



NUTRIGENOMICS – A NEW HORIZON IN PERIODONTICS

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Abstract:

Nutrigenomics is an emerging scientific research speciality which deals with the role of nutrition on gene expression. With excellence in uniqueness, as it focusses on individual response to specific nutrients depending on individual's unique genetic makeup, it is widely accepted among individuals. Globalization and economic progress have led to lifestyle diseases. Unhealthy habits and sedentary lifestyle have led to lifestyle diseases. The main aim of nutrigenomics is to provide personalized dietary information to the public based on individual's unique genetic make-up. The present review focusses on basic concepts of nutrigenomics, the role of diet on gene expression, how diets modify systemic diseases and nutrient – gene interactions.

Keywords: Nutrigenomics, Gene expression, Dietary information, Genetic make-up, Periodontitis.

1. INTRODUCTION:

Periodontitis is defined as a non-reversible tissue destruction resulting in progressive attachment loss, eventually leading to tooth loss.^[1] The successful management and treatment of periodontitis has achieved more importance in recent years with the recognition that periodontitis is a risk factor for a number of major systemic diseases, like diabetes mellitus, cardiovascular disease, and rheumatoid arthritis.^[2-4]

Destruction of periodontal tissue occurs as a result of host- immune inflammatory response to plaque bacteria. A variety of risk factors have been identified that modify the host response to bacterial challenge resulting in the development and progression of periodontal disease which in turn result in host mediated tissue damage.^[5] These risk factors include genetic, epigenetic, environmental and lifestyle/ behavioural factors. Among the risk factors, genetic risk factors have a potential role for cross susceptibility between periodontal diseases and variety of chronic diseases like type 2 diabetes mellitus, cardiovascular diseases and rheumatoid arthritis.

Nutrition can create a lifestyle impact on human health status.^[6] Modern molecular nutrition emphasis on promotion of health, reduction of disease risk and performance improvement through diet and lifestyle considerations. Nutrients that are important for

maintaining the periodontium have been the focus of epidemiological studies for many years. For example, vitamin A, folate and vitamin C helps in proper development and repair of mucosal and connective tissues; protein, calcium and phosphorus are incorporated into the structures of collagen, teeth and bone; omega fatty acids and vitamin D help to regulate immune function.^[7&8]

Antioxidants acts as a new platform for prevention and treatment of periodontal disease and diet should be supplemented with natural antioxidants like vitamin D, calcium and fish oils (omega 3 fatty acids)^[9]. Implementation of nutritional counselling will reduce inflammation and promotes better treatment outcome with periodontal therapy and ultimately prevention of tooth loss.

Nutrients and genomics interact^[6]. Knowledge regarding the mechanism behind periodontal tissue destruction and the magical role of nutrients and genetics led to a new genomic era "Nutrigenomics". The main aim of nutrigenomics is to unravel the link between nutrition and genome and to provide scientific knowledge for improved health status through dietary means.

2. ORIGIN OF NUTRIGENOMICS:

Health is influenced by diet. A well- known quote of Hippocrates is that 'let food be thy medicine and medicine be thy food'. So, the importance of nutrition has been focused and mentioned in the

ancient periods as well. Obesity and diabetes mellitus are the two main nutrition related health problems faced by the modern era and in order to prevent the development of these types of disease, research is focussing on how nutrients act at the molecular level. As a result, nutrition research shifted from Epidemiology and Physiology to Molecular Biology and Genetics and led to the origin of nutrigenomics. Genes may interact with dietary components. Nutrigenomics include interaction between genes and nutrition^[10].

Table1: Sequence of evolution of nutrigenomics

1980's	Companies started commercialising nutrigenomics.
1997	First nutrigenomics company launched
April 14, 2003	Genomic era launched by the launching of Human Genome Project in presence of former US president Bill Clinton and former British prime minister Tony Blair which contained the complete sequencing of Human Genome
2004	NuGo (European Nutrigenomics Organization) was born which aims to enhance future research efforts in nutrigenomics
2007	Nestle Research Centre combined with industrial fermentation
2008	Human Genome tests within 5 years as predicted by US Berkeley Scientist

3. DEFINITION AND BASIC CONCEPTS OF NUTRIGENOMICS:

Dietary factors interact with gene and modulate disease risk in certain individuals and populations who are at risk. This interaction between nutrition and genetics is called nutritional genomics^[11].

Nutritional genomics explains:

- ❖ Nutrigenetics
- ❖ Nutrigenomics

Nutrigenetics deals with the impact of genetic background of an individual on diet. Nutrigenomics is the research speciality which deals with the effects of nutrients on genes, proteins and metabolites^[12]. Nutrigenomics' goal is to prevent the onset and progression of various chronic diseases. Initial studies focussed on the effects of nutrients on expression of gene of an individual. However nowadays, nutrigenomics also includes the studies on nutritional factors that acts as a major component in protecting the genome^[13].

3.1 Five basic principles of nutrigenomics research are as follows: -

1. Gene expression or structure is altered by common dietary chemicals that act on human genome either directly or indirectly
2. Diet which is improper can act as a risk factor for disease in some individuals.
3. There are some diet regulator genes which play a role in the onset and progression of chronic illness.
4. The degree to which diet influence the balance between health and disease state mainly depends on the individual's genetic profile.
5. Daily intervention of personalized diet can be used to prevent or cure chronic diseases^[14].

4. DIET MODIFYING GENE EXPRESSION:

The role of diet as a predisposing factor for the progression of dental caries is well explained in the literature but its role in the progression of periodontal disease is least explained in literature^[15]. Diet can modulate the inflammatory and immune response that maintain the cell integrity and thereby promoting periodontal health^[16]. Diet is a powerful signal to our genes that can have a positive impact on our metabolism, longevity, and mental well-being. Nutrition acts as a dietary signature that can be metabolized and alter signal transduction pathways at proteins, enzymes and metabolites levels. Nutrigenomics studies these dietary signatures and gives information regarding the influence of nutrition on health and diseases.

Nutritional health is an interplay between the environmental factors influencing the dietary components and the genetic factors modulating the digestive system.^[17-20] Nutrigenomics is a novel and multifaceted approach which aims at elucidation of influence of bioactive feed components in the diet on human health. This is achieved by studying the interactions of bioactive feed components with genes and their effect on omic tools like transcriptome, proteome and metabolome.^[21] These omics tools like transcriptomics, proteomics and metabolomics modulate gene expression.^[22]

Genes are read or expressed to produce RNA through transcription and it is the first stage of gene expression. The cluster of all proteins in a cell is called proteome. Proteomics illustrate all proteins in a biological sample at the functional level. Metabolomics evaluate all metabolite levels in saliva, urine and blood plasma^[23]. The advantage of metabolomics is that the biochemical after effects of

mutations and variations in nutrition can be directly analysed ^[24]. Use of not the single tool, it's the combination of all these omic tools that matter in determining the influence of nutrition on gene expression and thereby the early diagnosis and management of diet related diseases ^[25]

Our biology shapes our diet, but our diet shapes our genetic function. A diet high in refined carbohydrates that promotes high blood glucose attacks DNA. Sulforaphane (broccoli), curcumin (turmeric), epigallocatechin gallate (green tea), and resveratrol (wine) are compounds which are effective in slowing or reversing DNA damage. Including cocoa in diet helps in treating periodontitis and improving periodontal health by increasing the levels of mRNA expression of glutathione reductase and superoxide dismutase 1 (SOD1), these in turn helps in cellular defense against oxidative stress. Periodontitis can be prevented by including 10% cocoa in diet has been proved in a study done in rat model where in administration of cocoa inhibited the ROS production^[26]. Cocoa consumption has resulted in downregulation of gene expression for nitric oxide synthase and prostaglandin endoperoxidase synthase which are considered as the major elements for the progression of periodontitis by stimulating the inflammatory response. There is an association between single nucleotide polymorphism in vitamin C transporter proteins and aggressive periodontitis ^[27] and single nucleotide polymorphisms in the vitamin D receptor gene and localized aggressive periodontitis ^[28]. 12-week intervention with phytonutrient grape seed extract lowers the levels of serum C-reactive protein in patients classified as interleukin-1POS than interleukin-1NEG, proving that individual's response to nutritional intervention depends solely on individual's unique genetic makeup ^[29]. Thus, nutrigenomics explain how diet modifies gene expression whereas nutrigenetics explains the response of an individual towards a specific diet and its effects on gene variations based on the unique genetic framework of the individual.

The main objective of nutrient gene interaction is to reproduce the recommendations regarding the risk and benefits of specific diet on individual's unique genetic makeup. Nutrigenomics is considered as an indispensable research area where the public can be made aware about the fact that personalised nutrition has an important role in the prevention and treatment of various chronic illness when it is combined with individual's specific genetic makeup.

5. DIET MODIFYING SYSTEMIC DISEASES:

Type 2 diabetes mellitus, cardiovascular diseases, obesity are the commonly occurring inflammatory diseases and conditions, which are often associated with periodontal disease. Nutrition is essential in keeping the balance between bacterial challenge and host immune inflammatory response, thereby serves as a vital component in preventing various inflammatory diseases and conditions ^[30].

5.1 CANCER

Diet rich in saturated fats and sugars and low in fruits, vegetables and fibres are found to be risk factors and can pave way to various chronic illness ^[31]. Many nutrition-related genes are involved in carcinogenesis and apoptosis, and are molecular targets for dietary chemoprevention. Dietary components such as selenium, retinoic acid, curcumin, and apigenin have their cancer preventive effect by inhibiting apoptosis ^[32]. Green tea, grapes, cruciferous vegetables are considered as food which helps in preventing the cancer risk. Diet rich in soy protein are found to reduce the breast cancer by 15% in case of premenopausal women ^[33]

5.2 CARDIOVASCULAR DISEASES

Epigenomic changes in the vessels contributes to hypertension through a diverse mechanism which targets RAAS (renin-angiotensin-aldosterone) system, the vascular wall and specific cell types within the vessels (figure 1). Epigenetic regulation may also affect the circulating blood cells that interact with vessels ^[34]. The angiotensin 1 α receptor (AT1aR), encoded by *Atgr1 α* , is significantly increased in spontaneously hypertensive rats (SHR) compared to the Wistar-Kyoto rats (WKY), this may be the reason for increased BP in SHR ^[35].

Cardiovascular diseases can be prevented by supplying diet rich with fibers which have the property to reduce the amount of plasma triglycerides and increase the amount of high-density lipoprotein cholesterol ^[15]. Study conducted among 50 men and women who were given diets rich in saturated fat, monounsaturated fat, or PUFA, the results revealed that more marked reductions in LDL cholesterol associated with the PUFA diet compared with the saturated fat diet in women who were carriers of the rarer A allele than in women who were homozygous for the G allele, but these findings are negative in men ^[36].

5.3 OBESITY

Obesity is a common diet related disorder. Obesity increases the chances of developing other chronic diseases like cancer and CVD^[37]. Individual variation seen in body weight and composition likely is influenced by genetic makeup as well as diet and activity patterns^[38]. It's been thought that 25% to 70% of variation in BMI may be due to genetic profile. A 2015 genome-wide association study (GWAS) and meta-analysis of BMI by the Genetic Investigation of Anthropometric Traits, or GIANT, consortium published in Nature identified 97 chromosomal regions, or loci, accounting for about 2.7% of variation in BMI, suggesting that common genetic variations account for more than 20% of BMI variation, even though most of that variability remains unexplained^[38].

5.4 DIABETICS MELLITUS

Diabetes mellitus is a disease of metabolic origin and is considered as a major risk factor for periodontitis. The degree of hyperglycaemia and periodontitis can be clearly correlated. Many scientific researchers have proved the association of type 2 diabetes and periodontitis as both diseases occur usually in their 40's and 50's.

There is an association between the variant genotypes of both interleukin-1A (interleukin-1A-889) and interleukin1B (interleukin-1B+3954 and interleukin-1B-511) and periodontitis in subjects with type 2 diabetes and this association is not seen in nondiabetic controls^[39]. Diet rich in zinc are proved to reduce the risk of type 2 diabetics' mellitus and ultimately periodontitis^[15].

6. NUTRIGENOMICS – A PATHBREAKING CONCEPT REVEALING THE LINK BETWEEN TYPE 2 DIABETES MELLITUS AND PERIODONTAL DISEASES

Nutrition has a definite role in periodontal therapy and it has been proved by various nutrigenomic tools. Various genome wide association studies conducted so far proved the role of micronutrient zinc, zinc transporter gene and the susceptibility for developing type 2 diabetes mellitus. For type 2 DM, genetic susceptibility is a critical factor and these genome wide association studies were able to identify a genetic susceptibility locus for type 2 diabetes mellitus which include single nucleotide polymorphism in a beta cell specific zinc transporter gene^[40]. The zinc transporter gene (SLC30A8, coding for ZnT8) is important in insulin storage and release.

Potential strategies were implemented highlighting the role of Zinc in beta cell functions and these strategies were aimed at treating type 2 DM and there by periodontitis^[41&42]. In near future, Zinc will evolve as a novel pharmacological agent for the treatment of diabetes mellitus and periodontitis as periodontitis is considered as the sixth complication of diabetes mellitus^[43] (figure 2).

Study conducted in rat model evaluated the effects of ZnT8 gene and beta cell function and concluded that ZnT8 gene is required for normal insulin crystallization and insulin release in vivo. Study conducted in cell line model of diabetes evaluated the specific role of zinc transporter gene (ZnT8), and zinc supplementation in improving the beta cell function. RNA knockdown resulted in reduced ZnT8 mRNA levels, and 46 % reduction in 2Nm glucose stimulated insulin secretion thereby proving the possible role of ZnT8 gene in insulin storage and release. Zinc supplementation was given to beta cell line model by incubating the RNA knockdown ZnT8 gene with a range of concentration of extracellular zinc. When its range reached to 100 IM, the insulin level reached to a level similar to that of control cells, proving the potential role of zinc supplementation in insulin secretion. These results can be implemented in the management of diabetes mellitus. The extracellular zinc supplementation modulates the expression of cross susceptibility gene – ZnT8 gene and thus increase the insulin secretion and prevent type 2 diabetes mellitus and thereby prevent the progression of periodontal disease (figure 3).

The difference in response of an individual to dietary modulation varies and this variability purely depends on individual's unique genetic make-up, implicating the possible role of nutrigenomics in the prevention and cure of chronic illness.

7. ADVANTAGES OF NUTRIGENOMICS:

- 1) Nutrigenomics helps in identifying specific nutrients which can modify gene expression in health and disease.
- 2) Genetic variations which alter nutrient gene interaction can be identified
- 3) It provides information to the public regarding the harmful effects of certain nutrients which causes chronic diseases
- 4) It helps in providing personalized dietary menu
- 5) It assists in providing better quality of life.
- 6) Early and better diagnosis of chronic diseases.
- 7) It provides knowledge regarding human biological function, balanced dietary practice and

response of individual's health to these dietary practices.

8. DISADVANTAGES OF NUTRIGENOMICS:

1) Ethical, legal and social issues are to be clarified regarding protection of personal data collected for formulating personalized dietary charts.

- 2) Only specific modifiable risk factors are mentioned.
- 3) Only specific nutrients and foods are focussed.
- 4) Increased cost associated with personalized diet.
- 5) Difference in socioeconomic status in urban and rural population to meet the demands and bioavailability of more nutritious foods.

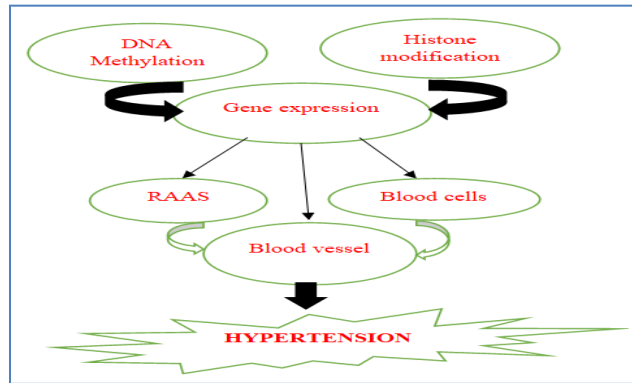


Figure 1: Epigenomic changes in the blood cells leading to hypertension

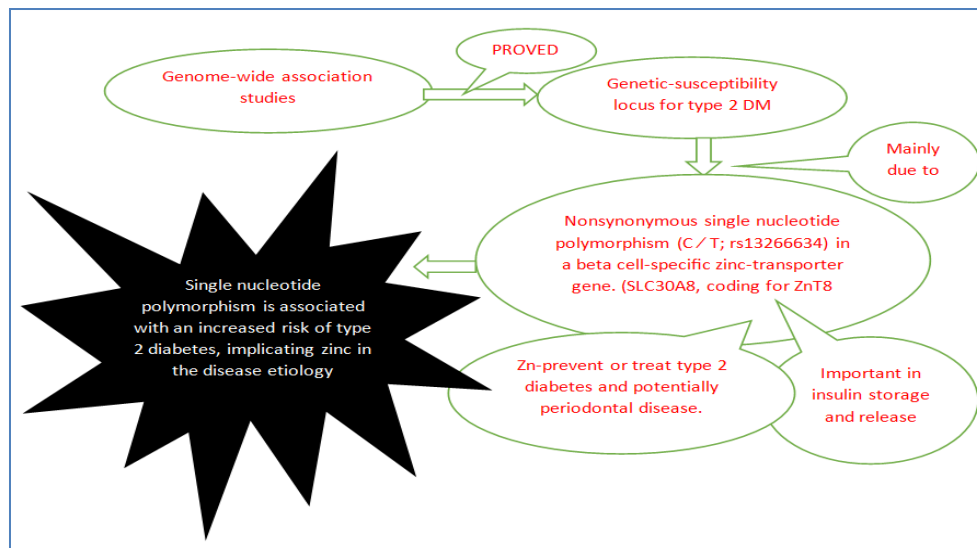


Figure 2: Role of Zinc in the disease etiology

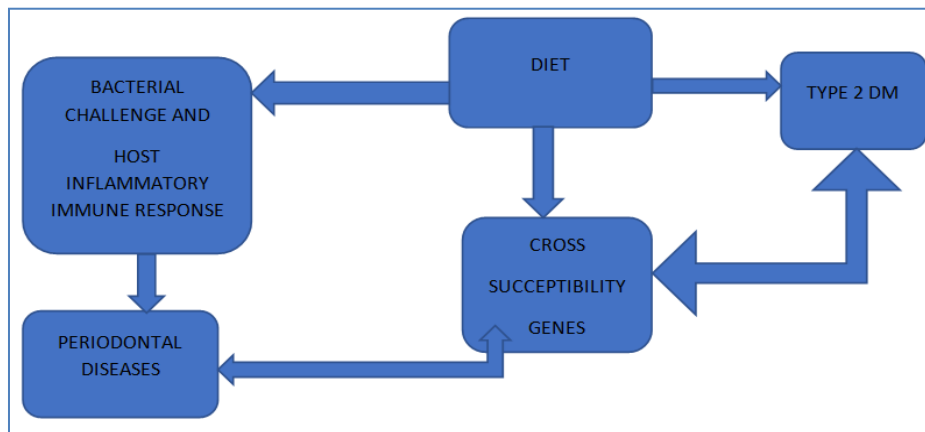


Figure 3: The linking mechanism

9. FUTURE PERSPECTIVES AND CONCLUSION:

Success of nutrigenomics depends on individual's attitude towards nutrigenomics. Nutrition and health research produce personalized food products. The main challenge in the field of nutrigenomics is to face all the demands put forward by the consumers. Moreover, benefits of nutrigenomics should be accessible to each and every one in a given population. Hence it should be made cost effective, by modifying the diet we are intaking, rather than adding supplements to our diet. The ultimate aim is to achieve a healthier, energetic population by providing tailored individual dietary advice. No doubt this wonderful field of science "nutrigenomics" will evolve as a potentially promising field in the coming years which makes life better, healthier and simpler. Individuals reaction to specific nutrients depends on individual's genetic makeup^[44]. Genetic testing will become necessary to identify those high-risk individual groups who may benefit from specific nutritional therapies^[45]. In future, there is scope that people depends on DNA analysis to overcome and avoid genetically related health hazards and diseases.

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