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A CAPSULATE ON NUTRIGENOMICS IN PERIODONTITIS

[1]Dr. Kirti Chawla B.D.S., M.D.S., [2]Dr. Shivani Bhardwaj B.D.S. and *[3]Dr. Vishal Garg B.D.S.

[1]Department of Periodontology, Faculty of Dentistry, Jamia Milia Islamia, New Delhi.
[2]Dental Cosmos Clinic, New Delhi.
[3]Maulana Azad Institute of Dental Sciences, New Delhi.

***Corresponding Author: Dr. Vishal Garg B.D.S..**
Maulana Azad Institute of Dental Sciences, New Delhi.

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ABSTRACT

Periodontal disease is an infectious process which occurs with the presence of bacteria and host response in the tissues surrounding the teeth and is further affected and modified by other local, environmental and genetic factors. Nutritional deficiency and changes in food preference have also been associated with it. It is well recognized that specific nutrients can modify immune and inflammatory responses as it has been associated with periodontitis along with cardiovascular diseases, rheumatoid arthritis, type 2 diabetes, and inflammatory bowel disease. The demand for antioxidant nutrients is increased with increase in the production of reactive oxygen species(ROS) at the time of inflammation which damages cellular tissues and alters the immune-cell function through the regulation of redox-regulated transcription factors. Nutrigenomics, also known as nutritional genomics, is defined as the study of the interaction of food constituents with our genes and how individual genetic attributes react to nutrients and other naturally occurring substances in the diet. It is an upcoming field with its potential to prevent, mitigate and treat chronic diseases using small, yet highly effective dietary change. This article summarizes the recent information regarding the nutrient-gene interactions and how diet triggers the underlying process of severe periodontitis.

KEYWORDS: Nutrigenomics, Diet-gene interaction, Nutrition, Periodontitis, periodontal disease.

INTRODUCTION

Genomics is the branch of molecular biology which is concerned with the detailed molecular characterization of the whole genome to gain a better understanding of the structure, function, evolution and mapping of genomes.[1] The genomic sequence of an organism can be done in two different areas, i.e., structural genomics where the characterization of the physical nature of whole genomes is performed and functional genomics where the characterization of the overall patterns of gene expression is analyzed. Mapping, detailed characterization of economic trait loci (ETL) and the identification of the relevant gene(s) controlling the trait can be easily identified by these approaches. This integrated information helps to access metabolic pathways through the physiological, nutritional and biochemical expertise of a trait of interest (phenotype).[2] The advent of the 'genomic era' has introduced the concept of nutritional genomics which aims to provide an exhaustive understanding of nutrition and genome for improved public health through dietary means.[3] Nutritional genomics, is defined as the study of how foods affect our genes and how individual genetic distinctions can affect the way we react to nutrients and other naturally occurring substances in the foods we consume (Figure 1).

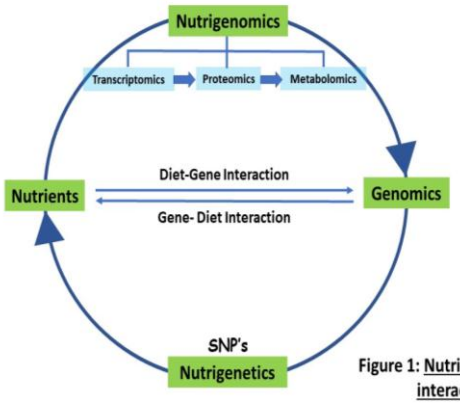

Figure 1: Nutrient-Genomic interaction

During the process of metabolism of dietary compounds, metabolites are formed which helps in early diagnosis of wide ranges of diseases. It has been proven scientifically that in the diseased oral cavity, the metabolic profiling of saliva helps in elucidating the underlying changes associated with periodontal diseases.[4] Studies have shown the increase in the level of many hosts and bacterial proteases(macronutrients) in a population

suffering from the periodontal disease is consistent with the elevated levels of dipeptides.[5][6]

Periodontitis is an inflammatory multifactorial disease in which the delicate balance between virulence factors of microorganisms and host response is altered which disintegrates the supporting structures of the teeth, thereby leading to tooth loss.[7] The attributable risk factors of periodontitis vary significantly which include dietary habits, genetic background of an individual, socio-economic status, and deleterious habits.[8][9] Also, periodontitis has been implicated in various systemic diseases such as type 2 diabetes mellitus, rheumatoid arthritis, cardiovascular disease and inflammatory bowel disease.[10]

The functionality of nutrients on human genome directly or indirectly via epigenetic mechanisms modulate expression of gene and protein at the molecular level.[11] The nutrients modulating the immune system and inflammatory responses are co-related.[12] Diets rich in carbohydrates, hyperlipidaemia and reduced concentrations of plasma total antioxidants lead to increased prevalence of periodontitis.

Nutritional genomics is a research field which reveals the relationship between nutrition and other dietary bioactive with the genomes and also provides scientific reasons for convalescent public health. This article aims to discuss the interaction of foods with our genetic system and the way by which human genetic variations react to such nutrients, and how diet triggers the underlying process of severe periodontitis.

NUTRIGENOMICS AND ITS ORIGIN

Nutrigenomics is an emerging field that deals with the study of the human genome and nutrient interactions through epigenetic and transcription factors along with the use of biomarkers which manipulate gene expression at an early phase of diet-related diseases to return the patient to a healthy state when intervened by nutrition.[13] It involves multiple scientific disciplines connecting knowledge from nutrition, genetics, physiology, biotechnology, bioinformatics, bio computation, ethics, and sociology.[14] According to the NCMHD Centre of Excellence for Nutritional Genomics, the theoretical basis behind this novel division of genomic research is best explained by the five principles of nutrigenomics:

1. Diet has the potential to be a severe risk factor for numerous diseases under certain situations.
2. Common dietary chemicals can affect the human genome, either directly or indirectly, to modify gene expression or arrangement.
3. The extent to which diet has an impact on the balance between healthy states and disease states may be contingent on an individual's genetic makeup.
4. It is probable for certain diet-regulated genes, as well as their standard, common variants, to be a factor in the onset, prevalence, advancement, and/or severity of chronic diseases.
5. Dietary mediation centred on knowledge of nutritional requirement, dietetic status, and genotype can be applied to inhibit, mitigate, or cure chronic disease.[15]

The first evidence showing the role of nutrition and genetics together was phenylketonuria in which the patients were affected by intake of food containing amino acid phenylalanine. Another example is lactose intolerance, where individuals cannot digest lactose products.[13] Single nucleotide polymorphism(SNP) have been responsible for the response of an individual to bioactive food components.[16] One such SNP with an expression of lactase gene was found years ago in Northern Europeans with which they were capable of utilizing nutritionally rich dairy products[17] Humans with low choline diet intake are known to develop a risk for organ dysfunction with modified SNP.[18] Nutrigenomic studies the influence of genetic variation on nutrition by correlating gene expression or SNPs with a nutrient's absorption, metabolism, elimination or biological effects.

DNA Methylation, histone modifications, and chromatin remodeling are the changes in chromatin structure which are carried out by altering environmental or internal factors and therefore can change gene expression.[19] DNA methylation and histone methylation can be affected by folate, vitamin B-12, methionine, choline, and betaine.[20] Every gene is expressed to produce functional RNA and protein molecules in the cell. Structural and comparative genomics involves mapping, sequencing and characterizing of the gene in a genome.[21]

INTERACTION OF MICRONUTRIENTS AT GENETIC LEVEL

Nutrients are dietary signals which affect metabolic production by influencing the expression of gene and protein and can be detected by cellular sensor systems.

VITAMIN A

Diets deficient in vitamin A have been associated with periodontium in the oral cavity.

A study reported that diets deficient in vitamin A led to hyperplasia of the gingival and subgingival epithelial tissues of dogs with increased susceptibility to periodontal disease particularly during the period of development of the periodontal tissues than in older animals.[22] An experimental study has shown changes in the gingival tissues around the necks of the molar teeth of rats on vitamin A-deficient diets which in severe cases were associated with deposits of "tartar".[23] A similar observation was found when animals were placed on vitamin A deficient diet, and it appeared that the molar periodontal tissues around the cervical and middle thirds of the first molar to be approximately one-half the width

of normal controls with the decrease of function.[24][25] (Table 1).

Table 1: The following table summarizes the genes associated with vitamin A and their SNPs (single nucleotide polymorphisms).

Vitamin A		
SNP	**Associated /nearest gene**	**Ref.**
rs3758539	Retinol binding protein-4 (RBP4)	[26][27]
rs116736522, rs34571439	Retinol binding protein-4 (RBP4)	[26]
G/A 5′ flanking region; rs61461737, A/G intron; rs10882280, C/A intron; rs11187545, A/G intron; and rs12265684, C/G intron	Retinol binding protein-4 (RBP4)	[27]
rs176990 and rs190910	Retinol-binding protein 1 (RBP1) gene	[28]
rs738409 (C>G)	Patatin-like phospholipase domain containing protein 3 (PNPLA3)	[29][30] [31] [32] [33]
rs6564851	Beta-carotene oxygenase 1 (BCO1)	[34] [35] [36] [37] [38]
rs12926540	Beta-carotene oxygenase 1 (BCO1)	[38]
rs7501331, rs12934922	Beta-carotene oxygenase 1 (BCO1)	[34] [39]
rs7196470	Beta-carotene oxygenase 1 (BCO1)	[40]
rs1247620, rs1358594, rs6834586	CXCL8	[40]
rs16994824, rs202313, rs5755368	Intestine specific homeobox (ISX)	[40]

VITAMIN C

Vitamin C in its aqueous phase is considered as a potent free radical scavenger. Ascorbate within the extracellular fluids is rapidly depleted (oxidized) at the time of oxidative stress.[41] An association between low intake of vitamin C and occurrence of periodontitis has been observed.[42] The role of dietary vitamin C as a contributing risk factor for periodontal disease was evaluated by utilizing the Third National Health and Nutrition Examination Survey (NHANES III) and concluded that those taking the lowest levels of vitamin C, and who also smoke, are likely to show the greatest clinical effect on the periodontal tissues.[43]

The low concentrations of vitamin C in plasma are related to the serology of periodontitis. P. gingivalis infection which may increase colonisation of P. gingivalis or disturb the healing of the infected periodontium.[44] Vitamin C deficiency is also characterized by increased capillary permeability, susceptibility to traumatic haemorrhages, hypo reactivity of the contractile elements of the peripheral blood vessels, sluggishness of blood flow.[45][46] and defective collagen synthesis leading to tissue dysfunction as a result of insufficient support of the capillary walls by the connective tissues.[47]

An experimental study on Guinea pigs revealed severe disturbances in the number and arrangement of the collagen fibre bundles in the periodontal membrane due to vitamin C deficiency. Fibres were virtually absent in the region just occlusal to the enamel organ and above the crest of the interdental bone septum. Cessation of bone deposition and generalized bone resorption which occurs extensively in areas where pressure normally occurred along the bone surfaces was reported.[48] It has been observed histologically that epithelial changes occurred along the enamel surfaces of molars as a result of apical migration of oral epithelium along the teeth of severely scorbutic guinea pigs.[49] Studies have suggested that local application of vitamin C-containing magnesium salt improves collagen synthesis and decreases gingival fibroblast inflammation.[50][51][52] (Table 2).

Table 2: The following table summarizes the genes associated with vitamin C and their SNPs (single nucleotide polymorphisms).

Vitamin C		
SNP	**Associated /nearest gene**	**Ref.**
rs10063949	SLC23A1 genes (Solute carrier family 23 (SLC23)	[28]
rs1279683	SLC23A2 genes	[28]
	SLC23A1 and SLC23A2 genes	[53] [54]
rs6139591	SLC23A2 genes	[53] [55] [56] [57]
rs2681116	SLC23A2 genes	[53] [55] [56] [57]
rs13037458	SLC23A2 genes	[53] [56]
rs4813725, rs1776964, rs1110277	SLC23A2 genes	[55] [53] [56]
rs1715365, rs35560557, rs4987219	SLC23A2 genes	[55] [53]
rs1776948, rs6133175,	SLC23A2 genes	[58]

VITAMIN D

Vitamin D is a fat-soluble prohormone that is crucial for the maintenance of bone and muscle health by promoting the absorption and metabolism of calcium and phosphate. Vitamin D deficiency has been associated with systemic diseases such as bone disease, cancer, autoimmune disease, infectious disease, type 1 and type 2 diabetes, hypertension, and heart disease.

Associations of CG, DHCR1, CYP2R1, VDR vitamin D receptor and CYP24A1 with serum levels of vitamin D have been identified.[59] Vitamin D exerts a strong suppressive effect on the expression of IL-2 and IFNγ in a VDR-regulated mechanism.[60] Studies have demonstrated the increased risk of generalized aggressive periodontitis (GAP) with short VDR (27823*C/*C allele) protein.[61] Dietary supplementation with calcium and vitamin D improves periodontal health, increases bone mineral density in the mandible and inhibit alveolar bone resorption.[62] [63]

Clinical studies have suggested that a deficiency of dietary vitamin D leads to periodontal inflammation and a delay in post-surgical periodontal healing.[64] [65] [66] (Table 3).

Table 3: The following table summarizes the genes associated with vitamin D and their SNPs (single nucleotide polymorphisms).

Vitamin D		
SNP	**Associated /nearest gene**	**Ref.**
rs10063949	SLC23A1 genes (Solute carrier family 23 (SLC23)	[28]
	VDR polymorphisms (BsmI, ApaI, TaqI and FokI)	[67] [68] [69] [70] [71] [72] [73]
	BsmI VDR genotype	[73] [74] [75]
	VDR Bsm I and Taq I polymorphisms	[76]
	Fok-I VDR polymorphism	[77]
	VDR Single nucleotide polymorphisms (TaqI, ApaI, and FokI)	[78]
rs1544410	BsmI VDR genotype	[69] [70]
rs7975232	ApaI VDR polymorphism	[69] [70]
rs731236	Taq I VDR polymorphisms	[69] [70]
rs2228570	Fok-I VDR polymorphism	[69] [70]
rs10735810	T allele of the VDR (Thr1Meth)	[79]

VITAMIN E

Vitamin E causes termination of free radical chain reactions, membrane stabilization, increased tendency for hemolysis and collagen breakdown affecting cross-linking of collagen.[80] Intake of α -Tocopherol more than the recommended daily allowance (RDA) is associated with decreased risk of cardiovascular diseases, improved immune function, and slowing the progression of many degenerative diseases.[81]

A correlation between the low level of vitamin E in gingival tissues and periodontal diseases has been reported.[82] A study on rats reported that vitamin E acts on healing and is considered as the lysosomal stabilizer which inhibits the inflammatory response and retards collagen synthesis and tensile strength.[83] Reduction in inflammation was observed when the sulcular fluid volume was compared before and after administration of vitamin E for patients with periodontal disease.[84]

An investigation for periodontal parameters and the levels of superoxide dismutase (SOD) activity in serum and saliva of patients with chronic periodontitis (CP) was evaluated with and without vitamin E supplementation and concluded that systemic and local SOD levels are lowered in chronic periodontitis. Adjunctive vitamin E supplementation improved periodontal healing as well as the antioxidant defense.[85] [86] An in-vitro study revealed decreased human periodontal ligament fibroblasts (HPdLF) viability with tocotrienols rich fraction (TRF) treatment.[87] (Table 4).

Table 4: The following table summarizes the genes associated with vitamin E and their SNPs (single nucleotide polymorphisms).

Vitamin E		
SNP	**Associated /nearest gene**	**Ref.**
	Apolipoprotein A-V (apoA-V) gene containing the minor allele of the −1131T polymorphism	[88] [89] [90] [91] [92] [93] [94] [95] [96] [97] [98] [99] [100]
rs2266788	Apolipoprotein A-V (apoA-V) gene	[101]
rs662799, rs2075291	Apolipoprotein A-V (apoA-V) gene	[102]
rs662799	Apolipoprotein A-V (apoA-V) gene	[103]
rs769450	APOE	[103]
rs1571513, rs9558203 rs16961116, rs12874168	SLC10A2	[104]

rs2065550		
rs675	APOA4	[105]

SELENIUM

Selenium, a trace nutrient, obtained from soil is necessary for optimal health.[106] The biological functions of selenium are mediated through selenoproteins which play critical roles in neuronal protection, immune response, viral suppression, glucose metabolism, and carcinogenesis.[107] [108] [109] Body selenium status regulates the expression of selenoproteins during translation through the post-transcriptional modification of selenocysteine-tRNA maturation and selenium availability for selenocysteine biosynthesis.[110]

Levels of glutathione, catalase, and selenium are significantly lower in diabetic patients with periodontitis and also in healthy individuals with periodontitis, but are highest in healthy controls, showing that the serum levels are inversely proportional to inflammation and tissue destruction.[111] (Table 5).

Table 5: The following table summarizes the genes associated with Selenium and their SNPs (single nucleotide polymorphisms).

SELENIUM		
SNP	**Associated /nearest gene**	**Ref.**
rs 1050450	GPx1(cytosolic glutathione peroxidase)	[112] [113] [114] [115] [116] [117] [118] [119]
	GPx3(plasma glutathione peroxidase)	[120]
rs 713041	GPx4(phospholipid hydroperoxide glutathione peroxidase)	[115] [121] [122] [123] [124]
rs 387789 rs 7579	SEPP (selenoprotein P)	[115] [125]
rs34713741	SelS (selenoprotein S)	[126] [127]
rsrs5845 rs5859	15 kDa (selenoprotein.)	[128]

ZINC

Zinc is a cofactor involved in enzyme-controlled processes which modulates the processes of auto-debridement and keratinocyte migration during wound repair.[129] It has been used as the vital component of periodontal dressings.[130] due to its antioxidant property by scavenging ROS along with neutralisation of bacterial toxins.[131] Zinc deficient diet leads to worsening of periodontal disease in patients with type 2 diabetes mellitus.[132] Higher values of gingival indices are reported in the zinc-deficient diet than those fed with zinc-containing diet.[133] A study has shown an increased susceptibility to periodontal disease as evident by higher measurements of the gingival index and increased plaque amount.[134] Parakeratosis of oral mucosa[135] and hyperkeratosis of the tongue (papillae)[134] is also reported in the zinc-deficient diet. (Table 6).

Table 6: The following table summarizes the genes associated with Zinc and their SNPs (single nucleotide polymorphisms).

ZINC		
SNP	**Associated gene**	**Ref**
	SLC30A2 gene	[136]
rs117153535 (G/T)	SLC30A2 gene	[137]
rs2464591 (C/T), rs2466296 (C/T), rs2466297 (A/G), rs2466299 (C/T), rs2466293 (C/T)	SLC30A8 gene	[138]
rs13266634 (C/T)	SLC30A8 gene	[139]
rs11558471 (A/G)	SLC30A8 gene	[140]
rs73924411 (C/T) rs11126936 (G/T)	SLC30A3 gene	[141]
rs10636 (C/G)	MT2A gene	[142]
rs1610216 A/G	MT2A gene	[143]
rs8052394 (A/C), rs11640851 (A/G)	MT1A gene	[144]
rs11126936 (A/C)	SLC30A3 gene	[145] [146]
rs233804	SLC39A8	[146]
rs4872479	SLC39A14 gene	[146]

ANTIOXIDANTS

The effects of antioxidant vitamins are viewed at the time of increased oxidative stress. It has been revealed that the most important small molecule antioxidant species is glutathione which exists in both oxidized (GSSG) and reduced (GSH) forms. Inflammatory states

promote a decrease in the amount of systemic GSH levels.[147] [56] Glutathione(GSH) is a chain-breaking antioxidant and plays a crucial role in regulating cellular redox reactions, downstream inflammatory events and maintaining appropriate cell and tissue vitamin C ratios, therefore, helps to preserve intracellular GSH.[148] [57] Patients with chronic periodontitis have lower levels of glutathione when detected in the crevicular gingival fluid.[149] [150]

CURCUMIN

Curcumin inhibits Vascular-endothelial-growth-factor (VEGF) expression.[151] It produces a significant reduction in the inflammatory infiltrated and increased collagen content and fibroblastic cell numbers.[152]

Studies have shown chemically modified curcumin prevents alveolar bone loss and lowers the production of IL-1β and matrix metalloproteinase (MMPs).[153] [154]

Curcumin has shown to inhibit activator protein 1 (AP-1) and prevent the receptor antagonist of nuclear factor kappa B ligand (RANKL) production induced by P. gingivalis infection.[155] It has exhibited inhibition of TNF-α and IL-1β gene expression and protein synthesis in cells stimulated with P. gingivalis in a dose-dependent manner.[156] Curcumin inhibits transcriptional gene associated with oxidative stress and inflammation thereby reducing oxidative stress and guards' protection against hazardous effects of radiation.[157]

Curcumin effectively inhibits cytokine gene expression at both the mRNA and the protein level and produce a dose-dependent inhibition of the activation of nuclear factor-(Kappa) kB in the gingival tissues.[158]

Therapeutic potential of chemically modified curcumins (CMCs2.5) and its congeners may help to prevent tissue damage during various chronic inflammatory diseases including periodontitis and may reduce the risks of systemic diseases associated with this local disorder.[159]

Treatment of the rats with systemically administered CMC 2.24 appeared to "normalize" the pathologically excessive levels of the various molecular weight forms of these gelatinolytic MMPs in the LPS-injected gingiva assessed either visually or by densitometric analysis of the zymograms. Chemically modified curcumin appears to have additional benefits by reducing the impact of this local inflammatory disease on systemic biomarkers of the host without (apparently) negatively affecting the mediators of constitutive connective tissue turnover.[160] (Table 7).

Table 7: The following table summarizes the genes associated with Curcumin.

Associated gene	Ref.
Haem oxygenase-1 gene (HO-1)	[161] [162] [163] [164] [165] [166]
Haem oxygenase-1 gene (HO-1) −413 A/T genotype	[167] [168]
Tumour necrosis factor-α (TNFα), Interleukin-1β (IL-1β)	[169] [170] [171] [172]
Matrix metalloproteinase gene expression	[173] [174] [175] [176] [177]

CUMIN

Nigella sativa (NS), or black cumin is known for inducing beneficial pharmacological effects in humans.[178] The extract of Nigella sativa(NS), thymoquinone (2-isopropyl-5-methyl-1, 4-benzoquinone, TQ) [179] is dependent on GSH, NADPH, or NADH for modulating cellular antioxidant defences.[180]

A study model reported the use of TQ in drinking water or an oral gel had statistically significant lower periodontal indices and subgingival bacterial counts in comparison with both the negative and positive control groups.[181] [182]

TQ-impregnated periodontal chip has been used as adjunctive treatment during the scaling and root planing, or for maintenance visits in chronic periodontitis.[183] The seeds of N. sativa have been widely studied for their antidiabetic effects[184] and its most abundant oil constituent, thymoquinone, and indazole-type alkaloids[185] is implicated as a major bioactive compound responsible for this activity.[186]

Oral administration of thymoquinone diminishes alveolar bone resorption in a rat periodontitis model.[187] (Table 8).

Table 8: The following table summarizes the genes associated with Cumin and their SNPs (single nucleotide polymorphisms).

CUMIN	
Associated gene	**Ref.**
Glutathione (GSH)	[188] [189] [190] [191]

INTERACTION OF MACRONUTRIENTS AT GENETIC LEVEL

PROTEIN

It has been observed that diet dramatically influences the activity of AMP-activated protein kinase (AMPK). Autophagy, a catabolic pathway is an essential response to external and internal insults mediated by mTOR (mammalian target of rapamycin)[192] to maintain the integrity of cells.[193]

mTOR inhibition upregulates the gene expression of antioxidant components (Cat catalase, Sod2 manganese superoxide dismutase, and Prdx3 peroxiredoxin-3) and

rejuvenate the ageing gingiva to some extent and relieve inflammation through eliminating oxidative stress.[194]

Foods with a high-protein in-take cause activation of mTOR resulting in enhanced expression of proopiomelanocortin (POMC) and repression of neuropeptide Y (NPY) in the hypothalamus and therefore low phosphorylation rates of AMPK.[195] [196] (Table 9).

Table 9: lists the macronutrients with associated gene.

ASSOCIATED GENE	MACRONUTRIENT	REF.
AMP-activated protein kinase (AMPK)	Protein	[197] [198] [199]
AMP-activated protein kinase (AMPK)	Lipids	[200] [201]
AMP-activated protein kinase (AMPK)	Carbohydrates	[202] [203]

LIPIDS

A high-fat diet is correlated with a decreased activity of AMPK phosphorylation in skeletal muscle, due to reduced expression of mRNA for the AMPK-α2 isoform leading to reduced glucose uptake whereas it promotes preadipocyte differentiation, lipolysis and the secretion of adipokines (TNFα) in adipose tissues thereby perpetuating the process.[204] [205] [79] [80]

Diets rich in hyperlipidaemia induce oxidative stress and downstream inflammation.[206][81] Adipocytes, take up lipoproteins formed by liver hepatocytes and convert to free fatty acids within the circulation. During oxidative stress, lipid peroxidation (a chain reaction induced by ROS attack on the polyunsaturated fatty acid [PUFA] side-chains of lipid membranes) arises,[207] [82] oxidized low-density lipoproteins (oxLDL) are formed which bind to a toll-like receptor(TLR-2/4) on inflammatory cell membranes via the protein-kinase-C enzyme and triggers the activation of NF-κB. NF-κB transcribes several proinflammatory cytokines.[206] [81]

Nutritional compounds such as omega-3 fatty acids (predominantly found in oily fish) and isoflavones have been shown to alter genes that code for cytokines, growth factors, cholesterol-metabolising enzymes and lipoproteins. It increases the concentrations of eicosapentaenoic acid and docosahexaenoic acid in tissues and downregulates inflammation.[208] [83]

A study has demonstrated decreased levels of the major inflammatory mediators' such as prostaglandin E2, prostaglandin F2 alpha, leukotriene B4 and platelet activating factor in gingival tissue which is responsible for bone destruction in periodontal disease. A recent longitudinal study showed an inverse relationship between the level of omega-3 fatty acids and incidences of periodontal disease in elderly patients.[209] [84]

Studies have shown 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.[210] [85]

CARBOHYDRATES

Diets high in complex carbohydrates are healthy, whereas those rich in refined carbohydrates can be significant causes of chronic inflammation.[11] [211]

Elevated glucose and lipid levels generate ROS at a rate that depletes endogenous antioxidant defences and results in oxidative stress. Investigators have noted that this "postprandial dysmetabolism" plays an important role in the genesis of inflammation. Multiple elevations in glucose eventually lead to chronic inflammatory pathologies.[211] [212]

A diet low in carbohydrates, rich in Omega-3 fatty acids, rich in vitamins C and D, and rich in fibres can significantly reduce gingival and periodontal inflammation.[213]

PERIODONTITIS AS A CONSEQUENCE OF GENOMIC EXPRESSION OF NUTRIENTS

Diet, lifestyle and nutrigenetic factors are some of the chief determinants leading to low serum or plasma nutrient level and hence results in periodontitis.[214] [215] Oral cavity undergoes various inflammatory changes when under oxidative stress by releasing free oxygen radicals into the extracellular environment.

Antioxidants are essential to sustain redox haemostasis so that balance between antioxidants and ROS is preserved. If balance shifts towards ROS then oxidative state of a cell starts to release pro-inflammatory process on activation of gene transcription factors such as Nuclear factor-kB (NF-kB) and Activating protein -1 (AP-1) resulting in direct or indirect tissue damage depending upon the degree of shift of reaction towards ROS. A small number of anti-inflammatory cytokines are also released. However, the overall effect is creating pro-inflammatory state and phase of tissue destruction.[216]

Indirect tissue damage occurs when various series of radical chain reactions take place affecting lipid, protein, and DNA. In lipid peroxidation, series of radical chain reactions attack the cell membrane, damages it and ultimately cell death. The product released during this reaction is isoprostanes which itself is a pro-inflammatory mediator and is used as a biomarker for oxidative stress. Protein oxidation forms a covalent bond with carbon-centered radicals thereby causing a fold in the protein molecule. A stable product, i.e., carbonyl groups are formed which is a biomarker for oxidative stress. DNA damage takes place when free radical causes hydroxylation of base pairs and breakage of strands. 8-

OHdG (8-Hydroxydeoxyguanosine) is the stable product of this reaction which can be used as a biomarker for oxidative stress.[216]

Anti-oxidant inhibits activation of gene transcription factors which in turn downregulates and switch off the inflammatory process when redox state shifts in favor of anti-oxidants.

Moreover, researchers have suggested that downregulation of hyperinflammatory events takes place via reduced glutathione (GSH) which is an intracellular antioxidant redox-regulator of NF-κB[217] depletion of GSH levels are seen in periodontitis.[218]

PUFAs of the omega-3 form (ω-3PUFAs) lowers postprandial triglyceride levels[232] [219] and put heads together anti-inflammatory and cardiovascular protective effects.[220] ω-3PUFAs also prevent lipid mediators of inflammation (such as prostaglandin E2, arachidonic acid, 5-lipoxygenase, andcyclooxygenase), modulate lymphokine production and expands antioxidant capacity[221] [222] [223], and are informed to decrease osteoclast activity[224]

INTERFACE BETWEEN SYSTEMIC HEALTH, NUTRIENTS, AND PERIODONTITIS

Diet and gene interaction reveals genes affecting different homeostatic pathways. New food products on the genetic grounds have been manufactured which may decrease the risk of chronic diseases.[225]

Studies have shown that gene expression of nutrients can be altered at gene regulation level, signal transduction and by modifying chromatin structure and protein function. For example, epigenetic variation can be caused by methylation of DNA.[19] These variations have increased the probability of associated micronutrient diseases, like type 2 diabetes mellitus, obesity, cardiovascular diseases and certain autoimmune diseases.[42] It has been reported that incidence of prostate cancer and breast cancers is low in Asia due to high intake of soy and isoflavone.[226]

Recent genomic studies for type 2 diabetes have revealed a genetic-susceptibility locus comprising a nonsynonymous single nucleotide polymorphism (C ⁄ T; rs13266634) in a beta-cell-specific zinc-transporter gene. This zinc transporter gene (SLC30A8, coding for ZnT8) is essential in insulin storage and release.[227] [228] [229] According to some researchers, adiponectin gene polymorphism is also closely related to insulin resistance. Oxidative stress results in reduced pancreatic beta-cell function, initiation of insulin resistance[230] and reduced intracellular antioxidant capacity.[231]

The vitamin D3 receptor (VDR) gene, transcriptional regulatory factor encodes the nuclear hormone receptor for vitamin D3 which is mainly involved in mineral metabolism and other metabolic pathways, such as those associated in the immune response and cancer. Polymorphism of the VDR gene has been connected to bone mineral density, and also numerous chronic diseases such as cancer – mainly breast cancer, prostate cancer and malignant melanoma – type 2 diabetes mellitus, Parkinson's disease, lung diseases, gastrointestinal disease, multiple sclerosis and periodontal disease.[232]

An observational study performed for over 14 years revealed an association between low consumption of wholegrain and development of periodontitis.[233] Statistical analyses of the US Third National Health and Nutrition Examination Survey (NHANES III) showed significant associations between obesity and periodontal disease, especially in younger subjects.[3]

Another study proposed the importance of Diacylglycerol (DAG) rich mustard oil in reducing arteriosclerotic factors like total cholesterol and non-LDL (low-density lipoprotein) cholesterol and increasing antiatherosclerotic factor such as high-density lipoprotein (HDL) cholesterol.[234] Some researchers also suggested that dietary fatty acids may attenuate the proinflammatory insulin-resistant state in obese adipose tissue. In a well-characterised model, it was viewed that c9, t11-CLA– enriched diet (cis-9, trans-11–conjugated linoleic acid) has antidiabetic effect focusing mainly on the molecular markers of insulin sensitivity and inflammation in adipose tissue of ob/ob C57BL-6 mice. Glucose and insulin metabolism was enhanced by feeding the c9, t11-CLA– enriched diet as compared with the control linoleic acid-rich diet. Therefore, anti-inflammatory strategies of nutrients can counteract the impact of obesity-induced insulin resistance.[235] Essential fatty acids (like α-Linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid) reduce the risk of cardiovascular diseases, breast cancer, shortening of pregnancy period, risks of preeclampsia, disorders of the nervous system and vision in infants, colon cancer, diabetes, obesity, and allergy.[236]

Impact of SNP array on the genetic analysis of human disorders has also been explained in the recent years[237] It can be used to measure both DNA polymorphism and dosage recommendations. SNP arrays are an ideal dais for identifying genetic variants regarding somatic and germline that lead to cancer.

CONCLUSION

Nutrigenomics is an unfolding new scientific area which has come up in recent years by researchers. Diet is an important environmental factor that interacts with the genome to modify the risk of disease. The insights showed the identity of many genes in which polymorphisms can affect the propensity to develop obesity and related conditions such as diabetes and cardiovascular disease. The negative effects of pro-inflammatory genetic variations can be prevented by specific nutritional products which would be beneficial

to a large number of population. Cutting edge work in this area at the moment involves further affirmation, upgradation, and standardization of the 'omic' technology platforms and how they are used for nutritional studies. Various studies are in progress aiming to define the effects of supplementation upon periodontal inflammation before periodontal treatment.

Further studies are needed for better understanding the nutritional status important for maintaining good health and preventing periodontal disease through modifiable epigenetic and transcription factors.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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