Review Article

Common Risk Factor Approach to Limit Noncommunicable Diseases and Periodontal Disease—The Molecular and Cellular Basis: A Narrative Review

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ABSTRACT

Introduction: The link between periodontal disease and noncommunicable diseases (NCDs) has been the subject of major research over the past several years. The primary objective of this review is to understand the cellular and molecular components that link common risk factors (exposure) in adult patients (population) with periodontal disease and other NCDs (outcome). The secondary objective is to interpret from existing literature the possibility of identifying the molecular plausibility of the Common Risk Factor Approach (CRFA). **Materials and Methods:** A literature search was performed in PubMed/MEDLINE, CINAHL, Web of Science, and Google Scholar for all published articles pertaining to the molecular and cellular basis of the risk factors between periodontal diseases and major NCDs. Data from all randomized and nonrandomized clinical trials, cross-sectional studies, case-control, cohort studies, literature, and systematic reviews were included. **Results:** Periodontal pathogens, stress, obesity, smoking, and dietary factors are some of the common risk factors between periodontal disease and NCDs. **Conclusion:** Understanding the molecular and cellular link of common risk factors between NCDs and periodontal disease would ensure the application of CRFA. The CRFA implies that controlling the risk factors associated with NCDs can have an incredible positive impact on regulating many chronic conditions, which would extend to periodontal health also.

Keywords: *Common risk factor approach, noncommunicable diseases, oral health, periodontal disease, risk factors*

Introduction

The noncommunicable diseases (NCDs) result in more than 71% of all deaths globally.[1] Controlling the growing epidemic of NCDs had been in the forefront of health initiatives. Periodontitis, an NCD with a multifactorial etiology, is a major public health concern worldwide.[2] It results in compromised oral functions such as dysfunction in speech and mastication with resultant nutritional deficiency.[2,3] An estimated 54 billion USD/year is the global cost of lost productivity due to severe periodontitis.[4] Various modifiable risk factors of NCDs, such as cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), diabetes, cancer, and periodontal disease, often co-occur in the same individual.[5] This co-occurrence of risk factors is termed as clustering.[6] An impetus for Common Risk Factor Approach (CRFA) for tackling the risk factors associated with NCDs has been cresting for a while in the world of health care.[7] CRFA is based on the concept that controlling a small number of shared

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risk factors can have tremendous impact on controlling a large number of chronic conditions.[8] A few advocacy initiatives focusing on CRFA in relation to oral health and general health have attempted to integrate oral health with NCDs.[9]

There are numerous cellular and molecular elements linking the common risk factors to the etiology of periodontal disease and NCDs [Figure 1]. This review aims at overcoming the paucity in literature pertaining to the commonality of risk factors between NCDs and Periodontal disease so that there is a better comprehension of the relationship between the conditions. The objective of this review is to understand the cellular and molecular components that link common risk factors (exposure) in adult patients (population) with periodontal disease and other NCDs (outcome). The secondary objective is to interpret from existing literature the possibility of identifying the molecular plausibility of CRFA.

Materials and Methods

This review was based on the question: What are the cellular and molecular components that link common risk factors (exposure) in adult patients (population) with periodontal disease and other NCDs (outcome)?

A literature search was performed in PubMed/MEDLINE, CINAHL, Web of Science, and Google Scholar for all published articles pertaining to molecular and cellular basis of the commonality of risk factors between periodontal diseases and major NCDs. The last search was performed on 1 May 2020. The following search terms were used: "noncommunicable diseases" (Mesh) or ["periodontitis" (Mesh) and "chronic periodontitis" (Mesh)] and "risk factors." As several researchers have tried to unravel the molecular and cellular aspects of the etiology of NCDs and periodontal disease, no restriction was placed on the years and language of publication. Publications in other languages were translated using google translator. Data from all randomized and nonrandomized clinical trials, cross-sectional studies, case-control, cohort studies, literature, and systematic reviews were included. Longitudinal studies and intervention studies with a minimum one-month follow-up were included. The reference of the included studies was checked for additional records. The Grey literature (Google scholar) was also searched along with hand searching for relevant articles in the various journals related to dental, periodontal, and NCD research. Open Grey literature of any unpublished trials and registry of clinical trials (clinical-trial.gov.in) were searched for trial protocols. The cross-reference of all studies was searched to include any relevant data. The studies and reviews pertaining to risk factors in patients suffering from periodontal diseases as classified by American Academy of Periodontology classification 1999 and NCDs like diabetes, CVDs, cancers, COPD were included. All the articles that did not refer to the risk factors for periodontal disease and NCDs were excluded.

The results of the searches run on different databases were compiled in the Mendeley reference manager (version 1.19.4), and duplicates were removed. For those articles that fulfilled the eligibility criteria, the full articles were retrieved. Any disagreements were mutually discussed between the two reviewers (L.P. and C.J.), and a consensus was reached. The search strategy identified a total of 457 articles. After the removal of duplicates, 345 articles were included for the title and abstract screening. Of 345 articles, 74 articles were included for full-text screening. Of these 74, 5 articles were excluded. The flow diagram of article selection is given in Figure 2. From the initial search, data on the molecular and cellular aspects of the commonality of risk factors between periodontal disease and NCDs were extracted. Data extraction was performed by one author (L.P.). The data were captured for author details, methodology of the study, risk factor studied (periodontal pathogen, smoking, stress, obesity, and nutritional status), and the molecular and cellular aspects of the risk factor in the etiology of the disease process. All the data collected were reviewed by a second reviewer (C.J.).

Results

Of the 457 articles from the initial search, 69 articles were included for the final review [Figure 2]. From the review, it was recognized that periodontal pathogens, stress, obesity, smoking, and dietary factors are some of the common risk factors between periodontal disease and NCDs. The molecular and cellular basis of the role of the risk factors in the pathogenesis of periodontal disease and NCDs includes the effects of reactive oxygen species (ROS), matrix metalloproteinases (MMPs), acute-phase reactants fibrinogen, plasminogen activator inhibitor 1, C-reactive proteins (CRPs), antimicrobial peptides, proinflammatory mediators interleukin (IL)-1, IL-2, IL-3, IL-4 IL-5, IL-8, IL-13,IL-17, IL-22, prostaglandin E2, transforming growth factor beta (TGF-β), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), cells of adaptive immunity such as T helper cells (Th1/Th2/Th17), cluster of differentiation (CD)4+CD25+ regulatory T cells, CD8+ T cells, B cells and memory T/B lymphocytes and cells of innate immunity dendritic cells, macrophages, natural killer (NK) cells, and neutrophils. The result has been summarized in Figure 1.

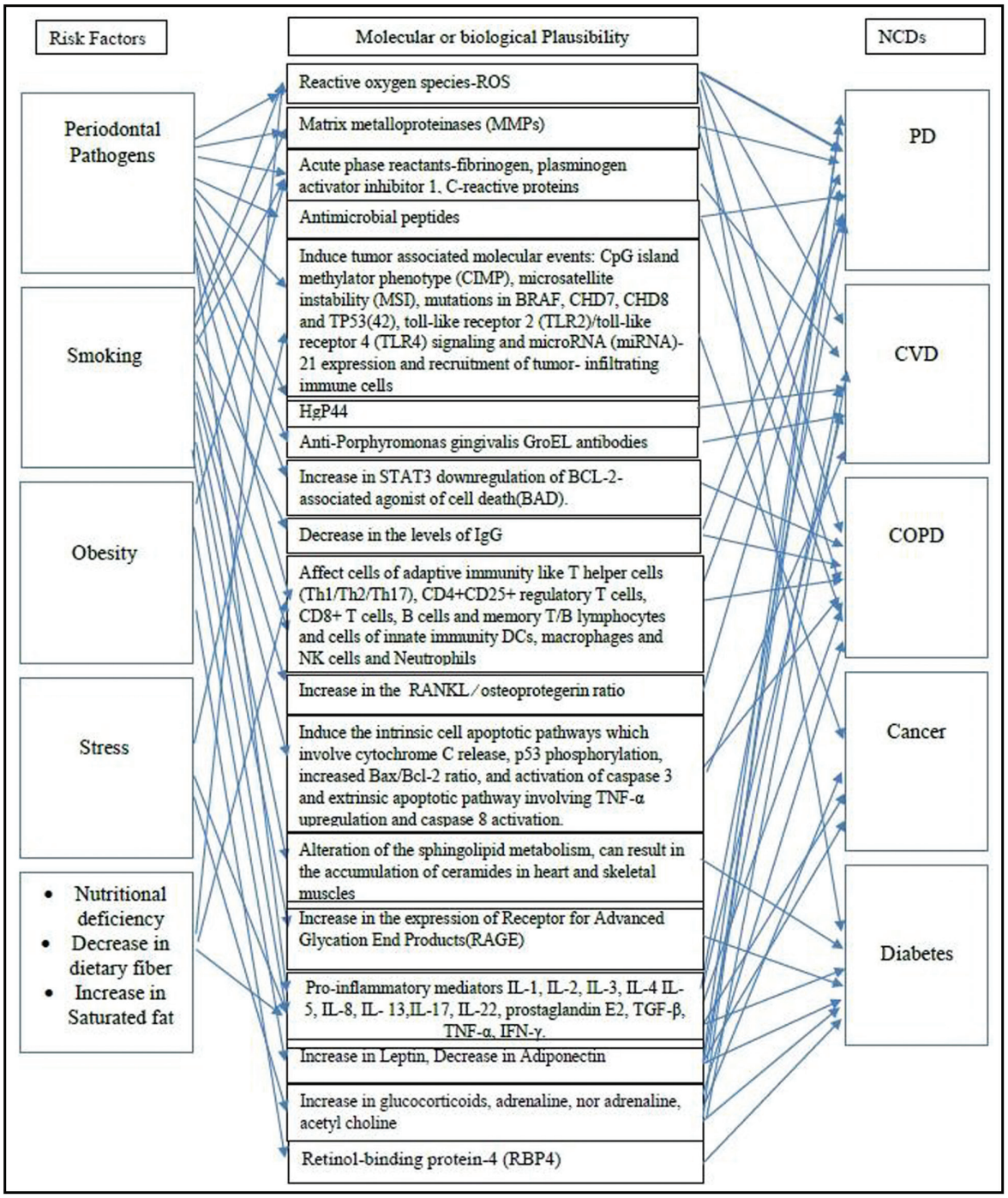

Figure 1: Molecular and cellular link between the risk factors for NCDs and PD. Bax = BCL2 associated X, apoptosis regulator, BCL= B-cell lymphoma 2, BRAF = proto-oncogene B-Raf, CD = cluster of differentiation, CHD7, 8 = chromodomain helicase DNA binding protein 7, protein 8, COPD = chronic obstructive pulmonary disease, CVD = cardiovascular disease, DC= dendritic cell, GroEL = chaperonin, IFN-γ = interferon gamma, IL = interleukin, NCD = noncommunicable disease, NK = natural killer cell, PD = periodontal disease, RANKL = receptor activator of nuclear factor kappa-B ligand, STAT3 = signal transducer and activator of transcription 3, TGF-β = transforming growth factor beta, TNF-α = tumor necrosis factor alpha

Discussion

The cellular and molecular link

The first concept explored in this review is the identification of the cellular and molecular components that link common risk factors in adult patients with periodontal disease and other NCDs.

Summary of evidence

Periodontal pathogens as risk factors

Tannarella forsythia, *Porphyromonas gingivalis* (Pg), *Aggregatibacter actinomycetemcomitans* (Aa), and *Prevotella intermedia* (Pi) are some of the important periodontal pathogens that have been isolated

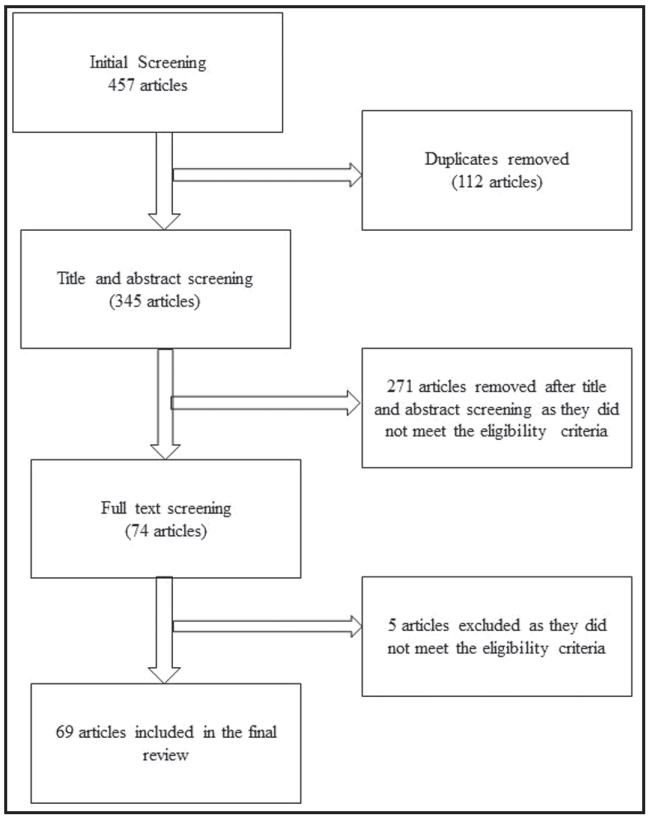

Figure 2: Flow diagram of the selection of articles

from the atherosclerotic plaque.[10,11] Pg can induce platelet aggregation through hemagglutinin domain protein HgP44.[12] Pg and Aa have been implicated in impaired endothelial cell (EC)–dependent vascular dilatation, which is a risk factor for CVD.[13] Studies have shown that Pg can penetrate the vascular ECs, mediate expression of macrophage chemoattractant peptide-1, and induce human aortic endothelial cellular apoptosis.[13] Pg can increase the pathogenic potential of *Pseudomonas aeruginosa* (Pa) in the etiology of COPD.[14] The coinvasion of respiratory epithelial cells by Pg and Pa results in an initial reduction in apoptosis of the cells due to the greater production of signal transducer and activator of transcription 3 and downregulation of B-cell lymphoma (BCL)-2–associated agonist of cell death.[14] After the initial reduction in the apoptosis, there is a rebound increase in the activity of Caspase 3 and this occurs within 12 h after the bacterial invasion.[15] The delayed apoptosis will allow the pathogens to remain in the intracellular compartment for a longer period of time and facilitate the establishment of a robust infection. Pi and Pg can cause release of antimicrobial peptides and IL-8 at the respiratory epithelial surface, resulting in development or exacerbation of COPD.[16] Pg and *Fusobacterium nucleatum* (Fn) facilitate the development of squamous cell carcinoma through the stimulation of Toll-like receptors (TLRs), TLR2/1, and TLR4.[17] Pg can promote the cellular infiltration of oral squamous cell carcinoma (OSCC) cell lines through gingipain-mediated activation of proenzyme proMMP9.[18] Repeated and chronic Pg infection can induce epithelial-to-mesenchymal transition of host cancer cells[18] and increase the stem cell markers of cancer, such as CD44 and CD133.[19] The virulence factors of Fn such as FadA adhesion gene of *F. nucleatum* (FadA) and Fap2 surface protein of *F. nucleatum* (Fap2) can promote adhesion to intestinal mucosa and immunosuppression[20] and contribute toward tumorigenesis and pathogenesis of colorectal carcinoma. The bacterial antigens such as major outer membrane proteins, lipopolysaccharides (LPS), type II fimbriae of Pg, and endotoxins can produce a local inflammatory response, which can get translated to a systemic phenomenon, resulting in an increased risk for the NCDs, including the progression of insulin resistance.[21,22] The antigens may be repositioned to the organs or tissues at sites that are distant from the periodontal tissues by dendritic cells of the innate immune response and elicit the production of inflammatory mediators, acute-phase reactants, and other effector molecules in those sites.[23] Studies have shown that IFN-γ and IL-1β can subdue the anticoagulant pathways, such as the protein C pathway, promoting atherogenesis.[24] Activation of hyperactive neutrophils as a result of the inflammatory state results in an elevation in ROS.[25] The increase in proinflammatory mediators and ROS interferes with the insulin signaling pathways and results in the development of tissue-specific insulin resistance. This, in turn, increases the oxidative stress in β-cells of islets of pancreas, weakens the secretion of insulin from the islets, and worsens the glycemic control.[26] The ROS and nitrogen species play an important role in endothelial dysfunction and resultant CVD, which can be explained on the basis of the interaction between nitric oxide (NO) and the ROS.[27] NO can restrict the activity of several ROS, such as superoxide anion, hydroxyl radical by combining with the superoxide in the ROS. When there is an imbalance in the rate of consumption of NO by superoxide and disproportionation of superoxide by the superoxide dismutase, oxidative damage of the cellular components is induced and the regulation of endothelial NO synthase (eNOS) levels is affected.[27] TNF-α and IL-6 and CRPs can reduce the endothelial production of eNOS.[27] This can result in reduced levels of NO, with resultant impaired endothelial function. Endothelial dysfunction can also arise from the inflammatory process activated by the Pg LPS, which will result in atherogenesis [Figure 3].[28]

Anti-Pg GroEL antibodies and autologous human heat shock protein 60 (HSP60) display a similarity in their molecular structure. Bacterial infection can trigger an increase in the antibody produced against HSP60, which is expressed in the endothelium at the region of division of blood vessels.[29] The cross-reactivity between the pathogens and the HSP60-expressing ECs may explain the link between CVDs, strokes, and periodontal pathogens.[30] Figure 3 gives an overview of the role of periodontal pathogens as a risk factor for NCDs and periodontal disease.

Smoking as a risk factor

Studies have shown an increase in the proportion of periodontal pathogens and an alteration in the immune response in smokers, creating an increased susceptibility to infections.[31] Smoking increases the release of enzymes myeloperoxidase, lysozyme, human neutrophil lipocalin, and MMPs, which are destructive to the periodontal tissues[32] and can adversely affect fibroblast migration, attachment, and collagen synthesis[33] in the periodontium. An increase in the receptor activator of nuclear factor kappa-B ligand (RANKL)/osteoprotegerin (OPG) ratio is seen in the saliva and serum of smokers due to a decrease in the levels of OPG.[34] This can result in an increase in osteoclastic resorption of the bone. Smoking can result in excessive production of ROS, which can cause cellular injuries such as breaks in the DNA strand and functional alterations in the myocardial mitochondria.[35] The ROS can promote the proliferation of cardiac fibroblasts with resultant cardiac remodeling and stimulate transcription factors such as nuclear factor kappa B (NF-κB). There is a resultant increase in the serum levels of proinflammatory cytokines and other molecules such as CRP, fibrinogen, and TNF-α.[36] The neutrophil response is impaired in smokers with reduced chemotaxis, impaired phagocytosis, which may be due to an alteration of the cytoplasmic domain 18 integrin and cytoplasmic domain 62L-selectin in the membrane of the neutrophils.[37] The macrophages as well as lymphocytes have an impaired phagocytic function and this can contribute to the chronic inflammatory state.[38] In the lungs, there is injury and repair of the lung tissue with remodeling of the airway walls with collagen depositions and hypersecretion of mucus. Lung parenchyma and alveolar walls are destroyed, and there is alveolar enlargement and emphysema.[38] Smoking can induce the intrinsic and extrinsic cell apoptotic pathways, thereby damaging the myocardium and lung parenchyma.[39] It can increase the tendency for stroke via disruption of the blood brain barrier, in addition to adversely affecting the cerebral circulation through the promotion of vascular damage and upsetting the neurovascular coupling, which functions to match the neuronal activity and the cerebral blood flow.[39]

The activation of the carcinogens in cigarette smoke by P450s is generally balanced by the detoxification process catalyzed by enzymes such as glutathione-S-transferases and uridine diphosphate (UDP)-glucuronosyl transferases and cellular repair systems such as direct base repair by alkyltransferases, excision of DNA damage by base and nucleotide excision repair, mismatch repair, and double-strand repair. Any imbalance in the activation–deactivation process results in the persistence of DNA adducts, which causes carcinogenic mutations.[40] Nicotinic receptors and other cellular receptors bind to nicotine and nitrosamines present in cigarette smoke and activate Protein kinase A and B, resulting in decreased apoptosis of cells.[41] These changes, apart from the gene silencing of tumor suppressor genes through enzymatic methylation, can result in the excessive proliferation of cells contributing to tumorigenesis.[40]

Cigarette smoke exposure has been shown to cause an increase in insulin resistance through its alteration of the sphingolipid metabolism, as a result of which there is accumulation of ceramides in the heart and skeletal muscles, which will alter the morphology and electron transport in these tissues.[42] Studies have identified neuronal nicotinic acetylcholine receptors expressed on pancreatic islet cells and other tissues, which can modulate insulin secretion by an intraganglionic mechanism and thus affect the pancreatic β-cell function negatively.[43] Smoking increases the expression of receptor for advanced glycation end products, which will aggravate the host proinflammatory responses[42] and affect the insulin signaling pathways with consequent worsening of glycemic control.[26] An overview of the cellular and molecular mechanisms revealing smoking as a common risk factor for NCDs and periodontal disease is given in Figure 4.

Obesity as a risk factor

The adipose tissue in obese individuals produces adipokines, which can be hormone-like proteins, cytokines, vascular hemostasis proteins, acute-phase proteins, etc.[44] The hepatic dyslipidemia and decreased insulin sensitivity promoted by obesity-induced TNF-α may result in the formation of advanced glycation end products, which will further stimulate the secretion of inflammatory cytokines. TNF-α can also recruit monocytes into a developing atherosclerotic lesion. IL-6, a cytokine, which is a procoagulant protein, is also secreted by the adipose tissue. IL-6 along with

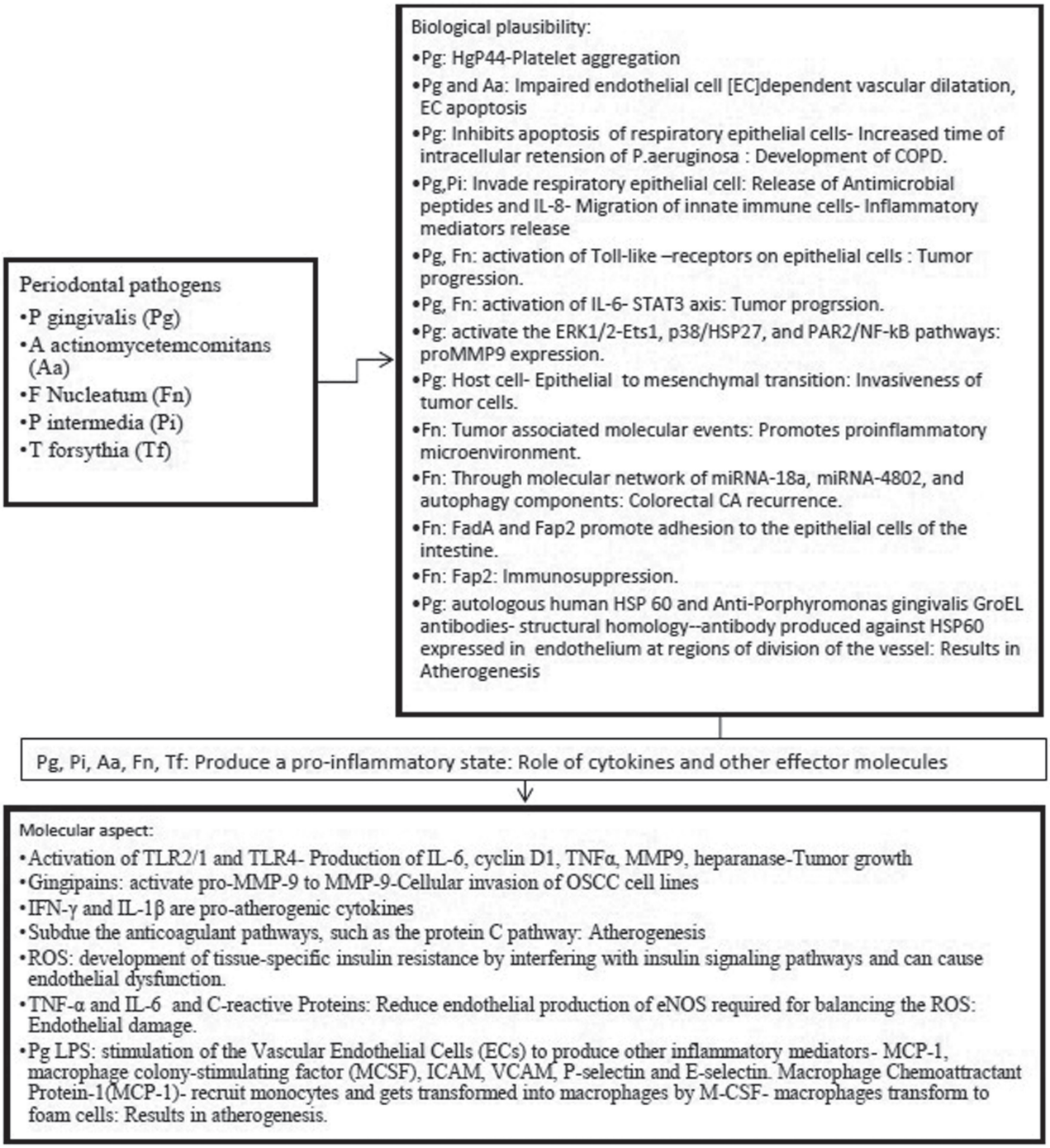

Figure 3: Periodontal pathogens as risk factors for NCDs. AR2 = aldose reductase 2, COPD = chronic obstructive pulmonary disease, eNOS = endothelial nitric oxide synthase, ERK1/2 = extracellular signal-regulated protein kinase1/2, Ets1 = ETS proto-oncogene 1, transcription factor, FadA = FadA adhesion gene of *F. nucleatum*, Fap2 = Fap2 surface protein of *F. nucleatum*, HSP = heat shock protein, ICAM = intercellular adhesion molecule, IFN-γ = interferon gamma, IL = interleukin, LPS = lipopolysaccharide, MCP-1 = macrophage chemoattractant peptide-1, M-CSF = macrophage colony-stimulating factor, MMP = matrix metalloproteinase, NCD = noncommunicable disease, NF-κB = nuclear factor kappa B, OSCC = oral squamous cell carcinoma, ROS = reactive oxygen species, STAT3 = signal transducer and activator of transcription 3, TLR = Toll-like receptor, TNF-α = tumor necrosis factor alpha, VCAM = vascular cell adhesion molecule

TGF-β promotes tumorigenesis,[45] and TNF-α and IL-6 stimulate the release of other inflammatory mediators contributing toward insulin resistance.[26] IL-6 increases the concentration plasminogen activator inhibitor-1 (PAI-1), which can prevent clot dissolution by its inhibitory effect on fibrinolysis, thus

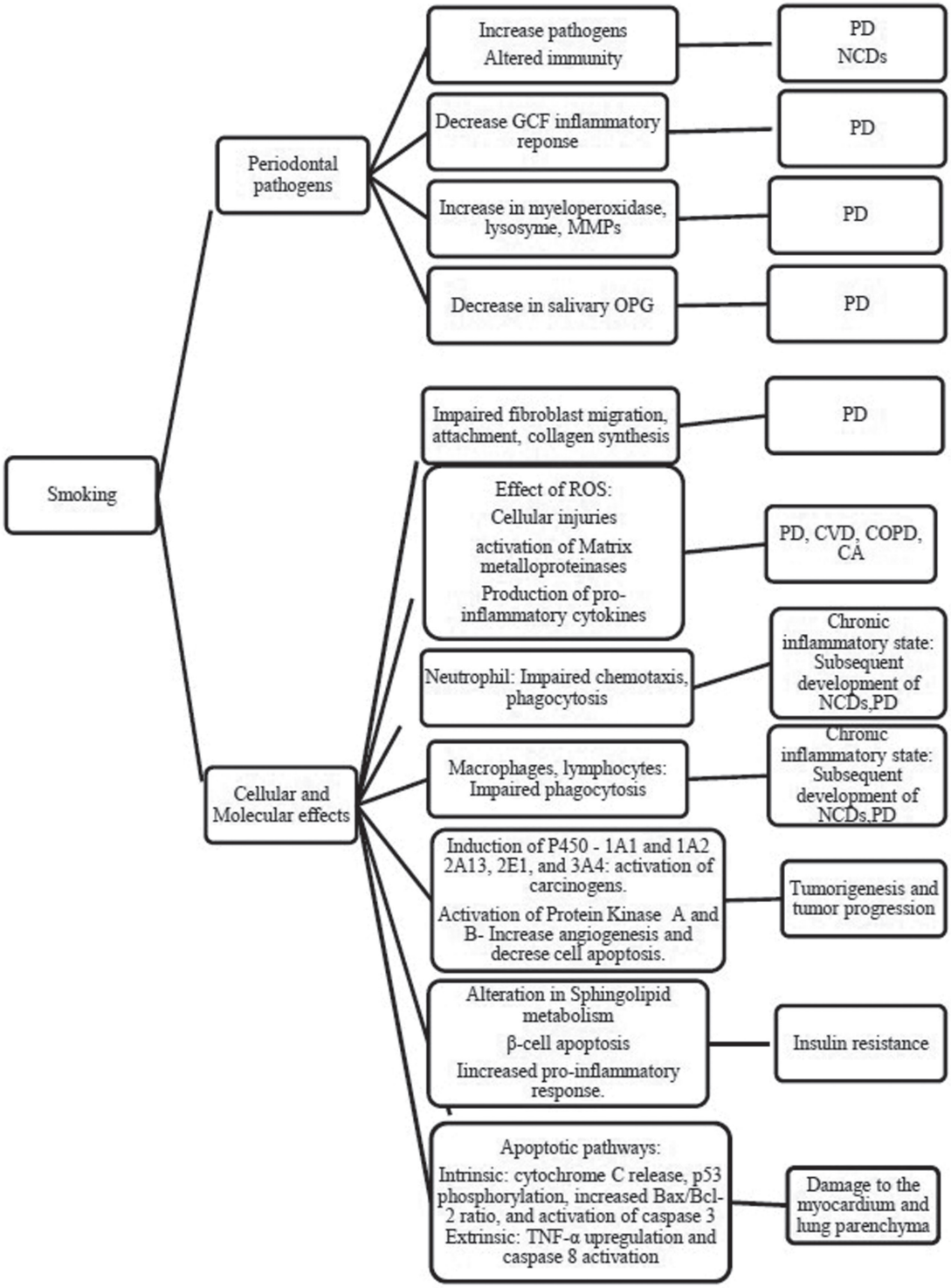

Figure 4: Smoking as a risk factor for NCDs and PD. CA = carcinoma, COPD = chronic obstructive pulmonary disease, CVD = cardiovascular disease, GCF = gingival crevicular fluid, MMP = matrix metalloproteinase, NCD = noncommunicable disease, OPG = osteoprotegerin, PD = periodontal disease, ROS = reactive oxygen species, TNF-α = tumor necrosis factor alpha

contributing toward thrombi formation.[44] Leptin, a cytokine secreted by adipocytes, may be involved in both decreasing and increasing bone formation through the central nervous pathways and through the influence on bone cells respectively. Leptin can facilitate the suppression of appetite. However, most obese individuals have leptin resistance wherein the appetite is not suppressed by the elevated levels of leptin. These individuals will demonstrate an increase in blood pressure due to the action of leptin, which will contribute to the development of CVD.[46] Leptin can stimulate proinflammatory response and impair

neutrophil function in the airway. An impairment of neutrophil function in the airways with reduced neutrophilic chemoattractant response leads to the lowering of pulmonary neutrophilia in response to harmful stimuli and injury.[47] Leptin paves the way for tumor growth, invasion, and metastasis through its action on receptors on the cancer cells, in addition to the promotion of angiogenesis[48] and stimulation of MMP-13 production. Obesity can affect cell-mediated immune response and adversely affect the lymphocytes and NK–T cells.[49] Circulation of ROS and inflammatory cytokines are increased in obese individuals, promoting an inflammatory state with oxidative stress, which stimulates the development of NCDs and periodontal destruction.[47,50] Adipose tissue macrophages are triggered in obesity and they produce IL-1β, which can stimulate the progression of tumor through vascular endothelial growth factor A release and angiogenesis.[48] Secreted nicotinamide phosphoribosyltransferase released from adipose tissue, which is referred to as visfatin, increases the viability of the breast cancer cells.[48] Insulin and insulin-like growth factor 1 are increased in obesity, and these factors act on insulin receptors and facilitate the proliferation and progression of tumor.[45] Non-esterified fatty acids are increased in obesity and type 2 diabetes, and these can affect the insulin–receptor signaling events, leading to an elevation in insulin resistance.[51] Retinol-binding protein-4 (RBP4), an adipokine, is involved in the reduction of phosphatidylinositol-3-OH kinase signaling in the muscle, which increases the insulin resistance. RBP4 can increase the levels of phosphoenolpyruvate carboxykinase in the liver, which is gluconeogenic.[51] Adiponectin, which is produced by adipocytes, has antiatherogenic, anti-inflammatory, and antitumorigenic properties.[52] Adiponectin stimulates fatty acid oxidation in an AMP-activated protein kinase and peroxisome proliferator-activated receptor-α dependent manner and it can increase insulin sensitivity.[53] The level of adiponectin in obese individuals is found to be decreased, which could be explained by the action of obesity-associated TNF-α, which is an inhibitor of adiponectin.[54] Omentin-1, an anti-inflammatory adipokine, can facilitate the apoptosis of hepatocellular carcinoma cells. Moreover, it can stabilize the tumor suppressor, p53. However, the level of omentin-1 is reduced in obesity.[48] Figure 5 gives an outline of the link between obesity, NCDs, and periodontal disease.

Stress as a risk factor

Stimulation of the hypothalamic–pituitary–adrenal axis during stress results in the release of glucocorticoids from the adrenal cortex.[55] Glucocorticoids can affect appetite, the eating behavior, and the weight gained, contributing to the accumulation of CVD risk factors,[56] and promote tumor growth. Chronic stress with an increase in noradrenaline and glucocorticoids along with IL-1, IL-6, TNF-α, and IL-8 can affect the surveillance and eradication of tumor cells. Inflammasomes, which are multiprotein complexes involved in the activation of caspase-1, are activated via the increase in extracellular ATP, IL-1β, and TNF-α in psychological stress and they facilitate tumorigenesis, angiogenesis, and metastasis.[57] Glucocorticoid can affect insulin sensitivity and can decrease insulin secretion.[58] Polymorphonuclear leukocyte chemotaxis and phagocytosis is reduced in stress. Cortisol escalates the growth of Pg and stress hormone noradrenaline increases the growth of *Eikenella corrodens* and increases the level of Arg-gingipain (rgpB), a virulence factor of Pg resulting in periodontal destruction.[59] The immunosuppression in stress will exacerbate the inflammatory response in COPD,[60] with an increase in the rate of destruction of pulmonary tissues. Stress arousal with the release of nocturnal stress hormones is associated with low telomerase activity, facilitating the initiation and progression of CVD.[61] An increase in basal cholinergic tone induced by anxiety and stress can result in an increase in acetylcholine release from parasympathetic nerves, which can control the smooth muscle tone of the airway and remodel the airway[62] and this, together with the inflammatory response, increases the airway obstruction. Stress can affect the behavioral pattern with an increase in deleterious habits such as smoking, which can contribute toward the destruction of the periodontium and the development of other NCDs.[55] A summary of the role of stress as a risk factor for NCDs and periodontal disease is given in Figure 6.

Nutritional deficiency as a risk factor

Membrane-derived fatty acids and their derivatives influence inflammation by modulating NF-κB pathways and by becoming the precursors of eicosanoid and docosanoid oxidation products.[63] The n-3 long chain polyunsaturated fatty acids (PUFAs) and their metabolites, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), through the action of P450 enzymes, have significant anti-inflammatory properties.[63] Polyphenols are other dietary antioxidants that have anti-inflammatory properties. Flavonoids in the diet can affect inflammation by inhibiting the release of IL-1β, TNF-α, and ROS and by the modulation of gene expression, mitochondrial interaction as well as by affecting intracellular signaling cascades that are responsible for controlling the neuronal survival and death. Resveratrol exerts anti-inflammatory properties

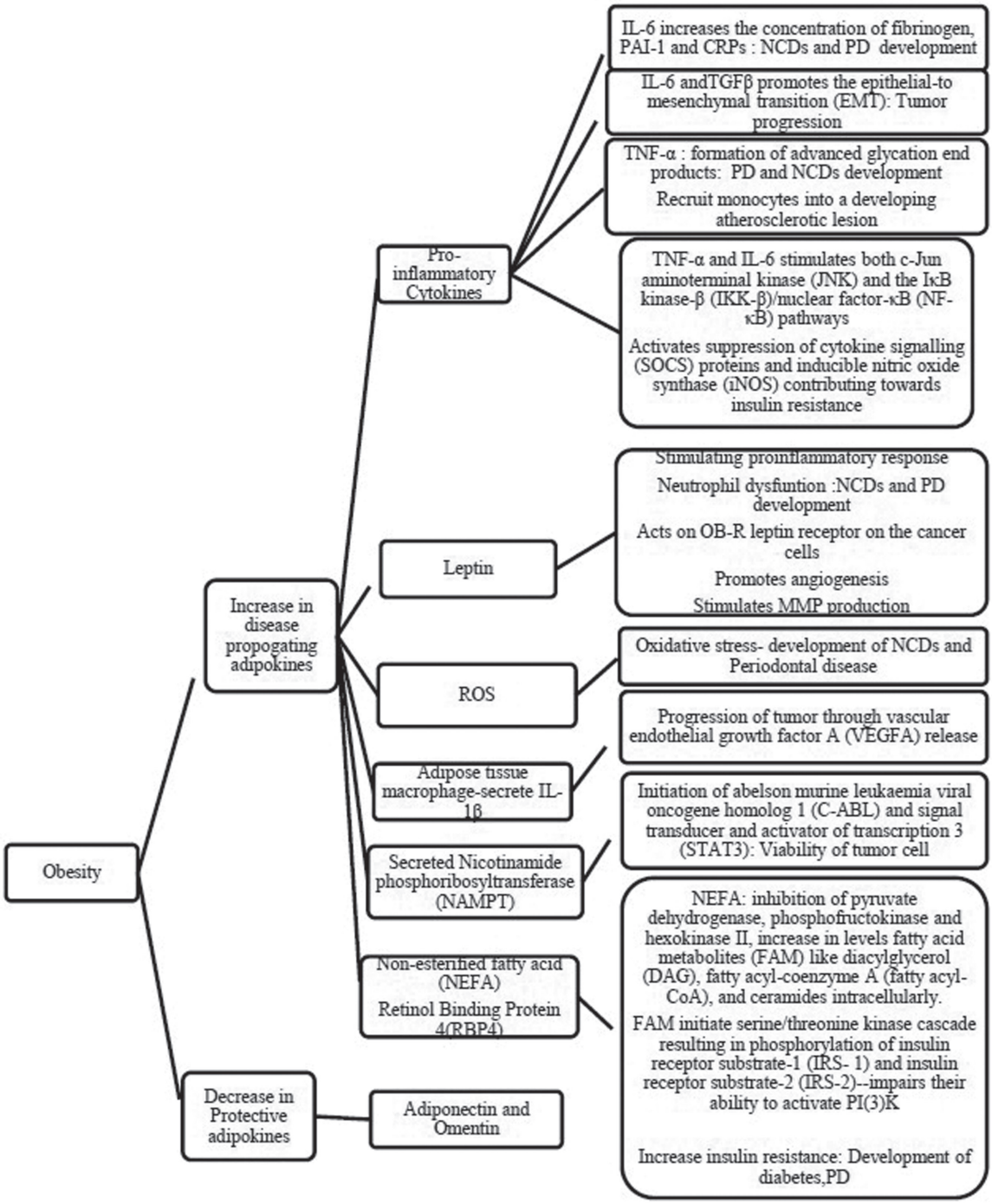

Figure 5: Obesity as a risk factor for NCDs and PD. C-ABL = tyrosine-protein kinase ABL (termed ABL as it was isolated from Abelson murine leukemia virus-C-ABL: mammalian genome; v-ABL: viral genome), IL = interleukin, MMP = matrix metalloproteinase, NCD = noncommunicable disease, NEFA = non-esterified fatty acid, OB-R = obesity receptor, PD = periodontal disease, PI(3) K = phosphatidylinositol-3-OH kinase, ROS = reactive oxygen species, TGF-β = transforming growth factor beta, TNF-α = tumor necrosis factor alpha

in airway epithelial cells and airways smooth muscle cells.[64] Vitamin A has an antioxidant role, vitamin B has an important role in the metabolism and proliferation of cells, and vitamin C plays an important role in the synthesis of collagen.[65] Vitamin E is an important extracellular antioxidant and it plays an important role in stabilizing the membrane structure. Vitamin E and Vitamin C can affect the lipid peroxidation chain reaction and protect the lung against oxidative damage.[66] Vitamins E and C can also protect DNA and prevent

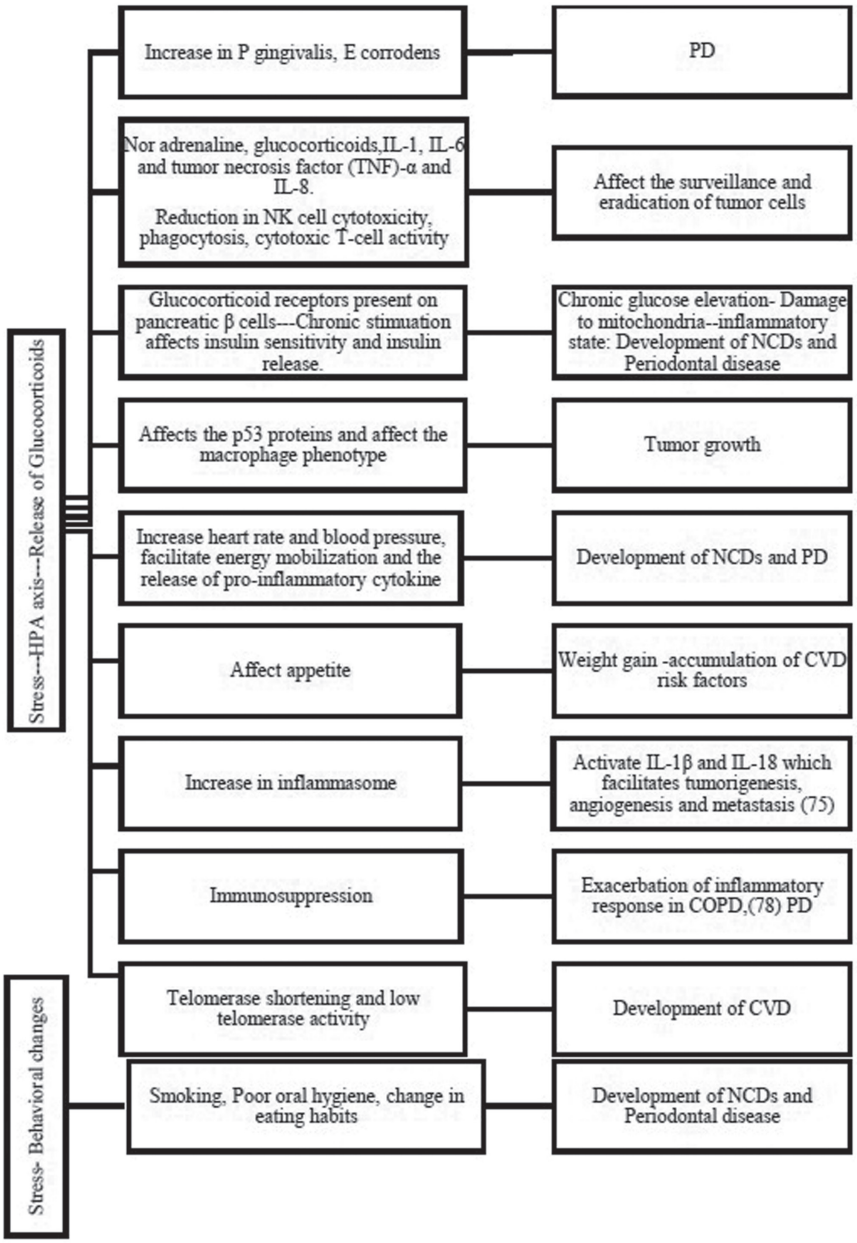

Figure 6: Stress as a risk factor for NCDs and PD. COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, CVD = cardiovascular disease, HPA = hypothalamic–pituitary–adrenal, IL = interleukin, NCD = noncommunicable disease, NK = natural killer, PAI-1 = plasminogen activator inhibitor-1, PD = periodontal disease

tumor initiation. Vitamin K forms a prerequisite for the formation of coagulation factors and is important for the formation of proteins osteocalcin and periostin, which are essential for bone metabolism.[65] Lycopene in diet can act as an antioxidant and Melatonin is another protective component of the diet, which is an ROS scavenger and stimulates the proliferation of osteoblasts. Lycopene can modify the risk for cancer by affecting tumor initiation, promotion, progression, and/or conversion.[67] Fiber content in the diet results in a reduction in serum levels of CRP and cytokines and increases the level of adiponectin.[63] Diet can affect the cellular immunity of the body and it has been noted that protein energy malnutrition, deficiency of vitamin A, folic acid, zinc, iron, and vitamin D can impair the NK cell development and functions of antigen-presenting cell, $CD4^+$ T cell.[68] Saturated fatty acid interacts with SNP in the genes for peptide adiponectin (adiponectin, C1Q and collagen domain containing [ADIPOQ]) and its receptor (adiponectin receptor 1 [ADIPOR1]) and thus modulate the effect of dietary fat modification on insulin resistance.[63] An increase in the levels of inflammatory cytokines, such as TNF-α and IL-1 due to a diet containing n-6 PUFAs, may mediate an increase in the

release of cellular adhesion molecules such as cadherins on the white blood cells, thus causing the cells to adhere to the vascular endothelium and increasing the risk for CVD.[63,64] Alcohol carcinogenesis could be attributed to the fact that ethanol can affect DNA methylation and can induce cytochrome P450 2E1, which can activate the procarcinogens present in food.[67] The molecular and cellular basis of the effect of nutrition is summarized in Figure 1.

Translation of molecular plausibility of CRFA: Evidence from literature

This review also delves into the research that establishes the concept of the shared risk factors between the NCDs and periodontal disease with a molecular and cellular link.

Summary of evidence

A systematic review has shown that the inflammatory mediators CRP and IL-6 had a significant association with both periodontitis and atherosclerosis[69] and ultrasensitive CRP is elevated in acute myocardial infarction, diabetes, and periodontal disease.[70] Abdominal obesity,[71] insulin resistance,[72] smoking,[73] periodontal pathogens,[74] stress, and depression[75] have been shown to be important common risk factors for NCDs and periodontal disease.

Limitations

Most of these studies are cross-sectional in nature and hence, the level of evidence on the extent of commonality of the risk factors of the conditions is debatable.

Conclusion

This grasp of the molecular basis should lead to research that delves into the quantification and numerical expression of the commonality of the risk factors of the NCDs and periodontal disease. Without this information, the opportunities for integration of periodontal disease prevention with NCDs through CRFA are not as compelling. The public health approach for the prevention of periodontal disease as a component of an integrated approach with NCD prevention activities, focusing on common risk factors, can pave the way toward better overall health with a concomitant reduction in healthcare costs.

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There are no conflicts of interest.

Authors' contributions

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Ethical policy and institutional review board statement

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Patient declaration of consent

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Data availability statement

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