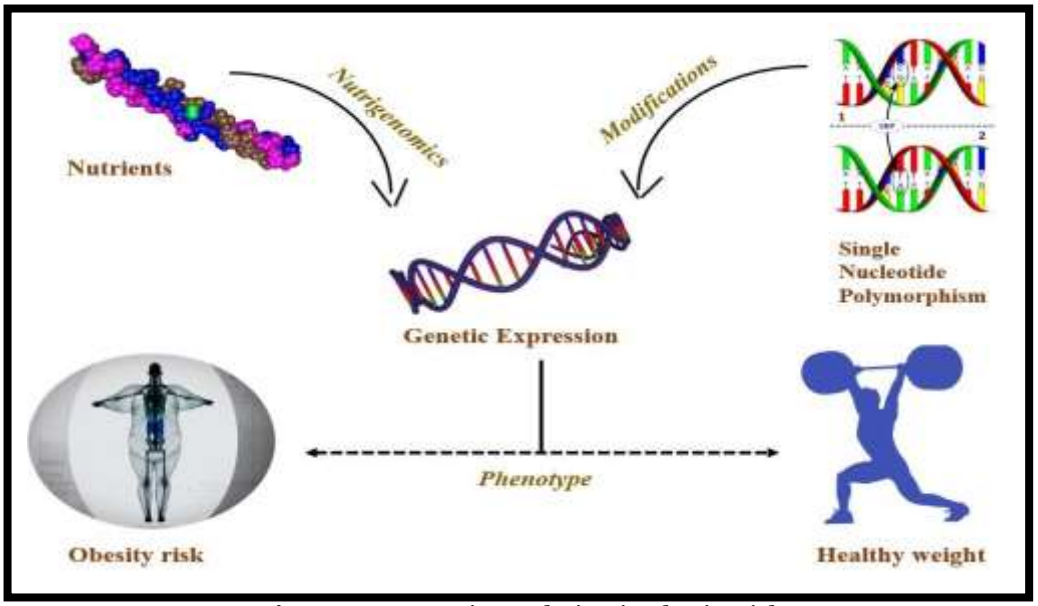

Fig. 3. Gene-nutrient relation in obesity risk

Nutrigenetic trials conducted among SNP variants using specific nutrient treatments have givenreliable results. In fat mass and obesity associated (FTO) gene showing rs9939609 polymorphism presents obesity risk on high fat diet. Same is true for rs8050136 of the FTO gene when carbohydrate intake is high. Conversely FTO rs1558902 gene show better weight loss response to increased protein intake. Increased consumption of milk products links to chances of developing obesity in LCT (lactase) gene rs4988235 variants. Increased total fat ingestion has similar effect on PPARG rs1801282 gene. Abdominal obesity is a common risk when vitamin E

supplementation is reduced in rs2301241 thioredoxin (TXN) genotype.Following a Mediterranean diet limits weight gain in rs2069827 SNP in IL6. Some of these metabolic alterations are multifactorial. The differential response of the genes is also governed by macronutrients, micronutrients and bioactive compounds. The neuropeptide genes that regulate food intake may undergo disrupted methylation patterns due to high fat and sugars. Protein deficient diets can cause abnormal histone modifications in vital genes affecting lipid and glucose levels. Non-alcoholic fatty liver, a consequence of obesity and high cholesterol can be aggravated by choline and folate deficiencies. The methylation pattern of lipogenic genes can be modulated by polyphenols and pterostilbene to avoid diet instigated obesity. Several clinical studies revealed that the supplementation of omega-3 fatty acids can mediate the genetic expression of polymorphism in PPARA and APOA1 genes affecting plasma triglyceride status (Ramos-Lopez et al., 2017).

CONCLUSION

Personalised nutritional intervention has been one of them prime focus of nutritional research in the past two decades. The emergence of nutrigenomics is a main reason for this. Current diet interventions although disease-specific, are generally population based. However, every person responds to food differently. The genetic variables, presence or absence of SNPs,efficiency of protein translation or other environmental factors can cause such differential response. In such cases individualised diet therapy would be the ideal choice. Nutrigenomics aims to identify biomarkers that will indicate disease susceptibility and determine the nutritional agents that can modulate the involved gene expression. In order to quantify such specific gene sets, advanced techniques of genomics, transcriptomics, proteomics and metabolomics must be utilized. It can demonstrate how nutrients alter DNA structure and the associated metabolic pathways. In terms of metabolic disorders like obesity, CVD and diabetesmellitus which are largely diet related, genomic profiling of nutrient interaction can beneficialin early detection and disease management in later stages. Understanding the specific gene- nutrient interaction that can regulate the disease risk factors makes it easier to mitigate them early on. Numerous seminal research has already been conducted in this field that has had promising results. Scientists and physicians are using these findings extensively in the field of preventive medicine to look for the potential etiological biomarkers in a person's genome and correct them using tailor-made nutritional therapy before the putative disease onset. Nutrigenomic studies collect comprehensive information regarding genetic makeup, heredity, ethnic profile, food habits and lifestyle. Governments and health care professionals should be careful in handling such sensitive data and establish guidelines to protect patient integrity and privacy. As a still expanding field of nutrition science application of nutrigenomics principlesare cautiously optimistic.

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