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Nutrigenomics: A new direction in periodontics

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Abstract
Nutrigenomics is an emerging science which investigates a certain area of nutrition that uses molecular tools to search, access and understand the several responses obtained through a certain diet applied between individual and population groups. Nutrition research is investigating on how nutrition can optimize and maintain cellular, tissue, organ and whole body homeostasis. This requires the understanding that how nutrients act at the molecular level which inturn involves a multitude of nutrient related interactions at the gene, protein and metabolic levels. As a result, nutrition research shifted from epidemiology and physiology to molecular biology and genetics and nutrigenomics was born. Nutrigenomics involves the characterization of gene products, their physiological function and their interactions. It focuses on the effect of nutrients on genome, proteome, metabolome and explains the relationship between these specific nutrients and nutrient regimes on human health. This article aims to review the interrelation between periodontal health and nutrigenomics.

Keywords: Nutrigenomics, periodontitis, nutrients, diet and dentistry

Introduction
Nutrigenomics is the science that uses genomic information along with high - throughput 'omics' technologies to address issues important to nutrition and health. Nutrigenomics is also called as nutritional genomics which refers to both the study of how diet affects genes and how genes affect diet. The term "nutrigenomics" was first described in 2001 from Pelegrin (2001). In 2004, NuGo (European Nutrigenomics Organization) was started and funded until June 2010 [1]. Nutrigenomics reveals the relationship between nutrition and the genome and to provide the scientific basis for improved public health through dietary means. The interactions between genotype and diet are important in determining the risk of the most common complex diseases, including periodontal diseases. Gingivitis and periodontitis are prevalent forms of periodontal disease in humans and are the result of inflammatory and immune responses to bacterial infections of the gingival tissues.

Periodontitis is a chronic and destructive disease of the periodontium, characterized by inflammation of periodontal tissue and alveolar bone loss or resorption. If the inflammatory response fails to remove the causative pathogens, the prolonged release of neutrophils, proteolytic enzymes, proinflammatory mediators and reactive oxygen species occurs, which in turn destroy the periodontal attachment. Host based risk factors such as genetic background of an individual, socioeconomic status, smoking and dietary habits have all been suggested to alter the innate susceptibility of the host to periodontal disease.

Recently it has been suggested that nutrition may be important in redressing the balance between microbial challenge and the host response because it has been implicated in a number of inflammatory diseases and conditions, including type II diabetes mellitus, cardiovascular disease, rheumatoid arthritis and inflammatory bowel disease, all of which have also been associated with periodontal disease. Diets high in saturated fats and sugars and low in fruit, vegetables and fiber are common risk factors associated with these chronic diseases. It is well established that specific nutrients can modulate immune and inflammatory responses. Based on the pathology of periodontal disease the assumption is that these nutrients could modulate periodontal health.

Omics technology in nutrition research - concepts
Nutrigenomics is the science that examines the response of individuals to dietary compounds, foods and diets using post-genomic and related technologies, which includes genomics,

transcriptomics, proteomics and metabolomics. Genomics is the study of the genome; an approach of mapping, sequencing and analysis of all genes present in the genome, focusing on resolving the variation in the genome between individuals. The transcriptome is the complete set of RNA that can be produced from the genome [2]. Transcriptomics is the study of the transcriptome, i.e. the gene expression at the level of the mRNA. Using either cDNA or oligonucleotide microarray technology, it describes the approach in which gene expression (mRNA) is analysed in a biological sample. Proteomics is the study of the proteome, and it addresses three categories of biological interest: protein expression, structure and function. It attempts to characterize all proteins in a biological sample, including their relative abundance, distribution, posttranslational modifications, functions, and interactions with other biological molecules [3].

Metabolomics is the scientific study of chemical processes involving metabolites. It tries to measure the level of all substances (other than DNA, RNA or protein) present in a sample; the metabolome comprises the complete set of metabolites synthesized by a biological system. It investigates metabolic regulation and fluxes in individual cells or tissues, in response to specific environmental changes [4].

Goals and strategies

1. The identification of transcription factors that function as nutrient sensors and the genes they target; the elucidation of the signalling pathways involved, and characterization of the main dietary signals.
2. The measurement and validation of cell and organ specific gene expression signatures of the metabolic consequences of specific micronutrients and macronutrients.
3. The elucidation of the interactions between nutrient related regulatory pathways and proinflammatory stress pathways.
4. To understand the process of metabolic dysregulation that leads to diet related diseases; the identification of genotypes that are risk factors for the development of diet related human diseases (such as diabetes, hypertension or atherosclerosis) and quantification of their impact.
5. The use of nutritional systems biology to develop biomarkers of early metabolic dysregulation and susceptibility (stress signatures) that are influenced by diet [5].

Nutrients modulate periodontal health

A diet can produce both topical and systemic effects on the body and tissues. Periodontitis is defined as an inflammatory disease of supporting tissues of teeth caused by groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with periodontal pocket formation, gingival recession or both.

The types include: chronic periodontitis, aggressive periodontitis, and necrotizing ulcerative gingivitis and periodontitis. Periodontal diseases are the result of bacterial infections of the gingival tissues. Therapy to decrease the levels of oral microorganisms can reduce gingivitis and stabilize periodontitis. Although dietary components play a major role in the pathogenesis of dental caries, diet plays primarily a modifying role in the progression of periodontal disease. A periodontal lesion is essentially a wound, and sufficient host resources must be available for optimal healing to take place. The food we eat contain nutrients that are considered to be either major or minor nutrients. Major nutrients are consumed in gram quantities and include protein, carbohydrates, lipids and water. The minor nutrients are required in milligram (mg) to microgram (µg) quantities and include vitamins and minerals.

The Food and Nutrition Board of the National Academy of Sciences has defined the dietary reference intake values for some nutrients as either a recommended dietary allowance or an adequate intake. Minerals make up about 4% of body weight and are found mainly in the skeleton, enzymes, hormones and vitamins. Minerals help to provide structure for bones and teeth, and maintain normal heart rhythm, muscle contraction, nerve conduction and the acid base balance. Minerals are integral parts of enzymes and hormones. Minerals can be classified as either major minerals (>100 mg/ day) or as trace minerals (< 100 mg / day). The major minerals are sodium (Na), potassium (K), calcium (Ca), magnesium (Mg), phosphorus (P) and sulfur (S). The trace minerals are iron (Fe), zinc (Zn), iodine (I), selenium (Se), fluoride (F), copper (Cu), cobalt (Co), chromium (Cr), manganese (Mn) and molybdenum (Mo). Specific nutrients can modulate immune and inflammatory responses. Based on the pathology of periodontal disease, the assumption is that these nutrients could modulate periodontal health.

Increased production of reactive oxygen species raises requirements for the antioxidant nutrients involved in defense. Antioxidant vitamins (vitamins A, E and C) and trace elements (selenium, zinc and copper) are known to be depleted during periods of inflammation. This can counteract reactive oxygen species damage to cellular tissues and modulate immune cell function through the regulation of redox regulated transcription factors and ultimately affect the production of cytokines and prostaglandins. These vitamins and trace elements are also known to play a pivotal role in maintaining epithelial tissue integrity and structure, which is also associated to periodontal health.

Intake of polyunsaturated fatty acids, predominantly found in oily fish, increase the tissue concentrations of eicosapentaenoic acid and docosahexaenoic acid, which are known to downregulate inflammation. Omega 3 polyunsaturated fatty acid metabolites may act as signals to prevent neutrophil mediated periodontal tissue damage. Many studies have investigated the genetic relationship between periodontal disease and type II diabetes. ZnT8 mediated zinc transport is important for normal beta cell function in insulin storage and release. Increased extracellular zinc concentration has been found to have a positive effect on glucose induced insulin secretion, indicating a potential benefit of zinc supplementation to susceptible type 2 diabetes individuals carrying the risk allele. Zinc supplementation may alter periodontal disease progression through changes in expression of the ZnT8 transporter gene [6].

Mechanisms revealing nutritional modifications of periodontal inflammation

Periodontitis is caused by the complex plaque biofilm, but most tissue destruction results from an abnormal inflammatory immune response in patients predisposed to the condition. Macronutrients and micronutrients modulate proinflammatory and antiinflammatory cascades, which influence a person's baseline inflammatory status. The functionality of nutrients in human biology extends beyond that of being fuels for energy production and cofactors in metabolism, to acting as molecular signals that are capable of modulating gene and protein expression at a molecular level. Diets high in complex carbohydrates are generally healthy,

whereas those rich in refined carbohydrates can be major causes of chronic inflammation. Elevated glucose and lipid levels generate reactive oxygen species at a rate that exceeds endogenous antioxidant defenses, and oxidative stress results. It is noted that "postprandial dysmetabolism" plays a role in the genesis of inflammation.

Diet induced hyperlipidemia induces oxidative stress and downstream inflammation, and lipoproteins formed by liver hepatocytes can be converted to free fatty acids within the circulation and taken up by adipocytes, thus acting as a basis of proinflammatory adipokines. Furthermore, in states of oxidative stress, lipid peroxidation arises, low density lipoproteins are oxidized and then bind to a group of pattern recognition receptors called "toll -like receptors" (TLR -2/4) on inflammatory cell membranes, triggering NF -κB activation via the protein kinase C enzyme and other related pathways. NF - κB transcribes several proinflammatory cytokines. So, the need for cooperative antioxidant cascades augmented to increase the antioxidant status is necessary to downregulate proinflammatory gene transcription.

Fish oils lower postprandial triglyceride levels and has antiinflammatory and cardiovascular protective effects. Omega3 polyunsaturated fatty acids also inhibit lipid mediators of inflammation (such as prostaglandin E2, arachidonic acid, 5 lipoxygenase and cyclo-oxygenase), modulate lymphokine production and upsurge antioxidant capacity and are reported to decrease osteoclast activity. It also causes downregulation of proinflammatory gene expression via the nuclear peroxisome proliferator activated receptors.

Micronutrients and periodontal therapy

Vitamin C is a powerful antioxidant, Based on the NHANES III survey, it was found that smokers with the lowest intake of vitamin C were likely to have the worst periodontal condition.[7] In an experimental periodontitis model in rats it was shown that vitamin C supplementation resulted in an elevated GSH:GSSG ratio in the gingival tissues of supplemented rats with periodontitis over non supplemented rats with periodontitis [8]. Furthermore, expression of genes encoding inflammatory peptides, including interleukin 1α and interleukin 1β, was more than two fold downregulated by vitamin C intake.

Vitamin D plays a role in innate immunity by the action of monocytes, macrophages and dendritic cells which express the vitamin D receptor (VDR), which when up regulated by activated Toll -like receptors -2/1, results in the intracellular production of $1,25(OH)_2$ D3 which in turn induces the release of LL -37 cathelicidin, a potent anti -microbial peptide. Role of vitamin D in periodontal health is supported by studies of polymorphisms in the VDR gene, which are reported in many studies to be associated with periodontitis. This mechanism is not restricted to immune cells alone. The promoter regions of the human cathelicidin antimicrobial peptide and defensin β2 genes contain common vitamin D response elements that mediate $1,25(OH)_2$ D3 dependent gene transcription [9].

Investigators have suggested that low calcium intake may be associated with alveolar bone resorption and calcium deficiency may be a risk factor for periodontal disease.[10] Magnesium deficiency has been suggested to be involved in the etiology of cardiovascular diseases, diabetes, preeclampsia, sickle cell disease and chronic alcoholism. It has been shown that a higher Mg/Ca ratio is associated with a significantly lower level of periodontitis [11]. In a randomized controlled double blind intervention, the adjunctive effects of ingesting whole fruit, vegetable, and berry concentrates in a powdered capsular form during nonsurgical periodontal therapy in 60 nonsmokers with mild to moderate periodontitis was elucidated. The result showed reductions in pocket depth and GCF volume posttherapy in the phytonutrient supplement verses the placebo group [12]. 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 [13].

Benefits from nutrigenomics

Nutrigenomics research will increase our understanding and knowledge of phenotype, genotype diet interactions in a holistic way with an ultimate aim of developing strategies to improve health management and to prevent diseases. In this regard, the identification of biomarkers that describe the changes from the healthy state to predisease and disease states is of paramount importance. Nutritional genomics is believed to deliver new biomarkers based on expression profiles/patterns generated from genomics, transcriptomics, proteomics and metabolomics studies. These biomarkers will be indicative of homeostasis or health, predisease and disease states [14].

Future

Nutrigenomics is surely expected to be the next wave for food industry, even though only a few practical ideas have emerged. The food industry recognizes the need for nutrigenomics research as a basis for developing the concept of "personalized diets," for identifying molecular biomarkers or new bioactive food ingredients, and for validating the effectiveness of these bioactive ingredients as functional food components or nutraceuticals. Identifying markers in the early phase of diet related diseases; this is the phase at which intervention with nutrition can return the patient to health. Markers can manipulate gene expression through use of nutrients or their combinations so as to improve productive as well as overall performance. Nutrigenomics is an emerging science with high expectations, but the major concerns are twofold. First, it is doubtful whether the goal of matching foods to individual genotypes to improve the health of those individuals can be attained or not. Secondly, the entry of personalized nutrigenomics foods in world's food markets depends on numerous hurdles being overcome: some scientific in nature, some technical and ethical issues.

Conclusion

The development of a personalising approach to nutrition for disease prevention and therapy will require a much more comprehensive understanding of nutrient gene interactions and their impact on phenotype in order to identify, evaluate, and prioritise appropriately targeted strategies for dietary intervention. While the challenges associated with unravelling the nutrigenomic disease interrelationship will not be easy, the public health implications are enormous. Because responses between individuals to dietary changes, even within genetic subgroups, may differ considerably, it will be necessary to combine nutrigenetic based advice with 'omic' biomarkers to test whether the personalised recommendation given actually produces the expected nutritional change and

health benefit within the individual. This repeating validation process is critical for success in the future.

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