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NUTRIGENOMICS IN PERIODONTICS- AN OVERVIEW

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ABSTRACT

Now that we have entered the postgenomic era, the association between the potential protective role of nutrients and periodontal diseases is well established. It is likely to know that interactions between the genotype and diet are important in determining periodontal disease risk. A change in dietary pattern represents a promising approach in reducing the risk of aging by modulating gene expression. One of the most practical applications of nutritional modulation of chronic disease is that they regulate the expression of key inflammatory genes. Nutrigenomics is a branch of nutritional genomics focusing on identifying and understanding molecular-level interaction between nutrients and other dietary bioactives with the genome. New techniques and knowledge from the Human Genome Project named as nutrigenomics are currently combined with already established scientific disciplines such as pharmacogenomics and toxicogenomics. This manuscript reviews the evidence for nutritional exposures in the etiology and makes recommendations for daily nutritional intake for periodontal prevention / treatment regime.

Key Words: Nutrigenomics, Nutrition, Periodontics, Pharmacogenomics

INTRODUCTION

Periodontitis, involving local microbial challenge and host responses, is an irreversible condition characterized by the destruction of tooth supporting tissues, periodontal ligament, alveolar bone and cementum, eventually resulting in a tipping of the bone-remodeling balance in favor of bone resorption and tooth exfoliation. It is widely regarded as the second most common disease worldwide, after dental decay and in the United States has a prevalence of 30-50% of the population, but only about 10% have severe forms.^[1]

There is an abundance of both empirical evidence and substantial theoretical justification for accepting the widespread belief that periodontal diseases have more than one cause i.e. they are of multifactorial etiology and complex in nature.^[2] Susceptibility to periodontal diseases involves the interplay between genetic, bacterial, environmental and nutritional factors. Common dietary chemicals act on the human genome, either directly or indirectly, to alter gene expression or structure. Genes are important in determining the function, but nutrition is able to modify the degree of gene expression.

Some individuals who are overtly healthy as they reach young adulthood will begin to experience the complications of chronic diseases such as cardiovascular disease, arthritis, osteoporosis, and Alzheimer's disease, whereas others will reach their 80s with minimal evidence of these debilitating conditions. This simple observation defines much of the future focus of the health care delivery system and the search by individuals for prolongation of healthy and productive lives. During our lifetime, nutrients can modify physiologic and pathologic processes through epigenetic mechanisms that are critical for gene expression.

History

- **On 1st April 1869**, the first isolation of DNA was made by Friedrich Miescher.
- **On 25th April 1953**, Watson and Crick published "the molecular structure of DNA".
- **In 1997**, the first nutrigenomics company was launched.
- **In 1999**, the name nutritional genomics was changed to genomics by Nancy Fogg-Johnson and Alex Merolli which provides powerful means of discovering hereditary factors in disease.

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If the genomic era was said to have a precise birth date, it was on April 14, 2003. That was when Human Genome Project^[3] was launched with the participation of former U.S President Bill Clinton and former British PM Tony Blair which contained the complete sequencing of the human genome. It was then realized that a new era in biological and medical sciences was beginning. This is often referred to as the ‘omics’-revolution.

- **In 2004**, NuGo (European Nutrigenomics Organization) was born and funded until June 2010.
- **In 2007**, Nestle Research Center joined the industrial platform of the Kluiver Centre for Genomics of industrial fermentation, Netherlands.
- **In 2008**, US Berkeley scientist predicted human genome tests within five years for \$100.

Practical Applications of Nutrigenomics^[4]

1. Genes and proteins expressed differentially in health and disease that are modifiable by nutrients are identified.
2. Genes, proteins, and metabolites are influenced by specific nutrients that are known to be beneficial or harmful are identified.
 - a. To identify genes, proteins, and metabolites that are altered by dietary fats associated with cardiovascular disease.
 - b. To identify genes, proteins, and metabolites that is altered by omega 3 fatty acids.
3. Genetic variations that alter the nutrient– gene interactions in applications 1 and 2 are identified.

Evolutionary Eating: Caveman Diet to Junk

From the Paleolithic era up to the Neolithic period, approximately 10,000 years ago, man was a nomad who lived by hunting and picking wild fruits and vegetables and his diet was basically made up of game (protein and lipids) as well as wild berries, vegetables and roots (carbohydrates with low glycemic index and high fiber content). Wherein in the modern era people consume high calorie diet that lead to plethora of health problems.

Target Gene Mechanism versus Signature Profile Biomarkers

One of the main applications in nutrigenomics research relates to health and prevention of chronic diseases (such as e.g., cardiovascular diseases, periodontitis, metabolic syndromes, cancer, etc) through diet. Also these disorders are multifactorial in origin and the loss of biological homeostasis maintenance and altered biochemical composition of cells can be primary cause in disease. So there is a need to understand the molecular mechanisms that describe homeostasis at biochemical, cellular and organ levels associated with the healthy and diseased states. As a result, there is a need for molecular biomarkers that allow early detection of the onset

of disease or, ideally, the pre-disease state. These early effect biomarkers should accurately reflect subtle changes in homeostasis and the efforts of the body to maintain it. However, the discovery of such biomarkers is not easy since diet-gene interactions are complex.

Unlike the comparative simplicity of the single-gene disorders, chronic diseases are likely the result of multiple genes and multiple variants of each gene interacting with multiple environmental factors, each combination making a relatively small contribution to overall homeostasis, function and health. Thus, to determine health status and reflecting the functional response to a bioactive food component, complete biomarker profiles of gene expression, protein expression and metabolite production will be more useful than single markers. To do this, the availability of advanced analytical techniques will be essential for the investigation of complete biomarker profiles of gene expression, protein expression and metabolite production.

It is well known that interleukin-1 gene polymorphisms are associated with severe periodontitis. Studies in nonhuman primates have shown that drugs that specifically block IL-1 and TNF- α dramatically and significantly reduce the tissue destruction even when the bacterial challenge is not reduced.

It is shown that persons with IL-1 genotype are consistent with haplotype-1, i.e carriage of allele 2 at both IL-1A (-889) and IL-B (+3953), had an increased risk of severe periodontitis.^[5] Since then 17 studies have been published that had evaluated the association of IL-1 genotypes with severity of periodontal disease in white adults.^[6] Fourteen of those reported statistically significant associations, whereas three failed to show association between IL-1 gene variation and the severity of periodontal disease.

It is well established that certain nutrients have direct effects on gene expression through both epigenetic mechanisms and modification of transcription factors.^[7] Polyunsaturated fatty acids (PUFAs) are one such example of nutrients that directly alter transcription factors through the nuclear peroxisome proliferator activated receptors (PPARs). These receptors bind to fatty acid ligands and then form a heterodimer complex with another nuclear receptor, retinoid-X- receptor. This heterodimer complex binds to specific DNA sequences to regulate gene expression. PPAR activation has been shown to modulate inflammation, including the inhibition of secretion of IL-1, 6, TNF- α by stimulated monocytes.^[8]

Other nutrients alter the oxidation–reduction status of the cell to indirectly influence transcription factor activity. Many antioxidants will alter the activation status of the transcription factor nuclear factor κ B, which is a key regulator of many genes.

Nutritional compounds such as n-3 fatty acids and isoflavones have been shown to alter genes that code for cytokines, growth factors, cholesterol-metabolizing enzymes and lipoproteins. There is a strong interaction between the dietary intake of PUFAs and the 5-LOX polymorphism.

A recent study found an association between one polymorphism in the inflammatory gene arachidonate 5-lipoxygenase (5-LOX) and risk of cardiovascular disease. Data reports have shown that persons who are homozygous for 5-LOX polymorphism have a greater thickness of the carotid arterial wall. However, there was a strong association between the dietary intake of PUFAs and the 5-LOX polymorphism and it was found that PUFAs are known to regulate the expression of several inflammatory genes.^[9]

Dietary Signatures

- Act as ligands for transcription factor receptors
- Be metabolized by primary or secondary metabolic pathways thereby altering concentrations of substrates or intermediates.
- Alter signal transduction pathways at the level of proteins, enzymes, metabolites- cell function.

Nutrients function as signals that are detected by sensory system in our body which interpret information from nutrients about dietary environment including transcription factor, change in gene, protein expression, metabolite production that specifically target the biological activities that are influenced by variations in key inflammatory genes and offer greater potential to modulate the clinical expression of some chronic diseases. Also different diet can produce different signal pattern.

Epigenetics

It can be defined as somatically heritable states of gene expression resulting from changes in chromatin structure without alteration in the DNA sequence, including DNA methylation, histone modifications and chromatin remodeling.^[10] Epigenetic modifications can be carried out by altering external or internal environmental factors and have the ability to change gene expression. In the past, epigenetics was focused on embryonic development, aging and cancer. Presently, epigenetics is exceptionally important, because nutrients and bioactive food components can alter the expression of genes at the transcriptional level. Folate, vitamin B-12, methionine, choline, betaine can affect DNA methylation and histone methylation. In recent years, epigenetics has become an emerging issue in broad range of diseases such as type 2 diabetes, obesity, periodontal diseases and neurocognitive disorders.

Studies that highlight the importance of interactions between genotype and diet in determining the risk of diseases.

- Individuals homozygous or heterozygous for a particular single nucleotide polymorphism in the estrogen receptor gene, and who consumed higher amounts of phytoestrogen and isoflavone was shown to have reduced prostate cancer risk (57% and 27%).^[11] (Chang et al 2006)
- No association was found between soy diet and cancer risk in subjects who are homozygous to a wide type allele. But individuals carrying a variant of N-acetyl transferase 2 gene and consumed high amount of cooked red meat was shown to have risk of colon cancer.^[12] (Hein et al DW 2002)
- Low dietary intake of PUFA and polymorphism of transcription factor had high levels of plasma triglyceride levels and low levels of high density cholesterol.^[13] (Low et al 2007)

Micronutrients in Gene Expression

Common chronic diseases are complex in their biochemical processes, and many of these diseases have strong genetic influences that explain a significant part of the variance in the clinical expression of the disease.

- However, it is almost certain that some genes will have more of an influence than others on the future course of a disease and on the effects that specific nutritional compounds have on overall health.

Diseases arise because of genetic predispositions to one or more of these stressors such as psychological stress, inflammatory stress, oxidative stress, metabolic stress. Nutrigenomics represents a major effort to improve our understanding of the role of nutrition and genomic interactions in at least the first three of these areas.

The role diet plays in the development and progression of dental caries has been well characterized in the literature, but the importance of nutrition as a predisposing factor for the development of periodontal disease is not well defined. Recently it has been suggested that nutrition is important in redressing the balance between microbial challenge and host response because it is implicated in a number of inflammatory diseases and conditions.^[14] (Vander Velden 2011)

Increase in oxidative stress is antagonized by a complex system of antioxidants which include antioxidant vitamins. However it has been demonstrated that the most important small molecule antioxidant species is glutathione. Glutathione exists in both oxidized (GSSG) and reduced (GSH) forms.

Specific nutrients (antioxidant vitamins A, C, E) and trace element selenium, copper, zinc can modulate the immune and inflammatory responses that maintain epithelial cell integrity and structure. The nutrients get depleted during inflammation with generation of Reactive Oxygen Species (ROS) causing damage to the cellular tissues.^[15] (Hornig 2007)

Moreover, selenium has further important redox functions, with selenium-dependent glutathione enzymes being involved in the reduction of damaging lipid and phospholipid hydroperoxides to harmless products.

Vitamin C acts as a powerful scavenger of free radical. The association between low intake of vitamin C and occurrence of periodontitis has been demonstrated, in a study by Nissada 2010.^[16]

Vitamin E terminates free radical chain reaction, stabilizes membrane structure. It is shown to have mitigatory effects on inflammation and collagen breakdown. A low level of vitamin E in gingival tissues of periodontitis patients has been reported. (Offenbacher 1990)^[17]

Omega 3 fatty acids such as n-3 PUFA (oily fish), increase the tissue concentration of eico-sapentaenoic acid, decosahexaenoic acid and down-regulate inflammation and inhibit bone loss in vitro. (Sun et al 2003)^[18]

DISCUSSION

Nutrigenomics and Periodontics

It has also been reported that the n-6 PUFA levels in the serum are higher in periodontitis patients, suggesting that an imbalance between n-6 and n-3 fatty acids may contribute to susceptibility to oral bone loss.^[18] (Requirand et al 2000)

The main functional value of pomegranate in oral health is its polyphenolic flavonoid content. The components of pomegranate juice were found to significantly inhibit cytokine IL-8, PGE₂, nitric oxide, human salivary α -amylase, α -glucosidase activity and found to reduce aspartate aminotransferase activity in saliva. The hydro-alcoholic extract from pomegranate fruit has shown to decrease the Colony Forming Unit (CFU) per milliliters of dental plaque by 84%. Local action and topical effects of antioxidant agents from pomegranate on the oral tissues have been hypothesized to have preventive effect against diseases of the oral cavity.

One minute rinsing with a mouthwash containing pomegranate extract successfully reduced the amount of microorganisms cultured from dental plaque.^[19] (Di Silvestro RA 2009) The seeds of *Garcinia mangostana* are reported to contain vitamin C. A composition in the form of a biodegradable gel, chip or ointment is provided for the treatment of periodontitis, comprising an antimicrobial or antibacterial activity against periodontal pathogen and forms a liquid crystal structure on contacting gingival fluid, which releases active ingredients gradually, to provide a sustained release dosage form.

The effect of *Morinda citrifolia* L. fruit juice significantly mitigated the gingival inflammation. The combination of

good oral hygiene and administration of this juice was a promising treatment for gingivitis and periodontitis because of its strong anti-inflammatory effects.

Results from a prospective, observational study carried out over 14 years revealed that men with high consumption of wholegrain were 23% less likely to develop periodontitis.^[20] (Merchant 2006)

A recent randomized double blind clinical trial investigated the potential clinical benefits of a powdered fruit and vegetable juice concentrate on the treatment of patients with chronic periodontitis and showed that there was increased pocket depth reduction following standard non surgical therapy compared to a placebo group.¹⁵ (Vander Veldon 2011)

- Research studies using an experimental gingivitis model have shown increased levels of bleeding on probing when participants were fed with a diet high in carbohydrates when compared to those on a low sugar diet.^[21] (Ashley 1984)
- This finding has been further supported by a study investigating volunteers placed on a primitive diet which was high in fibre, anti-oxidants, and fish oils, but low in refined sugars and with no oral hygiene measures.^[22] (Robinson 2000)

As would be expected plaque levels increased significantly and classic periodontal pathogens emerged within the bio-film, but unexpectedly gingival bleeding significantly reduced from 35% to 13%.

A rodent model of zinc deficiency has shown to have an increased susceptibility to periodontal disease progression, as revealed by increased plaque and higher gingival index measurements. As an example of the potential of nutrigenomics tool for assessing the role of nutrition in periodontal disease, the role of the micronutrient zinc, a zinc transporter gene and the risk of developing type 2 diabetes was investigated. Recent genome-wide association studies have identified a genetic-susceptibility locus for type 2 diabetes comprising a nonsynonymous single nucleotide polymorphism (C/T; rs13266634) in a β cell-specific zinc-transporter gene. This zinc transporter gene (SLC30A8, coding for ZnT8) may be important in insulin storage and release. ^[23, 24, 25]

In light of this new finding, the existing knowledge that zinc has a specific role in beta cell function takes on new significance with respect to potential strategies to prevent or treat type-2 diabetes and potentially periodontal disease.

The recommendations of 2011 European Workshop on Periodontology suggested that the dental team should consider including fish oils, fibre, fruits and vegetables and to reduce levels of refined sugars as part of a periodontal prevention / treatment regime and a general health benefit message.^[26] (Chapple et al 2012)

CONCLUSION

Nutrigenomics is the combination of molecular nutrition and multi-Omics applications. There is not one gen-Omics tool that can “do everything”. One of the goals of applying genomics and proteomics technologies to nutritional science is to match individuals and specific nutrients to achieve special health benefits. Nutritional products that specifically prevent the negative effects of pro-inflammatory genetic variations may represent excellent preventive agents that would benefit large segments of the population.

The current literature on the relationship between diet and periodontal disease is largely inconclusive; this is most likely due to a lack of clarity in assessment of nutritional status. Over the last few years improved understanding of ways to assess and investigate nutritional status has emerged along with the recognition of the importance of assessing nutritional intake, body composition and biochemical measures of nutrition.

A second multi-centre follow up study is currently in progress aiming to determine the effects of supplementation upon periodontal inflammation prior to periodontal treatment. Further studies are needed to better understand the use of nutrients or bioactive food components for maintaining good health and preventing periodontal disease through modifiable epigenetic mechanisms.

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