Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1172-1185 | ISSN:2251-6727

Bias in Estimating the Cross-sectional Smoking, Alcohol, and Diabetes Mellitus Type 2 Associations with Periodontitis at Adult

Brian Limantoro*

Undergraduate Student, Faculty of Dental Medicine, Airlangga University, Indonesia

(Received: 07 January 2024 Revised: 12 February 2024 Accepted: 06 March 2024)

KEYWORDS

Periodontitis, inflammation, diabetes mellitus, nicotine, chemotaxis, ethanol

ABSTRACT:

Background: Periodontitis is chronic inflammation of the gum tissue caused by the presence of subgingival microorganisms present in the oral cavity. Periodontitis is begun with the spreading of gingivitis to dental structures such as cementum, periodontium, and alveolar bone. In many situations, systemic factors may cause chronic periodontitis by manifesting as systemic disease, such as diabetes mellitus. These situations occur in society, especially for those who smoke and consume alcohol.

Purpose: This case report aims to describe the condition periodontal disease in individuals with diabetes mellitus who habitually smoke and consume alcohol. Cotinine and nicotine found in saliva and crevicular fluid due to cigarette use might impact tissue damage in periodontal disease. Additionally, alcohol can hinder T-cell function and neutrophil chemotaxis, potentially modifying immune responses and elevating the risk of periodontitis. In individuals diagnosed with diabetes mellitus, the immune system and cellular functions are getting weakened which can inhibit tissue repair and destruction of bacteria that could increase severity of periodontal conditions. These connections become our concerns to be explored about how these things relate to each other.

Methods: In this study, past scientific articles are taken from trusted scientific databases then filtered until there are only remaining scientific articles that are related with the topic. Articles submitted have been published a maximum of ten years ago, but past articles discussing certain topics that are considered still relevant are used in this review. Explorations due to these relations will figure the connections of causation between alcohol consumption, smoking, diabetes mellitus, and periodontitis.

Result: Bad habit such as smoking and alcoholism could manage the severity of gingival abnormality from gingivitis stage to periodontitis, especially in immunocompromised diabetes mellitus type 2 patients.

INTRODUCTION

Periodontal disease is a wide term that can conclude all abnormalities that occur at the periodontal tissue in two major forms such as gingivitis and periodontitis (Abdulkareem *et al.*, 2023). Majorly, developmental and the advancement of periodontal condition could be shown by increasing the number of opportunistic pathogenic bacteria emerging to form dental plaque and activate improper immune system reaction (Sudhakara *et al.*, 2018). Gingivitis is an inflammatory lesion that occurs at gingiva and might develop and progress by the time into a more destructive form called periodontitis (Hajishengallis, 2015). Periodontitis is a persistent inflammatory condition in the oral cavity and a global public health issue that affects periodontium which consists of gingival tissue, periodontal ligament, and alveolar bone. (Bogdan *et al*., 2020; Paul *et al.*, 2020). Periodontitis could represent some serious systemic and oral health problems in elderly oral cavity (Dioguardi *et al.*, 2020). Systemic diseases that could be indicated by performance of periodontitis are Alzheimer disease (AD), diabetes mellitus (DM), and cardiovascular disease (Leblhuber *et al.*, 2020; Stöhr *et al*., 2021; Ide and Linden, 2014). One of those diseases, diabetes mellitus, stands out as one of the most prevalent cases that has a close relation with periodontitis, especially diabetes mellitus type 2.

Diabetes mellitus type 2 occurs because of insulin resistance and deficiency of relative insulin number (Romano *et al.*, 2021). In the 1960s, an association between diabetes mellitus type 2 (T2DM) and periodontitis was revealed by scientific evidence (Liccardo *et al*., 2019). Periodontitis could be linked to elevated HbA1c levels and various notably more severe complications associated with diabetes which periodontitis could indicate poor glycemic control at undiagnosed diabetes mellitus type 2 (T2DM) patients (Wu *et al.*, 2020). Periodontitis is type of diabetes

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1172-1185 | ISSN:2251-6727

mellitus type 2 (T2DM) complication which means diabetes mellitus type 2 (T2DM) can promote the progression of periodontitis but periodontitis can also increase the number of IL-6, TNF-α, and CRP in systems to induce insulin resistance and initiate the earlier stage of diabetes mellitus type 2 (T2DM) at elderly patients (Graziani *et al.*, 2018). CRP or better known as C-reactive protein is an acute phase, nonspecific, and highly sensitive proinflammatory cytokines that are released into injured parts of a human's body (Sain and Kudva, 2021). From the study by meta-analysis method, it is observed that relative risk of developing diabetes mellitus type 2 (T2DM) is elevated over 20% in patients with periodontitis (Stöhr *et al.*, 2021). By other study, patients with diabetes mellitus (DM) have almost 90% increased risk of periodontitis (Nascimento *et al.*, 2018).

In further perspective, association between diabetes mellitus type 2 (T2DM) and periodontitis could be more activated by the inducement of other compounds such as alcohol and cigarettes that enter the human's system through bad habits such as smoking and drinking alcohol. Ethanol (alcohol) will activate compounds in cigarettes by some biochemical pathway to become carcinogens and initiate more pathologic conditions of human's periodontium (Zięba *et al.*, 2021). Past meta-analysis study reveals that the intake of alcohol is a prevalent risk element and associates in positive-correlated with the presence of periodontitis (Pulikkotil *et al.*, 2020). Another study also shows that consumption of cigarettes may lead to higher probability of periodontitis exposure (Baumeister *et al.*, 2021).

This study is very important since all populations in this world have moved away from their old habits and have chosen a modern way of life which is less healthy in terms of diet, especially by the existence of fast food. Otherwise, people nowadays are less moving because of all the conveniences of technology. Unproportional dietary patterns may lead to other complications such as cardiovascular disease and diabetes mellitus type 2 (T2DM) which frequently attacks populations at range of teenagers until elderly with indication of unproportional weight compared to their body length or better known as obesity and characterized by a dark velvety rash at back of necks and underarm region (Wang *et al.*, 2020; You *et al.*, 2022). This statement could give a perspective about correlation between darkened backs of neck and underarm region and other complications at many parts of the body or work systematically. People nowadays also prefer using conventional chemical mouthwash instead of brushing their teeth which are not effective enough to remove all debris from their oral cavity. This ineffectiveness in removing all debris may lead to periodontal disease such as gingivitis which may develop into periodontitis (Sälzer *et al.*, 2020). Some conventional chemical mouthwash may also cause oral site irritation of the users if the ingredients and compositions could not be tolerated by the users and lead to hypersensitivity or other immunopathology responses at the oral site such as periodontal tissue that holds one of the most important function as support system.

Nowadays, many people in this world have other bad habits such as smoking and drinking alcohol. Correlation between smoking either conventional cigarettes and electronic cigarettes (vapor) has been revealed to be causing many oral diseases, one of them is periodontal disease (Almeida-da-Silva *et al.*, 2021). Laterly, alcohol consumption may also cause another improper immune system reaction at oral site by activating cigarettes' compounds to be carcinogenic and lead to periodontal disease (Zięba *et al.*, 2021). Improper habit compilations at elderly which have a decreasing immune system will lead to more local and systemic complications where many symptoms of those complications can be observed and determined through abnormalities at their oral sites. Oral site is the most accessible portal for other dangerous compounds entering human's body so many complications can be determined by the symptoms shown at the oral site.

REVIEW

1. Clinical Aspects and Examinations for Periodontitis

Periodontitis which is a chronic phase of gingivitis generally caused by switching characteristic from symbiotic into dysbiotic of oral microbiome emerging, initiating progressive of periodontal tissue that surrounding teeth as support system, and finally will be causing tooth loss following an increasing in severity over time (Abdulkareem *et al.*, 2023). Periodontitis is linked with a diverse collection of bacterial organisms or opportunistic pathogenic bacteria that consists of anaerobic and microaerophilic bacteria such as and many more (Sanz *et al.*, 2010). At normal conditions, many commensal bacterium such as *Staphylococcus sp.*, *Streptococcus sp.*, *Actinomyces sp.*, *Prevotella melaninogenica*, *Prevotella intermedia*, *Veillonella*

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1172-1185 | ISSN:2251-6727

parvula, *Veillonella dispar*, *Haemophilus parainfluenzae*, *Fusobacterium nucleatum*, *Leptotrichia buccalis*, and *Campylobacter concisus* are cooperating synergistically to generate nitric oxide by reducing dietary nitrate in gradual conversion from nitrate (NO_3) into nitrite (NO_2) then converted again into nitric oxide (Surma *et al.*, 2021). Nitric oxide (NO) is a form of human's immune system to avoid pathogenesis of cardiovascular disease such as hypertension (Pignatelli *et al*., 2020). Past network analysis study about bacteria flora abundances and PCoA assessments based on 16S rRNA analysis has revealed and shown comparison of bacterium species taxa emerge and develop at healthy periodontal sites also periodontitis periodontal site (Funahashi *et al.*, 2019). A network connection diagram through analysis study about bacteria species taxa developing at both healthy and periodontitis periodontal sites was simplified by Nemoto *et al.* and relations of each bacteria species taxa can be defined through Figure 1.

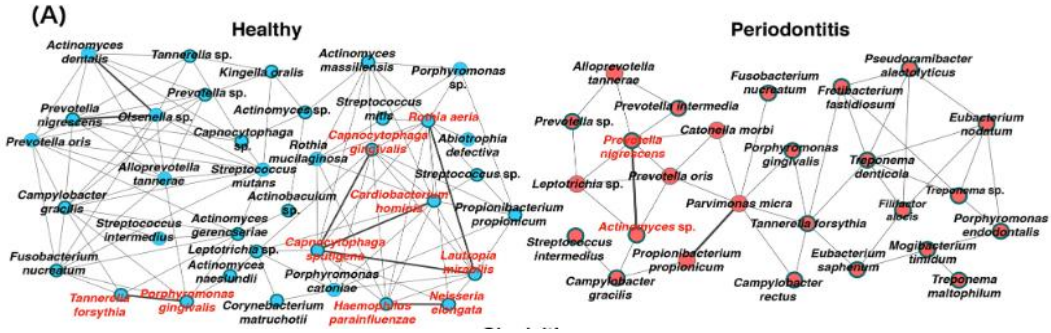


Figure 1 : Network connection of many bacteria species taxa associating together at both healthy and periodontitis periodontal site. All active core taxa are indicated with a bold circle and the interaction of one active core taxa to another core taxa is highlighted with bold strokes. Therefore, interacting core taxa is signed with red text for every status. Blue circle indicates interacting core taxa at the healthy periodontal sites meanwhile red circle indicates interacting core taxa at periodontitis periodontal site (Nemoto *et al*., 2021)

At unhygienic environment inside the oral cavity, the mixed group of bacteria will easily colonize the cervical areas of teeth crown and forming a biofilm named dental plaque which is a specialized niche for protecting them from antibiotics and antiseptics effects, then generate infections at periodontal tissue (Surma et al., 2021). Periodontitis and arterial hypertension are usually associated together and mostly happen in the elderly, man, cigarette smokers, obese people, diabetes mellitus type 2 sufferers, and lower social background (Del Pinto et al., 2020). The correlation the impact investigated revealed through observational study that there is a positive correlation between associations were found between bacterial load forming subgingival dental plaque, both of them show an increasing level (Desvarieux et al., 2010).

Further, hypertension T2DM are found to coexist as macrovascular and microvascular diseases that generate bidirectional risk means either hypertension and T2DM are giving cross-impacts to each other (Yildiz et al., 2020). Unfortunately, this clinical aspect that could be examined as the symptoms of presence of subgingival dental plaque and periodontitis has a very complex pathogenesis and the correlation of hypertension with diabetes mellitus type 2 (T2DM) managing periodontitis could not be solved totally (Ciulla and Vivona, 2020). Many past studies only can conclude that the pathologic mechanism of increasing systolic blood pressure is the result of human's immunity by producing systemic inflammation at the infected vascular endothelium (Ciulla and Vivona, 2020).

In fact, dysbiosis of oral microbiome in human's oral cavity can trigger many immune responses by releasing immunity factors such as prostaglandin, cytokines, and tumor necrosis factor alpha (TNF-α) as well (Figure 1). Prostaglandin and cytokines will associate together for bone resorption mechanisms and disturbance of alveolar bone metabolisms by triggering osteoclasts and proteolytic enzymes, consecutively (Figure 2). Whereas, tumor necrosis factor alpha (TNF-α) will trigger matrix metalloprotease which leading to connective tissue breakdown (Figure 2). All of these immunity components released lead into periodontitis which

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1172-1185 | ISSN:2251-6727

reduced alveolar bone level, seemed dental plaque, and periodontal pocket will easily get seemed (Figure 2).

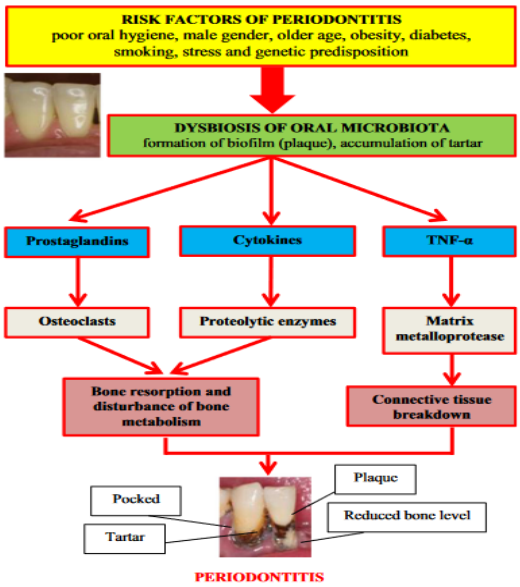
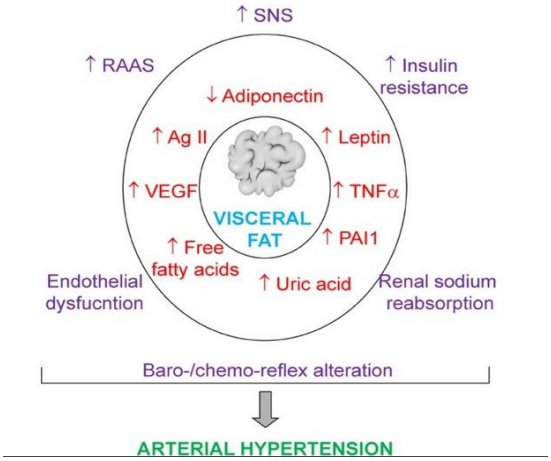


Figure 2: Schematic diagram of etiopathogenesis of periodontitis in perspective of oral microbiome dysbiosis (Surma *et al.*, 2021)

This arterial hypertension at periodontitis cases also could be triggered by presence of bacterial toxin in blood (bacteremia) at blood vessels that facilitate nutrition for oral cavity especially periodontal tissue and periodontal ligament. Increasing progression of atherosclerotic lesion is triggered by periodontal pathogens and past evaluational study has revealed that tested atheromas Indicated the presence of at least one of the designated periodontal pathogens which consist of *Tannerella forsythia*, *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans, and Prevotella intermedia* (Haraszthy et al., 2000). Acceleration of atherosclerosis progression will lead to direct damage of vascular endothelium and associate together with another oxidative stress in the human's oral cavity to generate arterial hypertension (Surma et al., 2021). Although correlation between arterial hypertension and diabetes mellitus type 2 (T2DM) in managing periodontitis could not be determined, many obese people have serious complications of diabetes mellitus type 2 (T2DM) and arterial hypertension (Seravalle and Grassi, 2017). From the Figure 3 below, it can be concluded that excessive visceral fat which can be found at obese people will increase insulin resistance which is the main factors of diabetes mellitus type 2 (T2DM) and lead to increasing renin-angiotensin-aldosterone system (RAAS) then cause arterial hypertension.



Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1172-1185 | ISSN:2251-6727

Figure 3: Correlation between Diabetes Mellitus Type 2 (T2DM) and arterial hypertension in schematic view (Seravalle & Grassi, 2017)

The most important point that must be known about periodontitis is its origin. Periodontitis is a destructive form of inflammatory lesion at the cervical part of the tooth named gingivitis as the result of lesion development and progression at the periodontal tissue (Hajishengallis, 2015). The statement means that gingivitis is the earlier form of lesion that resulted from emerging bacterium in biofilm formation named dental plaque which may always develop and progress into destructive form called periodontitis that is indicated by reducing and loosening of alveolar bone level (Surma et al., 2021). Gingivitis itself could be classified as mild gingivitis, chronic marginal gingivitis, and gingivitis with hyperplasia (Madiba and Bhayat, 2018; Coventry et al., 2000). Anatomical differences between normal periodontal site, three types of gingivitis periodontal site, and periodontitis periodontal site will be shown in Figure 4 below. Compared to gingivitis which is the earlier stage of this periodontal disease case, periodontitis tends to show a lot of destruction at the periodontal tissue (Figure 4). An observational study by comparing many aspects at gingivitis sites and periodontitis sites was conducted by Nemoto et al. to know the significance differences between gingivitis and periodontitis so the process of determining periodontal diseases in patients could be diagnosed clearly by generating some assessments. The study was using 21 patients with the mean age of 61.2 years consisting of 6 non-smoking men, a smoking man, and 14 women (Nemoto et al., 2021). It is observed that the probing depth and radiographic bone less at periodontitis sites show an increase significantly compared to gingivitis sites (Table 1).

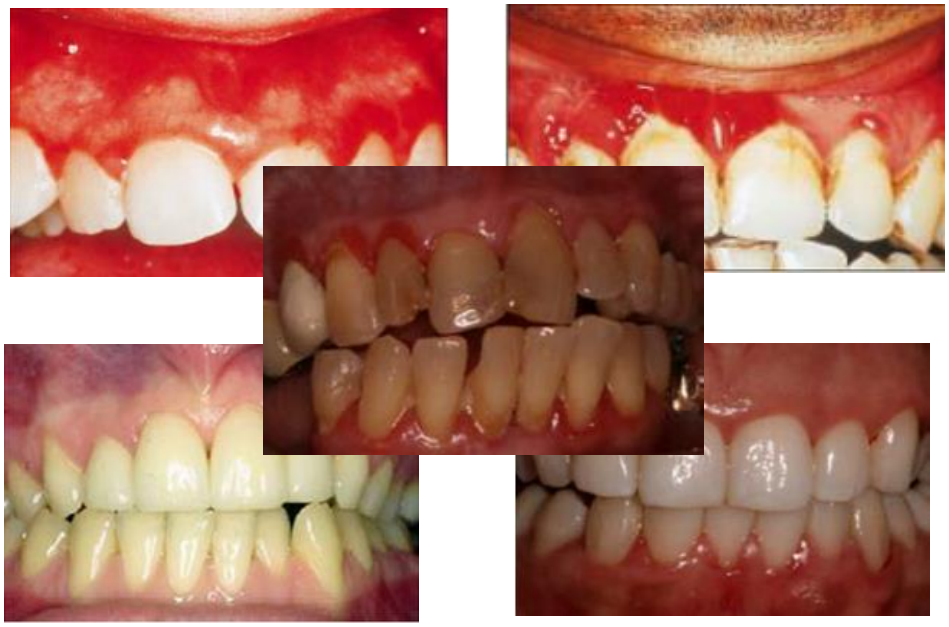


Figure 4 : Anatomical view of periodontal tissue at healthy site (upper left); mild gingivitis site (upper right); chronic marginal gingivitis site (center left); gingivitis with hyperplasia (center right); and periodontitis at the bottom row (Madiba and Bhayat, 2018; Coventry *et al.*, 2000).

In patients with gingivitis, there is some bleeding at the periodontal site but there is no damage to the periodontal membrane and alveolar bone so the level of periodontal tissue is not reduced and it can be treated and repaired (Madiba and Bhayat, 2018). In patients with periodontitis, there are some reducing levels of periodontal tissue, damaging of periodontal membrane and alveolar bone, loosening teeth, and abnormal gap named pocket will be developing between teeth and the periodontal tissue which are conducted chronically and becoming very difficult to be treated and repaired (Madiba and Bhayat, 2018; Coventry et al., 2000).

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1172-1185 | ISSN:2251-6727

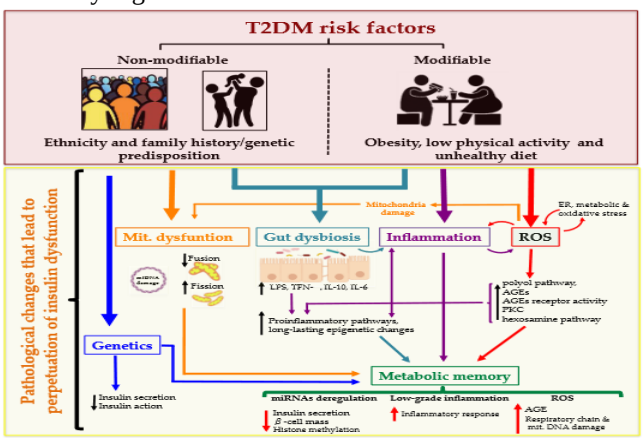
Table 1

Site	PD (mm)	Radiographic bone loss (mm)	BOP (% of patients)
Healthy	2.4 ± 0.6†	2.70 ± 1.08†	0
Gingivitis	2.6 ± 0.5*	2.76 ± 1.08*	100
Periodontitis	6.4 ± 1.3*†	5.98 ± 1.78*†	100

Table 1 : Quantitative clinical characteristics of study participants (by using 21 patients consisting of 7 men and 14 women with ages of 61.2±15.3 years) were represented by mean ± standard deviations. Measurement parameter in this study was notated by PD (in mm); radiographic bone loss (in mm); and BOP (in %) which PD means probing depth; BOP means bleeding on probing. Significance signs were shown by † symbol that indicates significant differences between healthy and periodontitis sites and * symbol that indicates significant differences between gingivitis and periodontitis sites (Nemoto *et al.*, 2021).

2. Effects of Diabetes Mellitus Type 2 and Its Complication in Managing Periodontitis

Based on World Health Organization (WHO) regulations, diabetes mellitus is defined as chronic metabolic disease that is characterized by increasing levels of blood glucose which leads to damage to the heart, vasculature, eyes, and kidney (Galicia-Garcia et al., 2020). The most common diabetes mellitus cases are diabetes mellitus type 2 (T2DM) which is signed by insulin resistance and leads to inadequate tissue response to insulin that is released by β-islet of pancreas (Galicia-Garcia et al., 2020). Earlier, overconsumption of carbohydrate and fat will be tolerated by the increases of insulin secretion in order to maintain the homeostasis of blood glucose to be at the normal range but insulin secretion from β-cells of pancreas is not more capable enough to maintain the homeostasis of blood glucose and lead to hyperglycemia (Goyal and Jialal, 2022). Based on International Diabetes Federation data at 2019, diabetes mellitus has caused 463 million adults aged at range of 20 until 79 years which have very high risk of diabetes mellitus type 2 (T2DM) and this number is predicted to be rising up into 700 million at 2045 (Galicia-Garcia et al., 2020). Most of diabetes mellitus type 2 sufferers are having higher body fat percentage which are distributed mostly at abdominal part or better known as obese which may trigger insulin resistance through inflammatory mechanisms, increases of free fatty acid releasing, and dysregulation of adipokine (Goyal and Jialal, 2022). Beside unhealthy lifestyle, diabetes mellitus type 2 (T2DM) could be conducted by genetics or ethnicity factors which may lead to mitotic dysfunction and gut dysbiosis then affecting metabolic memory (Figure 5). Affected metabolic memory will cause deregulation of microRNA (miRNA) which is a conservative material genetics acting as a regulator in human gene and leading to decrease of insulin secretion because of β-cells decreases (Figure 5). The other side effect of this metabolic memory disturbance is damage to the DNA mitotic cycle and respiratory chain (Figure 5).



Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1172-1185 | ISSN:2251-6727

Figure 5 : Scheme of diabetes mellitus type 2 (T2DM) risk factors in causing pathological changes that lead to insulin dysfunction (Galicia-Garcia *et al.*, 2020).

Interestingly, abnormal increases of blood pressure is a good prognosis marker for long-term cardiovascular diseases and outcome in diabetes mellitus type 2 (T2DM) patients (Sower et al., 2001). Diabetes mellitus type 2 (T2DM) patients have three until six times higher risk to develop arterial hypertension compared to patients without diabetes mellitus type 2 (Lastra et al., 2014). Diabetes mellitus type 2 (T2DM) also associated with another major complication such as cardiovascular autonomic neuropathy which tend to be associated with parasympathetic nerve and sympathetic nerve only at advanced stage of the complication (Serhiyenko and Serhiyenko, 2015; Hage and Iskandrian, 2011). At periodontal tissue, there are a lot of blood capillaries and branches of trigeminal nerve that innervate and facilitate nutrition for the tissue itself, alveolar bone, and teeth. In the patients with diabetes mellitus (T2DM) that obesity or excess of fat at the abdominal part, arterial hypertension mostly is caused by atherosclerosis or blockage of blood vessels by plaque of fat (Surma et al., 2021). The other association with the nervous system that is manipulated by the existence of this complication will force the cardiovascular system to pump more blood to the blood vessels at periodontal tissue. Overpumping activation will lead to destruction of the blood vessel's wall and may lead to bleeding of the periodontal site. From Figure 5, diabetes mellitus type 2 (T2DM) most common factor, obesity, could manage inflammation which also may cause blood vessel destruction that lead to blood leakage from blood vessels. The bleeding at the periodontal sites laterly may initiate the abnormality named gingivitis which is the earlier phase of periodontal disease (Zini et al., 2021). By the time, gingivitis which triggers the gap formation between the outer side of tooth with its place at periodontal sites to be filled with the bleed. The bleeding will develop and increase the gap between the outer border of tooth with the periodontal site then suppress the periodontal tissue, alveolar bone, and make an abnormal structure called pockets which make it become irreversible periodontal disease (Madiba and Bhayat, 2018).

3. Effects of alcohol consumption and smoking and Its Complication in Managing Periodontitis

The use of tobacco and alcohol poses a significant public health issue (GBD 2019 Risk Factors Collaborators, 2020). The correlation between periodontitis and smoking and alcohol has garnered significant focus, given that both factors are potentially amendable behavioral risk factors (Wang et al., 2016; Chapple et al., 2017; Leite et al., 2018; Pulikkotil et al., 2020). However, there remains ambiguity surrounding the character of the link between smoking and alcohol consumption and the onset and advancement of periodontitis. Determining causality and whether modifying these risk factors can diminish the risk of periodontal issues is less definite. Establishing causation is crucial for guiding public policies and clinical interventions.

Periodontitis is an inflammatory oral condition triggered by the interplay between pathogenic bacteria and the host's response, culminating in attachment loss and eventual tooth loss (Kornman, 2008). Szabo et al. in 1999 illustrated that alcohol disrupts T-cell function and neutrophil chemotaxis, potentially modifying immune responses and heightening the susceptibility to periodontitis. Ethanol, the predominant type of alcohol present in alcoholic beverages and widely used in various industrial processes, is also referred to as ethyl alcohol and has the chemical formula C2H5OH. Understanding ethanol's metabolism is crucial for comprehending its associated pathophysiological mechanisms due to its close connection to biological effects (Figure 6). The first segment of this section emphasizes the ethanol-to-acetaldehyde conversion, while the latter part delves into the metamorphosis of acetaldehyde into acetate. The key player in the initial oxidative metabolism of ethanol is the cytosolic alcohol dehydrogenase (ADH), resulting in the generation of NADH (Cederbaum, 2012). (Crabb 1995; Edenberg 2000). In humans, seven genes (ADH1 to ADH7) encode various subunits (a, b1, b2, b3, c1, c2, p, v, r, and l) for alcohol dehydrogenase (ADH) (Cederbaum 2012). These subunits pair up to create isoenzymes categorized into five classes based on their enzymatic characteristics (Crabb 1995). ADH Class I, composed of subunits coded by ADH1, ADH2, and ADH3, plays a vital role in the metabolism of alcohol. Although variations in ADH isoenzymes have been identified, there seems to be no direct association with a specific alcohol-related ailment or alterations in alcohol metabolism. Nevertheless, certain studies indicate that alcohol elimination is slower in a fasting state compared to a fed state due to reduced

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1172-1185 | ISSN:2251-6727

levels of ADH (Cederbaum 2012). Approximately the microsomal pathway, involving the cytochrome P450 (CYP) family, is responsible for about 10% of the body's ethanol metabolism (Hamitouche et al. 2006). While CYP1A2 and CYP3A4 are acknowledged participants, CYP2E1 is recognized as the primary cytochrome P450 (CYP) during the initial (Kunitoh et al. 1996; Cederbaum 2012). The transformation the conversion of ethanol to acetaldehyde results in ROS, playing a significant role in the toxicity of alcohol (Ekstrom and Ingelman, 1989). Moreover, ethanol enhances its own metabolism by shielding CYP2E1 from ubiquitination and degradation carried out by the proteasome complex (Zhukov and Ingelman 1999; Lu and Cederbaum 2008).

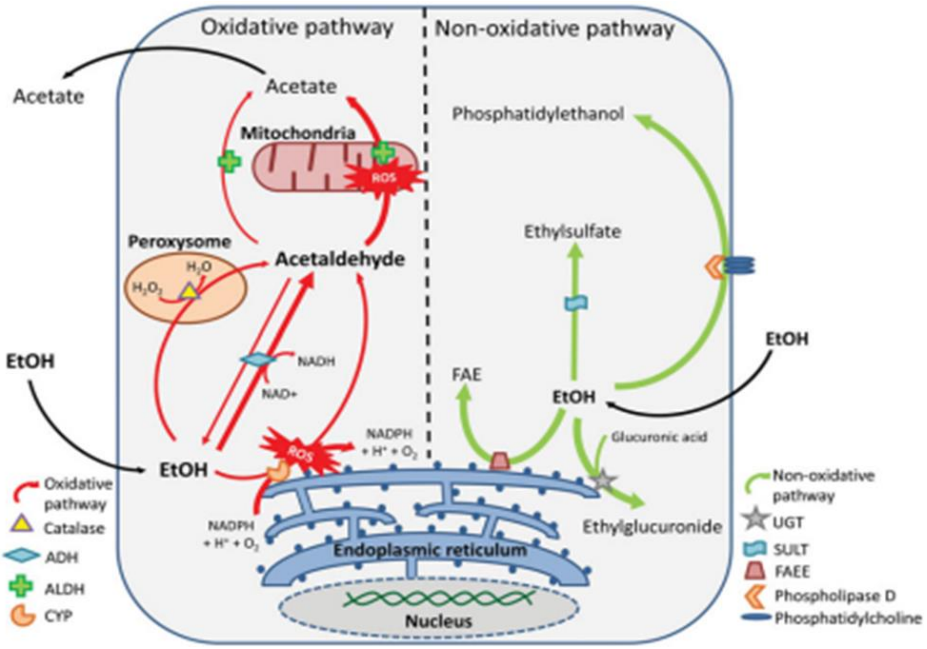


Figure 6 : Oxidative and non-oxidative ethanol metabolic pathways in the hepatocyte. ADH: alcohol dehydrogenase; ALDH: aldehyde dehydrogenase; CYP: cytochrome P450; EtOH: ethanol; FAE: fatty acid ester; FAEE: fatty acid ethyl ester; SULT: sulfotransferase; UGT: uridine diphosphate glucuronyltransferase (Dare *et al*., 2019)

The activation of xenobiotics, particularly substances derived from tobacco like polycyclic aromatic hydrocarbons, is believed to involve significant contributions from Cytochrome P450 (CYP) enzymes, specifically CYP1A1 and CYP2E1 (Kadlubar & Hammons, 1987) and nitrosamines (Guengerich et al., 1991). Conversely, the detoxification of these activated metabolites involves glutathione S-transferase (GST) M1 and N-acetyltransferase (NAT1 and NAT2). Polymorphisms in CYP1A1 and CYP2E1 have been linked to increased enzymes' catalytic functions. Furthermore, the absence of the GSTM1 genotype and mutations in the NAT gene lead to an inefficient detoxification of xenobiotics. Notably, recent findings indicate that the increased susceptibility to periodontitis, particularly in smokers, is associated with the slow acetylator genotype of NAT2 (Meisel et al., 2000; Kocher et al., 2002). Hence, genetic variations in other enzymes responsible for metabolizing xenobiotics, such as CYPs and GSTs, could contribute to an individual's susceptibility to periodontitis. A study by Kim-JS et al. in 2004 provided evidence that the CYP2E1 enzyme might elevate the risk of periodontitis associated with smoking (OR 5 3.3, 95% 5 0.7–16.5) (Kim-JS et al., 2004).

Every commercially available tobacco product, encompassing (Edwards et al., 2021). Out of the seven tobacco-specific nitrosamines identified in unburned, cured tobacco, three of them – N'-nitrosonornicotine (NNN), 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and its primary metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanal (NNAL) - have garnered the most significant focus (Hecht and Hoffmann, 2016). Additionally, there is indication of their endogenous generation, specifically through the nitrosation of nornicotine (Knezevich et al., 2013).

Nicotine serves as the addictive element in all tobacco items, including smokeless tobacco (Clarke et al., 1981).

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1172-1185 | ISSN:2251-6727

The distinction lies in the fact nicotine is characterized. Despite this seemingly minor distinction, there is a notable difference in biological activity (Schuller, 2007). The metabolic pathway of nicotine involves its transformation processed by cytochrome P450 2A6 (CYP2A6) at the 5'-position, it produces α-hydroxynicotine, which is in equilibrium with the nicotinium ion. These substances then undergo additional oxidation facilitated by aldehyde oxidase and CYP2A6, ultimately forming cotinine, the principal metabolite of nicotine (Murphy, 2021).

The occurrence of cotinine and nicotine in the saliva and crevicular fluid of individuals who smoke could significantly impact the tissue damage observed in periodontal disease. Laboratory studies have indicated that nicotine has an inhibitory effect on lymphocyte growth (Neher, 1974) and induces a temporary initial dilation of blood vessels, succeeded by constriction, upon administration in rabbits (Clarke et al., 1981). The gingival inflammation reduction observed in smokers during a recent four-week experimental period gingivitis study might be attributed to the vasoconstrictive impact of nicotine (Bergstrom and Preber, 1986). Several laboratory studies have indicated that nicotine, at concentrations similar to those found in human smokers, induces a notable decrease in PHA (phytohemagglutinin)-stimulated DNA synthesis in human peripheral blood lymphocytes and inhibits DNA synthesis in cells (Altmann et al., 1984). A laboratory study has demonstrated that nicotine leads to abnormal growth of fibroblasts (Raulin et al., 1984). Laboratory investigations involving tobacco smoke have indicated a decrease in polymorphonuclear leukocytes (PMNs) and macrophages, along with a reduction in T-lymphocyte proliferation (Holt and Keast, 1977). The presence of cotinine and nicotine in saliva and gingival crevicular fluid has many implications and may, in part, explain the increased susceptibility to periodontal disease in smokers versus non-smokers (Rivera, 1986). The role of the presence of cotinine/nicotine in the saliva and gingival crevicular fluid of smokers and the relationship to an increased propensity for and severity of periodontal disease remain to be elucidated, as do the mechanisms of these effects.

DISCUSSION

We could know that periodontitis is a more destructive form of periodontal disease and chronic phase of gingivitis that is irreversible. Its existence initially was triggered by the emerging opportunistic pathogenic bacterium that are emerging in human's oral cavity then followed by phenotype switching into pathogenic, specifically at periodontal tissue, and causing bleeding at periodontal tissue and developing into more destructive form that reduces alveolar bone so the pocket structure that is formed between outer tooth border and periodontal tissue can be easily seen. It also has a close relation with other systemic complications that are related with the vascular system and association of hormonal system inside it to manage the regulatory system in human's body to achieve homeostasis conditions, such as insulin hormone in maintaining human's blood glucose by decreasing the amount glucose in blood blow while the value is more than normal value.

Many systemic complications such as diabetes mellitus type 2 which get associated together with other related complications such as arterial hypertension because of atherosclerosis or blockage of blood vessels with fat component will play crucial role in managing periodontal disease that is initiated with gingivitis (Seravalle and Grassi, 2017). Advanced damages and complications at systemic complex that are branching to oral site will increase the effect of the complication and cause more destructive type of periodontal disorder by increasing the rate of blood vessel damage and blood leakage from blood vessel that may fill any nearest gap, such as places for teeth at periodontal site, then the blood will make a bigger gap between outer border of tooth and periodontal site and suppress the periodontal tissue and alveolar bone level get reduced which is irreversible to be treated. These damages itself cannot be separated from inflammation that affects the immune system and causes vasodilation of blood vessels. Inflammation also affects metabolic memory that may increase insulin resistance that make people unable to respond to an ordinary level of insulin which will lead to hyperglycemia, a symptom of diabetes mellitus. Diabetes mellitus type 2 (T2DM) itself may also cause gut dysbiosis which is associated together with proinflammatory components to trigger the inflammation process. Otherwise, obesity risk factors can activate metabolic and oxidative stress which may also affect metabolic memory and lead to insulin resistance too (Galicia-Garcia *et al.*, 2020). Not only bad habits and lifestyle, periodontal diseases are mostly caused by genetic or ethnicity factors which may lead to mitotic cycle dysfunction that will lead to insulin

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1172-1185 | ISSN:2251-6727

resistance too. Insulin resistance is very crucial in the function of maintaining blood glucose which cell receptors for insulin are unable to respond to insulin and result in the proper result to convert glucose into another form named glycogen while blood glucose level is increasing too high. Laterly, insulin resistance may also cause another disturbance at human's integrated systemic functions which can associate together with arterial hypertension by the presence of fat that may block the flow of circulated blood and lead to massive force to pump blood passing through the blood vessels. This overpumping mechanism will trigger blood vessel destruction that may cause blood leakage and bleeding at affected periodontal sites. The analogical thinking is not different since the movement of blood can happen through gaps that exist near them. Many observational and molecular studies are obtained to fix up the complete mechanisms of single direction or bidirectional effect of arterial hypertension with emergence of bacterium at periodontal sites. According to Figure 2 and Figure 3, it can be concluded that dysbiosis of microbiome and arterial hypertension can trigger and activate one of the most important cytokines in human's body which is will work by causing inflammation for a final result of necrosis or cell death (Seravalle and Grassi, 2017). It means there are possibilities that caused cells are abnormal immunity cells which can affect other healthy immunity cells at a wider range. More activated tumor necrosis factor- alpha may enhance more severe oral cavity problems to give more opportunity for emergence and development of pathogenic microbiome and massive inflammation of blood in blood vessels. This simultaneous mechanism may lead to gingivitis and destructive form of periodontitis much faster than gingivitis or periodontitis site at people without diabetes mellitus type 2 (T2DM) and its complications.

Modern lifestyles really hit very different nowadays, in which alcohol and smoking culture are spreading very fast until most teenagers are becoming active users of alcohol or smoking or even both of them. Majority populations in this world have become or had become alcoholic and active smokers, especially men. Psychologically, people have uncontrolled emotions which trigger them to consume alcohol and cigarettes exaggeratedly in order to relieve their stress. Unconsciously, it will trigger them to always consume alcohol and cigarettes which have addictive effects. The combination of alcohol and cigarette usage will increase the severity of periodontal disease. Activation of these components are associated with xenobiotic metabolism which may produce carcinogens which suppress the production of all immunity cells such as lymphocytes, polymorphonuclear cells, and macrophages that will give a bigger opportunity for dysbiotic microbiomes to develop further and cause more damage to periodontal sites. Polymorphism of cytochromes that are acting in xenobiotic metabolism may also lead into enhancement of catalytic activities of associated enzymes which may contribute to individual susceptibility at development of periodontal diseases. Nicotinic compounds in cigarettes may also cause tissue destruction at periodontal tissue if these compounds are found in saliva and crevicular fluid. Generally, all of these statements here can be marked that disturbance in producing immunity components by ethanol and nicotine will lead to massive development of dysbiosis microbiome at their oral cavity in managing gingivitis which might lead it into periodontitis faster as they lose their proper immunity system for helping the controlling of dysbiosis microbiome at their oral cavity (Surma *et al.*, 2021).

More clinical studies that are more focusing with samples of study come from elderly patients with obese body weight, tested positive for diabetes mellitus type 2 (T2DM), and have periodontal diseases at their periodontal sites to obtain more specific data and enhance more evidence to support the statements revealed. Past studies just show the specific results at single complication or bad behavior in managing chronic periodontal disease, periodontitis. The data has been found to support some of our statements but relations between emergence and phenotype switching of opportunistic pathogenic bacterium into pathogenic with arterial hypertension are another study to be discovered with clinical study for strengthening the statements about these complications. In the next few years, these complications will become very frequent since many people are not aware of a healthy lifestyle and bad habits which could lead them to get affected with other systemic complications. These systemic complications may lead to other oral diseases if people prefer to be lazy for brushing their teeth that might remain dental plaques for growth and development of opportunistic pathogenic bacterium at periodontal sites. Low awareness of people about their oral cavity conditions is one of the dentist's challenges in finding the best ways to fix the advanced stages of their patients' oral diseases so this case is quite interesting to observe and discover for obtaining more precise and accurate

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1172-1185 | ISSN:2251-6727

data also strong statements for dentist's references in dealing with their patients' oral diseases.

But even so, our review has clarified how the bad habits of today's population such as consuming fast food, being lazy to do physical activity, being active smoker and alcoholic, and being lazy to maintain oral hygiene can trigger periodontal disease which will develop very quickly into periodontitis and this development does not rule out the possibility of causing more severe damage and really could not be helped anymore when these populations do not change their lifestyle.

ACKNOWLEDGEMENT

We would like to thank Drg. Tantiana M.Kes for the revision, helpful discussions as well as her support and encouragement in technical help for arranging this article. This article will also be dedicated to the Department of Oral Biology, Faculty of Dental Medicine, Airlangga University.

CONCLUSION

Complex bad behavior such as frequent smoking, and alcoholic culture will manage to faster development of periodontal disease from gingivitis into destructive forms named periodontitis, especially at populations that are getting lazy for maintaining their oral health and preferring to use mouthwash that is less effective to clean outer border of tooth and area between tooth and marginal gingiva which may remain dental plaques as initiator of periodontal diseases in oral cavity. Even though many systemic complications such as diabetes mellitus type 2 will play a crucial role in managing periodontal disease that is initiated with gingivitis.

References

[1] Abdulkareem, Ali A., *et al*., 2023. *Current concepts in the pathogenesis of periodontitis: from symbiosis to dysbiosis*. *Journal of Oral Microbiology*, vol. 15:2197779.

[2] Almeida-da-Silva, Cassio Luiz Coutinho, *et al*., 2021. *Effects of electronic cigarette aerosol exposure on oral and systemic health*. *Biomedical Journal*, vol. 44,. pp. 252-259.

[3] Baumeister, Sebastian-Eiger, *et al*., 2021. T*esting the association between tobacco smoking, alcohol consumption, and risk of periodontitis: A Mendelian randomization study*. *Journal of Clinical Periodontology*, vol. 48, no. 11,. pp. 1414-1420.

[4] Bergstrom, J. and Preber, H., 1986. *The influence of cigarette smoking on the development of experimental gingivitis/Periodont.* Res 21,. pp. 668.

[5] Bogdan, Maria, *et al*., 2020. *Possible Involvement of Vitamin C in Periodontal Disease-Diabetes Mellitus Association*. *Nutrients*. vol. 12. no. 2,. p. 553.

[6] Cederbaum, A. I., 2012. *Alcohol metabolism. Clin Liver Dis. 16(4),*. pp. 667-685.

[7] Chapple, I. L., *et al*., 2017., *Interaction of lifestyle, behaviour or systemic diseases with dental caries and periodontal diseases: Consensus report of group 2 of the joint EFP/ORCA workshop on the boundaries between caries and periodontal diseases. Journal of Clinical Periodontology, 44 (Suppl. 18),*. pp. S39–S51.

[8] Ciulla, M., and P. Vivona. 2020. *Is there an association between periodontitis and arterial hypertension? Journal of Dental Research*, vol. 5, no. 17,. p. 27.

[9] Clarke, N. G,, Shephard, B. C., and Hirsch, R., 1981. *The effects of intraarterial epinephrine and nicotine on gingival circulation. Oral Surg Oral Med Oral Path 52*,. pp. 577.

[10] Coventry, John, *et al*., 2000. *ABC of oral health - Periodontal disease*. *BMJ Clinical Research*, vol. 321, no. 7252,. pp. 36-9.

[11] Crabb, D. W., 1995. *Ethanol oxidizing enzymes: roles in alcohol metabolism and alcoholic liver disease. Prog Liver Dis. 13*,. pp. 151-172.

[12] Del Pinto, Rita, *et al*., 2020. *Periodontitis and hypertension: is the association causal? High Blood Pressure & Cardiovascular Prevention*, vol. 27,. pp. 281-289.

[13] Desvarieux, Moise, *et al*., 2010. *PERIODONTAL BACTERIA AND HYPERTENSION: The Oral Infections and Vascular Disease Epidemiology Study (INVEST). J Hypertens*, vol. 28, no. 7,. pp. 1413-1421.

[14] Dioguardi, Mario, *et al*., 2020. *The Role of Periodontitis and Periodontal Bacteria in the Onset and Progression of Alzheimer's Disease: A Systematic Review. Journal of Clinical Medicine*. vol. 9. no. 2,. p. 495.

[15] Edenberg, H. J. 2000. *Regulation of the mammalian alcohol dehydrogenase genes. Prog Nucl Acid Res Mol Biol. 64*,. pp. 295–341.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1172-1185 | ISSN:2251-6727

[16] *Edwards, S. H., et al., 2021. Tobacco-specific nitrosamines in the tobacco and mainstream smoke of commercial little cigars. Chem. Res. Toxicol 34,*. pp. 1034-1045.

[17] *Ekstrom, G., Ingelman-Sundberg, M., 1989. Rat liver microsomal € NADPH-supported oxidase activity and lipid peroxidation dependent on ethanol-inducible cytochrome P-450 (P450IIE1). Biochem Pharmacol. 38(8),*. pp. 1313-1319.

[18] Funahashi, Kenta, *et al.*, 2019. Functional dysbiosis within dental plaque microbiota in cleft lip and palate patients. *Progress in Orthodontics*, 20:11.

[19] Galicia-Garcia, Unai, *et al*., 2020. Pathophysiology of Type 2 Diabetes Mellitus. *International Journal of Molecular Sciences*, vol. 21, no. 17,. p. 6275.

[20] GBD 2019 Risk Factors Collaborators. *2020. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019.* Lancet, 396(10258),. pp. 1223–1249.

[21] Guengerich, F. P., Kim, D. H. & Iwasaki, M. *1991. Role of human cytochrome P-450 IIE1 in the oxidation of many low molecular weight cancer suspects.* Chemical Research in Toxicology 4,. pp. 168–179.

[22] Goyal, Rajeev, and Ishwarlal Jialal. 2022. *Diabetes Mellitus Type 2. Europe PMC*. https://europepmc.org/article/nbk/nbk513253.

[23] Graziani, F., *et al.*, 2018. A systematic review and meta- analysis of epidemiologic observational evidence on the effect of periodontitis on diabetes an update of the EFP-AAP review. *Journal of Clinical Periodontology*, vol. 45, no. 2,. pp. 167-187.

[24] Hage, FG, and AE Iskandrian. 2011. Cardiac autonomic denervation in diabetes mellitus. *Circulatory Cardiovascular Imaging*, vol. 4,. pp. 79-81.

[25] Hajishengallis, George. 2015. Periodontitis: from microbial immune subversion to systemic inflammation. *Nature Reviews Immunology*, vol. 15, no. 1,. pp. 30-44.

[26] Hamitouche, S., *et al., 2006. Ethanol oxidation into acetaldehyde by 16 recombinant human cytochrome P450 isoforms: role of CYP2C isoforms in human liver microsomes.* Toxicol Lett. 167(3),. pp. 221-230.

[27] Haraszthy, V., *et al.*, 2000. Identification of periodontal pathogens in atheromatous plaques. *Journal of Periodontology*, vol. 71, no. 1554-60.

[28] Hatsukami, D., Stead, L. F., & Gupta, P. C. 2008. *Tobacco addiction. Lancet* 371,. pp. 2027–2038.

[29] Hecht, S. S., Stepanov, I., & Carmella, S. G. 2016. *Exposure and metabolic activation biomarkers of carcinogenic tobacco-specific nitrosamines.* Acc. Chem. Res 49,. pp. 106-114.

[30] Holt, P. G., and Keast, D. *1977. Environmentally induced changes in immunological function: Acute and chronic effects of inhalation of tobacco smoke and other atmospheric contaminants in man and experimental animals.* Bacterial Rev 41,. p. 205.

[31] Ide, M., and GJ Linden. 2014. *Periodontitis, cardiovascular disease and pregnancy outcome – focal infection revisited?*. *British Dental Journal*, vol. 217, no. 8,. pp. 467-474.

[32] Kadlubar, F. F. & Hammons, G. J. *1987. Cytochrome P450 in metabolism of chemical carcinogens. In: Mammalian Cytochromes P450, eds. Guengerich*, F. P., Vol. 2,. pp. 81– 130.

[33] Kim, J-S. 2004. Polymorphisms in genes coding for enzymes metabolizing smoking-derived substances and the risk of periodontitis. Blackwell Munksgaard,. pp. 960

[34] Knezevich, A., *et al., 2013. Nornicotine nitrosation in saliva and its relation to endogenous synthesis of N'-nitrosonornicotine in humans. Nicotine Tob*. Res 15,. pp. 591–595.

[35] Kocher, T., *et al., 2002. Association between bone loss in periodontal disease and polymorphism of N-acetyltransferase (NAT2). Journal of Clinical Periodontology 29,*. pp. 21-27.

[36] Kornman, K. S. 2008. *Mapping the pathogenesis of periodontitis: a new look. J Periodontol 79,*. pp. 1560–1568.

[37] Kunitoh, S., *et al., 1996. Metabolism of acetaldehyde to acetate by rat hepatic P450s: presence of different metabolic pathway from acetaldehyde dehydrogenase system*. Alcohol Clin Exp Res. 20(s1),. pp. 22A–24A.

[38] Lastra, G., *et al.*, 2014. *Type 2 diabetes mellitus and hypertension: An update*. *Endocrinology and Metabolism Clinics North America*, vol. 43,. pp. 103-122.

[39] Dare, B. L., Lagente, V., Gicquel, T. 2019. *Ethanol and its metabolites: update on toxicity, benefits, and focus on immunomodulatory effects.* Informa

UK Limited, trading as Taylor & Francis Group,. pp.2

[40] Leblhuber, Friedrich, *et al*., 2020. Knock-on Effect of Periodontitis to the Pathogenesis of Alzheimer's Disease. *The Central European Journal of Medicine*, vol. 132,. pp. 493-498.

[41] *Leite, F. R. M., et al., 2018. Effect of smoking on periodontitis: A systematic review and meta-regression. American Journal of Preventive Medicine*, 54(6),. pp. 831–841.

[42] Liccardo, Daniela, *et al.*, 2019. *Periodontal Disease: A Risk Factor for Diabetes and Cardiovascular Disease. International Journal of Molecular Sciences*, vol. 20. no. 6,. p. 1414.

[43] Lu Y, Cederbaum AI. *2008. CYP2E1 and oxidative liver injury by alcohol. Free Rad Biol* Med. 44(5):723–738.

[44] Madiba, Thommy, and Ahmed Bhayat. 2018. *Periodontal disease - risk factors and treatment options*. *South African Dental Journal*, vol. 73, no. 9,. pp. 571-575.

[45] Meisel, P., *et al., 2000.* P*olymorphism of the N-acetyltransferase (NAT2), smoking and the potential risk of periodontal disease. Archives of Toxicology* 74,. pp. 343–348.

[46] Murphy, S. E. 2021. *Biochemistry of nicotine metabolism and its relevance to lung cancer*. *J. Biol. Chem*,. p. 296

[47] Nascimento, GG, *et al*., 2018. *Does diabetes increase the risk of periodontitis? A systematic review and meta-regression analysis of longitudinal prospective studies*. *Acta Diabetol*, vol. 55, no. 7,. pp. 653-667.

[48] Neher, G. H. 1974. *Nicotine-induced depression of lymphocyte growth. Toxico, Appi Pharmacol 27*,. p. 253.

[49] Nemoto, Takashi, *et al*., 2021. *Discrimination of Bacterial Community Structures among Healthy, Gingivitis, and Periodontitis Statuses through Integrated Metatranscriptomic and Network Analyses*. *mSystems*, vol. 6, no. 6,. e00886-21

[50] Paul, Oindrila, *et al*., 2020. *Inflammation in Periodontal Disease: Possible Link to Vascular Disease*. *Frontiers in Physiology*, vol. 11.

[51] Pignatelli, Pamela, *et al*., 2020. *How Periodontal Disease and Presence of Nitric Oxide Reducing Oral Bacteria Can Affect Blood Pressure*. *International Journal of Molecular Sciences*, vol. 21, no. 20.

[52] Pulikkotil, S. J., *et al., 2020. Alcohol consumption is associated with periodontitis. A systematic review and meta-analysis of observational studies*. Community Dental Health, 37(1),. pp. 12-21

[53] Raulin, L., *et al., 1988. The effect of nicotine on the attachment of human fibroblasts to glass and human root surfaces in vitro*. *JPeriodontol 59*,. p. 318

[54] Rivera-Hidalgo, F. 1986. *Smoking and periodontal disease*—A re[1]view of the literature. *J Periodontol 57*,. p. 617

[55] Romano, Federica, *et al*., 2021. *Bidirectional Association between Metabolic Control in Type-2 Diabetes Mellitus and Periodontitis Inflammatory Burden: A Cross-Sectional Study in an Italian Population. Journal of Clinical Medicine*, vol. 10, no. 8,. p. 1787.

[56] Sain, Rajsi, and Praveen Kudva. 2021. *Clinico-biochemical evaluation of relationship between periodontitis and C- reactive protein: A case control study. Journal of Advanced Medical and Dental Sciences Research*, vol. 9, no. 3,. pp. 11-16.

[57] Sälzer, Sonja, *et al*., 2020. *Contemporary practices for mechanical oral hygiene to prevent periodontal disease. Periodontology 2000*, vol. 48, no. 1,. pp. 35-44.

[58] Sanz, M., *et al*., 2010. *European work- shop in periodontal health and cardiovascular disease---scientific evidence on the association between periodontal and cardiovascular diseases: a review of the literature*. *European Heart Journal Supplements*, vol. 12,. pp. B3-B12.

[59] Schuller, H. M. 2007. *Nitrosamines as nicotinic receptor ligands*. Life Sci. 80,. pp. 2274–2280

[60] Seravalle, Gino, and Guido Grassi. 2017. *Obesity and hypertension*. *Pharmacological Research*, vol. 122,. pp. 1-7.

[61] Serhiyenko, VA, and AA Serhiyenko. 2015. *Diabetic cardiac autonomic neuropathy: Do we have any treatment perspectives?*. *World Journal of Diabetes*, vol. 6,. pp. 245-258.

[62] Sower, JR, *et al.*, 2001. *Diabetes, hypertension, and cardiovascular disease: An update*. *Hypertension*, vol. 37,. pp. 1053-1059.

[63] Stöhr, Julia, *et al*., 2021. *Bidirectional association between periodontal disease and diabetes mellitus: a systematic review and meta-analysis of cohort studies*. *Scientific Reports*, vol. 11:13686.

[64] Sudhakara, Preethi, *et al*., 2018. *Oral Dysbiotic Communities and Their Implications in Systemic Diseases*. *Dentistry Journal*, vol. 6, no. 2,. p. 10.

[65] Surma, Stanislaw, *et al.*, 2021. *Periodontitis, Blood Pressure, and the Risk and Control of Arterial Hypertension: Epidemiological, Clinical, and Pathophysiological Aspects—Review of the Literature and Clinical Trials*. *Current Hypertension Reports*, vol. 23, no. 27,. pp. 1-14.

[66] Szabo, G. 1999. *Consequences of alcohol consumption on host defence. Alcohol.*, pp. 830–841.

[67] Wang, J., *et al., 2016. Alcohol consumption and risk of periodontitis: A meta-analysis. Journal of Clinical Periodontology*, 43(7),. pp. 572–583.

[68] Wang, Mina, *et al*., 2020. *Diabetes and cancer: Epidemiological and biological links*. *World Journal of Diabetes*, vol. 11, no. 6,. pp. 227-238.

[69] Warr, G ., and Martin, R. R., 1973. *In vitro migration of human alveolar macrophages: Effects of cigarette smoking. Infect Immun* 8,. p. 222.

[70] Wu, Chen-zhou, *et al*., 2020. *Epidemiologic relationship between periodontitis and type 2 diabetes mellitus*. *BMC Oral Health*, vol. 20:204.

[71] Yildiz, Mehmed, *et al*., 2020. *Hypertension and diabetes mellitus: highlights of a complex relationship*. *Current Opinion in Cardiology*, vol. 35, no. 4,. pp. 397-404.

[72] You, Wei, *et al*., 2022. *Case Report: A Chinese Family of Type A Insulin Resistance Syndrome With Diabetes Mellitus, With a Novel Heterozygous Missense Mutation of the Insulin Receptor Gene*. *Frontiers in Endocrinology*, vol. 13:895424.

[73] Zhukov A, Ingelman-Sundberg M., 1999. *Relationship between cytochrome P450 catalytic cycling and stability: fast degradation of ethanol-inducible cytochrome P450 2E1 (CYP2E1) in hepatoma cells is abolished by inactivation of its electron donor NADPH-cytochrome P450 reductase.* Biochem J. 340(Pt 2),. pp. 453–458.

[74] Zięba, Sara, *et al*., 2021. *Ethanol- and Cigarette Smoke-Related Alternations in Oral Redox Homeostasis*. *Frontiers in Physiology*, vol. 12.

[75] Zini, Avraham, *et al*., 2021. *Effects of an oral hygiene regimen on progression of gingivitis/early periodontitis: A randomized controlled trial*. *Canadian Journal of Dental Hygiene*, vol. 55, no. 2,. pp. 85-94.