FOLLOW UP STUDY TO INVESTIGATE THE ROLE OF PHYSICAL ACTIVITY IN PERIODONTAL POCKETING

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Master's thesis
Public Health
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May 2019

UNIVERSITY OF EASTERN FINLAND, Faculty of Health Sciences
Public health
RAZZAQ, S.: Follow up study to investigate the role of physical activity in periodontal pocketing
Master's thesis, 64 pages.
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May 2019

Key words: longitudinal study; physical activity; periodontal pocketing; periodontitis

FOLLOW UP STUDY TO INVESTIGATE THE ROLE OF PHYSICAL ACTIVITY IN PERIODONTAL POCKETING

The aim of this study was to assess how physical activity affects the development of periodontal pocketing in a longitudinal setting.

The study utilized data on 1225 subjects aged 30 years or older at baseline who partook clinical oral examination and answered questions about physical activity in both the Health 2000 and Health 2011 Surveys carried out in Finland. Physical activity was measured through self-reported questionnaire related to frequency of leisure-time and commuting physical activity. Periodontitis was assessed clinically by counting the number of teeth with deepened periodontal pockets ≥ 4mm. Difference in average number of teeth with deepened periodontal pockets ≥ 4mm among subjects according to the levels of physical activity was analyzed with the help of Kruskal Wallis test. Association between physical activity and number of teeth with deepened periodontal pockets ≥ 4mm was assessed through Poisson regression analysis after being adjusted for confounders.

Differences in mean number of teeth with deepened periodontal pockets ≥ 4mm according to the level of physical activity performed by the subjects were not statistically significant. However, statistically significant association was observed between subjects performing less than ideal level of physical activity, having a higher risk of deepened periodontal pockets ≥ 4mm.

The results of this study demonstrated that decreased levels of physical activity has an association with increased risk of deepened periodontal pockets ≥ 4mm. Further research is recommended to explore the underlying mechanism of association between physical activity and periodontitis.

ACKNOWLEGMENTS

This thesis has become a reality for me through the help and support of many people. I would like to extend my heartfelt gratitude to all of them.

Foremost, All Praise belongs to Lord Almighty for giving me the strength and ability to take this endeavor and complete it.

I would like to express special gratitude and thanks to my supervisor Professor Liisa Suominen for her constant guidance, help, encouragement and invaluable comments. Her thorough knowledge and expertise has immensely guided me in learning and understanding the entire process of thesis writing. My sincere thanks to Assistant Professor Sohaib Khan for his immense support, guidance and help throughout the Master's degree and for putting his efforts in giving me an office in the department. I would like to thank Professor Tomi-Pekka Tuomainen for his time, guidance and invaluable comments. I would also like to thank the faculty and staff of the Institute of Public Health and Clinical Nutrition, University of Eastern Finland for their contribution to my Master's degree and especially for accommodating me and my daughter in the department during the last stages of my thesis.

I would also like to express appreciation for Tuija Jääskeläinen for her help in accessing data and Katja Borodulin for her guidance during the research work. I'm very grateful to my friend Yamna Rehman for all her time and help in this thesis. I owe her greatly for always been there when I needed help. I'm very grateful to my special friend Unaiza Idrees for her constant motivation and moral support throughout this time.

Lastly, I wouldn't have been able to complete it without the prayers of my parents Abdul Razzaq and Durr-e-Afshan Razzaq, encouragement of my siblings Kanza Razzaq, Hamza Razzaq and Raza Razzaq, and support of my husband Zaid Alam. Special thanks to little Khadija Zaid for letting her mother work.
I would like to dedicate this thesis to my beloved parents who taught me perseverance and hard work.
Thankyou
Shanza Razzaq

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ABRREVIATIONS

CAL – Clinical attachment loss

CD 14 – Cluster of differentiation 14

CDC/APP – Centers for Diseases Control and Prevention, and the American Academy of Periodontology

CPITN – Community periodontal index of treatment needs

CPI – Community periodontal index

CPR – C reactive protein

EE – Energy expenditure

EMD – Enamel matrix derivatives

FFA – Free fatty acid

GCF – Gingival crevicular fluid

GLUT 4 – Glucose transporter isoform 4

GTR – Guided tissue regeneration

IL – Interleukin

IPAQ – International physical activity questionnaire

LDD – Low dose doxycycline

LDL – Low density lipoprotein

MMP – Matrix metalloproteinase

NETs – Neutrophil extracellular traps

NOD – Nucleotide-binding oligomerization domain

PAMPs – Pathogen-associated molecular patterns

PD – Probing depth

PRRs – Pattern recognition receptors

SDD – Subantimicrobial dose of doxycycline

TNF-α – Tumor necrosis factor alfa

WHO – World Health Organization

1 INTRODUCTION

Carious lesions, periodontal disease, oral infectious diseases, oral cancer, tooth loss, lesions of hereditary origin and oral and maxillofacial trauma are amongst the most common oral diseases that affect oral health. Interestingly, the main causes of oral diseases are same as that of the four most common chronic diseases (cardiovascular diseases, cancer, chronic respiratory diseases and diabetes). These are unhealthy lifestyle, poor dietary habits, tobacco and alcohol use (World Health Organization 2012).

Periodontitis is bacterially induced chronic inflammatory disease affecting nearly 11% of people across the world (Richards 2014). It is one of the most important global oral health burdens (World Health Organization 2017). The salient features of this disease include inflammation of gingiva, pocket formation, alveolar bone resorption and ultimate tooth loss (The American Academy of Periodontology 1999). Oral cavity, being home to a number of bacterial species, can be a gateway to the microbial spread reaching other body parts, particularly in susceptible individuals. Many studies point that patients with periodontitis are more prone to inflammation, type 2 diabetes mellitus, obesity and other relevant systemic complications (Nagpal *et al.* 2015), therefore this multifactorial disease influences an individual's quality of life (Hugoson & Norderyd 2008).

Physical activity is defined as the use and movement of skeletal muscles of the body resulting in expenditure of energy (Caspersen *et al.* 1985). Until the last century, physical activity has been the signature of human lifestyle, but since then the demand of physical work has greatly decreased. The innovative lifestyle changes over the years, have led to a decrease in physical activity, and with it the accumulative development of health issues (Vaynman & Gomez-pinilla 2006). Unhealthy and sedentary lifestyle has been indicated as a risk factor for various chronic diseases such as coronary heart disease, type 2 diabetes mellitus, obesity and cancer (Tir *et al*. 2017).

Physical activity has been repeatedly linked with overall improved health. An increase in physical activity has proven primary and secondary preventive effects for chronic diseases (Marques *et al*. 2018). Patients suffering with such diseases have shown improved functional capacity and quality of life with addition of regular physical activity in their lives (Marques *et al*. 2017). Studies have shown that even minimal amount of physical activity tends to reduce mortality and has a positive health effect for chronic

diseases (Marques *et al*. 2018). There has been an emerging interest and focus on the health benefits of physical activity across the world (Marques *et al.* 2017).

Periodontitis essentially shares the same risk factors with chronic diseases (Petersen & Ogawa 2012), and it has been associated with various diseases such as cardiovascular disease, diabetes mellitus, obesity and oral complications during pregnancy (Oliveira *et al.* 2015). It was recently proposed that individuals who are physically active may have a lower risk of periodontitis, however, there are only a counted number of studies done so far, to find an association between physical activity and periodontitis, a chronic disease (Bawadi *et al.* 2011). Health promoting behaviours which include normal weight gain, regular exercise and good dietary intake decreases the prevalence of periodontitis (Al-Zahrani *et al*. 2005). Besides, inflammatory biomarkers (Interleukin 1β and C- reactive protein) associated with periodontitis were found to be in lesser quantity in gingival crevicular fluid of physically active individuals (Sanders *et al.* 2009).

Previously, one longitudinal study evaluated the effect of combined healthy lifestyle factors on the incidence of periodontitis in old people (Iwasaki *et al*. 2018). However, more longitudinal exploration is required to assess causality. To the best of our knowledge, this will be the first longitudinal study exploring the association of physical activity with periodontal pocketing in adults and elderly people, both. This study also aims to find the impact of positive modifying behaviour on oral health, as well as to recommend the public health community to put more emphasis on improving the quality of life through such behaviour.

2 LITERATURE REVIEW

3 Periodontitis

3.1.1 Introduction and definition

World Health Organization (2012) states, 'Oral health is a state of being free from mouth and facial pain, oral and throat cancer, oral infection and sores, periodontal (gum) disease, tooth decay, tooth loss, and other diseases and disorders that limit an individual's capacity in biting, chewing, smiling, speaking, and psychosocial wellbeing.' Good oral health has been repeatedly linked with a better quality of life according to numerous studies (Masoe *et al.* 2015). Conversely, poor oral health leads to a bad quality of life, often because its linked to certain chronic and systemic diseases (Malecki *et al*. 2015).

The supportive structures of teeth are affected in multiple diseased conditions, collectively known as periodontal diseases (The American Academy of Periodontology 1999, Al Jehani 2014). Such periodontal diseases broadly consist of gingivitis and periodontitis, and are in fact bacterially mediated inflammatory diseases affecting the health of periodontium (Socransky and Haffajee 1992). Gingivitis is the inflammation of gingiva, a reversible process characterized clinically by redness, bleeding and edema of gingiva as well as changes in gingival contour and adaptation, and increased gingival crevicular fluid (GCF) flow (The American Academy of Periodontology 1999). It is caused by an increase in the quantity of harmful bacteria in oral cavity, which then form a sticky polymicrobial biofilm called plaque, on the tooth structure. If plaque is allowed to stay on the tooth for a longer time it becomes a mineralized structure called calculus, which is more difficult to remove than plaque (University of Maryland Medical Center 2013). If left untreated, periodontitis follows gingivitis in susceptible individuals, which is an irreversible destruction of gingival connective tissue and dental bone support due to inflammatory process triggered by periodontal bacteria (Offenbacher 1996, Al Jehani 2014). Clinically, what distinguishes periodontitis from gingivitis is the permanent loss of tooth supporting structure i.e. periodontal ligament and alveolar bone. In addition, epithelial attachment is disrupted and migrates along the root surface. This disruption of periodontal ligament and resorption of alveolar bone can ultimately result in tooth loss (The American Academy of Periodontology 1999, University of Maryland Medical Center 2013).

3.1.2 Pathogenesis

The etiology and pathogenesis of periodontitis is rather complex; a number of variables and modifying systemic and local factors are involved in this disease causation (Offenbacher 1996). Microorganisms are essentially the primary etiological factor in pathogenesis of periodontitis (Wolff *et al.* 1994), but the periodontal pathogen will only result in disease if certain criteria are fulfilled i-e, 1) it must have the virulence factor; 2) it must contain the essential genetic composition necessary for starting disease process; 3) the host must be sensitive to pathogen (host susceptibility); 4) the number of pathogens must surpass the threshold to cause disease in host; 5) the pathogens should be located correctly; 6) the process is not halted by other bacterial species thriving simultaneously; and 7) the local environment should be supportive and liable for the expression of the pathogens' virulence properties (Socransky & Haffajee 1992). Besides, a number of environmental, genetic, and host immune response factors are also involved (Wolff *et al*. 1994, Offenbacher 1996). Smoking (Loos *et al*. 2004) and diabetes are potential risk factors that influence the progression and severity of periodontitis by affecting host immune response (Kornman 2008). Certain conditions with periodontal disease manifestations include genetic, neoplastic, immunosuppressive, hematological, dermatological or granulomatous disorders (Page & Kornman 1997).

Bacterial etiology

Socranksy *et al.* discovered and categorized the oral microbiota found in subgingival plaque into six microbial complexes. The bacterial species are clustered together to form red, orange, green, yellow and purple complexes. The ‘‘red’’ cluster is made up of *Porphyromonas gingivalis, Bacteroides forsythus* and *Treponema denticola.* The ‘‘orange’’ cluster is made up of *Fusobacterium nucleatum/periodonticum* subspecies, *Prevotella intermedia, Prevotella nigrescens, Peptostreptucoccus micros,* and *Eubacterium nodatum, Campylobacter rectus, Campylobacter showae, Streptococcus consteltatus and Campylobacter graellis.* The ‘‘green’’ cluster is formed by 3 *Capnocytophaga* species: *Campylobacter concisus. Eikenella corrodens* and *Actinobacillus actinomycetemcomitans* serotype a. Whereas, the ‘‘yellow’’ cluster is formed by a group of streptococci: *Streptococcus mitis, Streptococcus sanguis*, *Streptococcus oralis, Streptococcus gordinii and Streptococcus intermedius*. And the ‘‘purple’’ cluster is made up of *Actinomyces odontolyticus* and *Veillonella parvula*. *Actinomyces naeslundii* genospecies 2 *(Actinomyces viscosus), Selenomonas noxia* and

Aggregatibacter actinomycetemcomitans (previously known as *Actinomyces Actinomycetemcomitans)* did not form clusters with other species (Socransky *et al*. 1998).

The ‘‘green’’, ‘‘yellow’’ and ‘‘purple’’ complexes are amongst the early colonizers of tooth surfaces. The ‘‘orange’’ and ‘‘red’’ complexes are, not only closely related but also Gram-negative species, and are thought to constitute true periodontal pathogens as they are found more commonly in deep periodontal pockets (Socransky *et al*. 1998, Ximénez-Fyvie 2000). The ‘‘red’’ complex has shown strong affinity with pocket depth and bleeding on probing (Socransky *et al*. 1998, Haffajee *et al*. 2008) and is known as a ‘disease-related’ complex (Haffajee *et al*. 2008). Amongst the red complex *Porphyromonas gingivalis* is thought to be important in adult periodontitis (Haffajee & Socransky 1994, Socransky *et al*. 1998, Yang *et al.* 2004). *Aggregatibacter actinomycetemcomitans* is known for causing localized and aggressive forms of periodontitis (Carvalho-Filho *et al*. 2016). Haffajee, Socransky and his team members conducted a research to evaluate the features of microbiota of supragingival plaque, and whether it differs from that of subgingival plaque. They found out that the six microbial complexes in supragingival plaque were essentially the same as in subgingival plaque (Haffajee *et al*. 2008). However, the difference is that ‘‘red’’ and ‘‘orange’’ complex species are in greater numbers in subgingival plaque, whereas supragingival plaque has higher number of ‘‘green’’ and ‘‘purple’’ complex species and *Actinomyces* species (Ximénez-Fyvie 2000). Still, at sites of inflammation, there is increased number of ‘‘red’’ and ‘‘orange’’ complex species in supragingival plaque as well. This can be explained by deep pocket formation and increased GCF associated with inflammation (Haffajee *et al*. 2008). Virulence factors which include adhesion molecules, proteases, leukotoxins and fimbriae assists periodontopathogenic bacteria to colonize in oral environment (Offenbacher 1996).

Oral biofilm

The oral environment contains shedding soft tissue surfaces of buccal mucosa and non-shedding hard tissue surfaces of teeth, which are a habitat for multiple bacterial and viral species constituting the microbial ecosystem (Spratt & Pratten 2003, Jakubovics 2015, Meyle & Chapple 2015). In healthy periodontium, a symbiotic relationship is maintained amongst the microbial ecosystem (Meyle & Chapple 2015). Within these microorganisms, oral cavity harbor nearly 1000 various bacterial species (Keijser *et al.* 2008), with most individuals hosting up to 200 species and a single site containing up to 100 species embedded in the biofilm (Larsen & Fiehn 2015). The biofilm formed by these microorganisms on teeth are

commonly referred as ‘dental plaque’ (Spratt & Pratten 2003). Enamel is the only hard non-shedding surface in a healthy mouth that can be colonized. A salivary pellicle covers it within seconds of cleaning, and soon after it is colonized by bacteria in the saliva. There are nearly 10^8 to 10^9 bacteria per ml of saliva, besides proteins and glycoproteins. These molecules help in selectively binding and aggregation of bacteria to tooth surface while providing nutrition at the same time (Spratt & Patten 2003). First, Streptococcus species which are early colonizers starts co-aggregating amongst themselves and also with *Actinomyces* species. As plaque accumulation continues, the late colonizers which are anaerobic bacteria such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum, Prevotella intermedia, Veillonella* and *Capnocytophaga* also co-aggregates and makes up an important proportion of the bacterial population. Here, *P. gingivalis* co-aggregates with the primary colonizers; *Streptococcus gordonii* (Spratt & Pratten 2003, Jakubovics 2015). Once dental plaque is matured, it consists of a complex and dynamic biofilm with various microenvironments (Spratt & Pratten 2003). Recent studies have pointed that when tissue homeostasis is challenged by certain bacteria known as ‘‘keystone pathogens’’, affecting the composition of commensals microbiota and modulating host innate and adaptive immune response, a dysbiotic relationship is established resulting in periodontitis (Carvalho-Filho *et al*. 2016, Boutin *et al*. 2017).

Hypotheses

The concept of dental plaque as the etiological agent of periodontitis has undergone various transitions as the knowledge regarding it’s etiopathogenesis has evolved over time. During the early nineteen hundred, scientists regarded the four different groups of pathogens (Amoebae, spirochetes, streptococcus and fusiform) discovered in the dental plaque as the etiological agents of periodontitis, known as the ‘‘Specific Plaque Hypothesis’’ (Rosier *et al*. 2014). In the mid to late nineties, studies couldn’t point out a single pathogen as causative agent, rather the entire microbial flora of plaque was thought to be involved in periodontal destruction. ‘‘Non-Specific Plaque Hypothesis’’ suggested that periodontal disease is the result of increase in number of microorganisms in subgingival plaque beyond a threshold level that can impede host immune resistance mechanisms (Rosier *et al*. 2014). ‘‘Ecological Plaque Hypothesis’’ combines the basic concepts of both specific and non-specific plaque hypotheses. According to this hypothesis, ‘changes in the environmental conditions lead to ecological shift’. This ecological shift results in increased amount of putative pathogens (or their pathogenic traits), which in turn increases GCF to gingival tissues. The GCF flow brings with itself host immune

cells, as well as nutrients for these putative pathogens, exacerbating the harmful process (Marsh 1994, Rosier *et al*. 2014).

Recent advancement in knowledge has led to a clearer understanding of the microbial composition and interaction of subgingival plaque and has suggested synergy and dysbiosis amongst heterotypic microbial communities (Hajishengallis & Lamont 2012). In ‘‘Polymicrobial Synergy and Dysbiosis (PSD) model’’, microorganisms in heterotypic community show synergistic traits and dysbiosis results due to imbalance in tissue homeostasis and regular immune functioning. These polymicrobial communities are capable of communicating within by complex signaling mechanisms, whereby overt pathogenicity is maintained by host immune system creating a controlled immuno-inflammatory state in normal healthy gingiva (Hajishengallis *et al*. 2012, Rosier *et al*. 2014, Lamont & Hajishengallis 2015). The shift in balance from homeostasis to dysbiosis occurs due to presence of even low amounts of ‘keystone pathogens’ such as *Porphyromonas gingivalis*. These ‘keystone pathogens’ interacts with host immune factors, leaving it impaired and increasing the virulence and pathogenicity of the entire community (Hajishengallis *et al*. 2012, Jiao *et al*. 2014, Lamont & Hajishengallis 2015).

Host immune system

An infection or inflammation can be a triggering factor that activates two distinct yet closely interlinked and complex host immune responses i-e innate and adaptive immunity (Silva *et al*. 2015). The innate immune system is a homeostatic defense mechanism, and is the first line of defense in event of an invading microorganism or inflammatory process providing immediate protection to the host (Van Dyke & Kornman 2008, Silva *et al*. 2015). It works by recognizing and removing foreign substances, recruiting immune cells, activating complement system and adaptive immune system. Phagocytic cells which include polymorphonuclear neutrophils, macrophages, and monocytes, helps in triggering the release of chemical mediators, such as cytokines. The complement system and acute phase response is activated with the release of these chemical mediators, and helps the antibodies in eradicating pathogens or presenting them for destruction by other cells (Van Dyke & Kornman 2008). The initial response against periodontopathogenic bacteria in innate immune system is facilitated by pattern recognition receptors (PRRs) that bind pathogen-associated molecular patterns (PAMPs), found in a wide range of organisms. These receptor types include nucleotide-binding oligomerization domain (NOD) proteins, toll-like receptors,

cluster of differentiation 14 (CD14), lectins, complement receptor-3, and scavenger receptors 3,9 (Silva *et al*. 2015).

The most important phagocytic cells are polymorphonuclear neutrophils, found abundantly in blood. They are the first line of defense in event of an infection or inflammation, and are therefore found in great numbers in acute phase of periodontal infection, being recruited through junctional epithelium into the gingival crevice (Meyle & Chapple 2015, Cortés-Vieyra *et al*. 2016). The mechanism of defense function of neutrophils involve activation, adhesion, recruitment, apoptosis and efferocytosis (Herrmann & Meyle 2015). They are able to kill microorganisms intracellularly through oxygen dependent or oxygen independent pathways, as well as extracellularly, in which case they form neutrophil extracellular traps (NETs) or by releasing neutrophilic cytoplasmic granules (Nicu & Loos 2016). Activated neutrophils can release proteinases into surrounding tissues, which along with these cytoplasmic granules and NETs can cause degradation and destruction of host tissues such as collagen and basement membrane (Cortés-Vieyra *et al*. 2016). Neutrophils have the ability to produce many cytokines and chemokines, which can influence the inflammatory response, as well as the immune response (Silva *et al*. 2015, Cortés-Vieyra *et al*. 2016). The defect in functioning of neutrophils can result in severe form of periodontitis. In rare and congenital disorders, neutrophil defects such as impaired chemotaxis (Chediak Higashi syndrome and Papillon-Lefevre syndrome), impaired migration (Leukocyte adhesion deficiency type I, Leukocyte adhesion deficiency type II), defect in quantity of neutrophils (agranulocytosis, cyclic neutropenia), increases the susceptibility of periodontal infections in patients with such disorders (Cortés-Vieyra *et al*. 2016, Nicu & Loos 2016).

In periodontitis, the acute inflammatory response mediated by phagocytic cells is basically protective. But, in susceptible patients who are prone to periodontitis, there is failure of response to remove these inflammatory cells and tissues do not return to homeostasis. Hence, chronic inflammation pursues as adaptive immunity has taken control, where plasma cells and lymphocytes predominate in tissues (Van Dyke & van Winkelhoff 2013). Adaptive immunity is specific in comparison to the non-specific innate immunity, with the ability of recognizing pathogens, eliminating them and keeping a memory of pathogen's antigen signature for averting future infections (Van Dyke & Kornman 2008). Cytokines trigger this response thereby activating cell-mediated and humoral immunity. T-cells (cell-mediated) play a pivotal role in adaptive immunity, they recognize the foreign antigen and target them, which in turn prompts B-cells (humoral immunity) to produce specific antibodies (IgA, IgG, and IgM) (Van

Dyke & Kornman 2008, Van Dyke & van Winkelhoff 2013, Campbell *et al*. 2016). CD4+ and CD8 cell surface proteins expressed by T-cells are receptors for antigen recognition. T-cell activation can take many forms; they turn into interleukin producing CD4+ helper T-cells or CD8 cytotoxic T-cells (Gonzales 2015, Silva *et al*. 2015).

Most of the tissue destruction in periodontal disease is ironically caused by the defensive mechanisms, hence host immune inflammatory reaction to subgingivally located biofilm is the determining factor of disease susceptibility (Preshaw & Taylor 2011). The inflammatory response is mediated by inflow and activation of lymphocytes, monocytes, fibroblasts and other host cells (The American Academy of Periodontology 1999, Preshaw & Taylor 2011). The PRRs of immune cells identify PAMPs found in microorganisms and produce pro-inflammatory mediators (Silva *et al*. 2015). These pro-inflammatory mediators consist of catabolic cytokines (e.g., tumor necrosis factor alpha and interleukins [IL] 1β, IL-6, IL-8), chemokines, arachidonic acid metabolites (e.g., prostaglandin E2) and other destructive mediators such as the matrix metalloproteinases (MMPs) (The American Academy of Periodontology 1999, Preshaw & Taylor 2011). The network of cytokines interacts and functions in complex ways, and it is their regulation and balance that determines the magnitude of periodontal tissue destruction (Preshaw & Taylor 2011).

MMPs are tissue-derived proteolytic enzymes, destructive to extracellular matrix and basement membrane. So far, there are 24 MMPs identified in humans and are classified as collagenases, gelatinases, stromelysins, matrilysins and membrane type MMPs. Skeletal homeostasis, wound healing, tissue turnover and inflammatory diseases are the physiological and pathological processes which involve MMPs. MMPs account for the regulation of immune response in periodontal disease and causes extracellular matrix destruction as a result of imbalance between their inhibiting (tissue inhibitors of matrix metalloproteinases) and activating factors. Collagen type I is the main extracellular matrix component of soft and hard tissues of periodontium and therefore its destruction is thought of as a major aspect in the destruction of periodontal tissues (Silva *et al*. 2015). Collagenolytic matrix metalloproteinases collagenase-2 (MMP-8), produced mainly by neutrophils, is the major collagenase in gingival tissues and GCF (80% of collagenases), and is shown to play a central role in the loss of periodontal support. The other important MMPs include collagenase-3 (MMP-13) and a gelatinase MMP-9, found to be associated with inflamed periodontal tissues (Hernández *et al.* 2009, Silva *et al*. 2015).

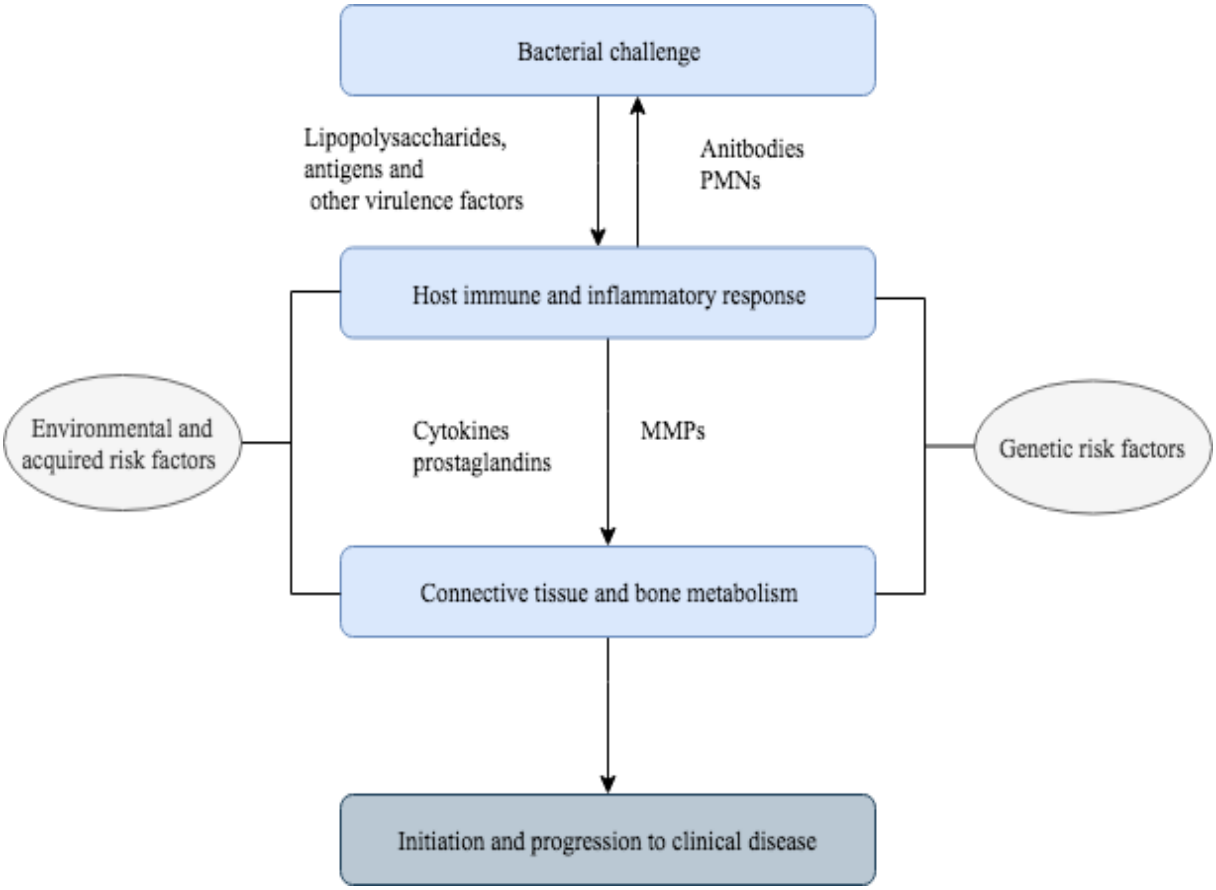

Figure 1. Pathogenesis of periodontitis (Modified from Page & Kornman 1997).

3.1.3 Epidemiology of periodontitis

The worldwide prevalence of of periodontal diseases is between 20% to 50% in both developed and developing countries (Nazir 2017). The prevalence varies according to locality, availability and accessibility of healthcare services and socioeconomic background (World Health Organization 2012). The Global Burden of Disease Study (2010) has reported severe form of periodontitis as the sixth-most prevalent disease in the world, affecting nearly 11.2% of world's population (Kassebaum *et al*. 2014, Richards 2014, Mahanonda *et al*. 2016). However, there is a recorded variation in the prevalence of periodontitis, because the criterion of defining the disease is not uniform across the world (Eke & Genco 2007).

In Finland, the Health 2000 Survey has identified periodontitis as frequent oral disease among adult Finns. A periodontal pocket depth of ≥ 4 mm is found in 64% of the population, and a deep periodontal pocket depth of ≥ 6 mm is found in 21% of the population. This prevalence was also found to be higher in males, as periodontal pocket ≥ 4 mm is reported in 72% of males and 57% of females. Some improvement in periodontal health has also been observed

in Finland, as indicated by a decrease in the number of subjects with developed periodontal pocket from 77% (1980's) to 64% (2000) (Suominen-Taipale *et al*. 2008).

3.1.4 Measurement of periodontal status

In order to assess the prevalence, incidence and clinical diagnosis of periodontitis in oral epidemiological studies, measurements such as periodontal pocket depth, bleeding on probing, gingival recession, clinical attachment loss, alveolar bone loss pattern evaluated by x-ray imaging are used (Page & Eke 2007, Eke *et al*. 2012). Various indices have been developed over time, since it is inconvenient to use all the parameters simultaneously. The first of its kind was Russell's periodontal index, developed in 1956. The scores of this index are based on gingival inflammation but periodontal pocket depth is not considered (Table 1) (Page & Eke 2007). The community periodontal index of treatment needs (CPITN), now known as the community periodontal index (CPI), was developed by World Health Organization (WHO), and has been widely used across the world to evaluate treatment needs and not the prevalence of periodontal disease (Page & Eke 2007). CPI is based on highest score per mouth quadrant. This index is from 0 to 4; 0 equates to health, 1 equates to bleeding on probing, 2 equates to calculus, 3 equates to shallow pocketing of 4mm or 5mm, 4 equates to pocket depth ≥ 6mm (Miyazaki *et al*. 1990). However, this index is also flawed as it only considered periodontal pocket depth (Page & Eke 2007), and not attachment loss (Holmgren 1994).

National Health Examination (1981) used a modified version of Russell's periodontal index which also took into account the periodontal pocket depth (Table 2) (Page & Eke 2007). Nowadays, measurements of periodontal pocket depth and clinical attachment loss are more frequently used in epidemiological studies for case definitions of periodontitis (Page & Eke 2007). A review by Savage *et al*. (2009) has given the definition of periodontitis as a minimum diagnostic value based on 2mm of clinical attachment loss and 3mm of pocket depth at a given site. The Centers for Diseases Control and Prevention, and the American Academy of Periodontology (CDC/AAP) recommendations for case definition of periodontitis are based on the measurement of clinical attachment loss (CAL) and probing depth (PD) and are categorized as mild, moderate, or severe disease (Table 3) (Eke *et al.* 2012).

Table 1 Periodontal Index by Russell (Newman *et al.* 2006).

CASE DEFINITION	SCORE RANGE
Clinically normal supportive tissues	0 - 0.2
Simple gingivitis	0.3 - 0.9
Beginning of destructive periodontal disease	1.0 - 1.9
Established destructive periodontal disease	2.0 - 4.9
Terminal disease	5.0 - 8.0

Table 2 Scores and Criteria for Periodontal Disease Index (PDI) (Newman *et al*. 2011).

0	Absence of inflammation
1	Mild to moderate inflammation of gingiva not extending all around the tooth
2	Mild to moderate severe gingivitis extending all around the tooth
3	Severe gingivitis characterized by emphasized redness, tendency to bleed and ulcerate
4	Gingival crevice extending apical to the CEJ in any of the measured areas, but not more than 3mm
5	Gingival crevice in any of the measured areas of the tooth 3-6mm apical to the CEJ
6	Gingival crevice in any of the measured areas more that 6mm apical to the CEJ

Table 3 Definition of periodontitis by CDC/AAP (Eke *et al.* 2012).

CASE	DEFINITION
No periodontitis	No evidence of mild, moderate, or severe periodontitis
Mild periodontitis	≥ 2 interproximal sites with ≥ 3mm CAL, and ≥ 2 interproximal sites with ≥ 4mm PD (not on same tooth), or one site with ≥ 5mm PD
Moderate periodontitis	≥ 2 interproximal sites with ≥ 4mm CAL (not on same tooth), or ≥ 2 interproximal sites with ≥ 5mm PD (not on same tooth)
Severe periodontitis	≥ 2 interproximal sites with ≥ 6mm CAL (not on same tooth), and ≥ 1 interproximal sites with ≥ 5mm PD

3.1.5 Treatment of chronic periodontitis

In Finland, the working group selected by the Finnish Medical Society Duodecim and the Finnish Dental Society Apollonia has given the Current Care Guidelines for periodontitis. These are evidence-based and gives guidance for clinical evaluation, early diagnosis, treatment and prevention of chronic periodontitis (Periodontitis: Current Care Guidelines 2016). The primary aim of periodontal therapy is mechanical infection control i-e scaling and root planing, as well as efforts aimed at maintaining daily self-performed oral hygiene and professional removal of microbial biofilm and plaque retention on a regular basis (Kinane *et al*. 2017). Adjunctive therapy including systemic and local antibiotic use, guided tissue regeneration (GTR) or enamel matrix derivatives (EMD) for correcting bony defects, and flap surgery may be used in addition to the mechanical infection control (Swedish Council on Health Technology Assessment 2004). Early diagnosis and treatment of periodontitis is essential in order to prevent the harmful consequences to patient's oral and general health (Periodontitis: Current Care Guidelines 2016).

Recently, host modulation therapy, a new treatment modality has been explored for treating chronic periodontitis (Kinane *et al*. 2017). The host modulation therapy uses low dose doxycycline (LDD) which works primarily by inhibiting MMPs, without having any antibiotic effect. It suppresses the breakdown of connective tissue (Golub *et al*. 2016). A review done by Golub and his colleagues on host modulation therapy presented that a subantimicrobial dose of doxycycline (SDD) two times a day, has shown impressive results not only for treating periodontitis, but for other systemic inflammatory diseases such as diabetes mellitus and arthritis (Golub *et al*. 2016). Other new treatment options include laser therapy and tissue engineering for tissue repair and regeneration (Kinane *et al.* 2017).

3.2 Physical activity and Periodontitis

3.2.1 Physical activity

Introduction and definition

Caspersen *et al*. (1985) defined physical activity as "any bodily movement produced by skeletal muscles that results in energy expenditure." It is a continuous variable, measured in kilocalories (kcal) and expressed in the form of rate (kcal per unit time). The unit of time used in reference to physical activity are the day and the week. The energy expenditure related to

physical activity is evaluated by the amount of skeletal musculature causing body movements and the frequency, duration and intensity of such contractions. There are various methods used in categorizing physical activity. One of the common methods of categorization is to identify physical activity with activities of daily living such as sleeping, working and leisure time activities. Another method is based on the intensity of physical activity (light, moderate, and high) or whether it is intentional or compulsory (Caspersen *et al*. 1985).

It is important to note that physical activity has been used erroneously synonymous to exercise, it is however, a subcategory of physical activity. Exercise is a type of physical activity that is intentional, organized, repetitive bodily movements with the ultimate aim of improving one or more aspects of physical fitness. Physical fitness gauges the ability to perform physical activity. It is an attributable characteristic, and has health related and athletic components. The health related components include muscular endurance and strength, flexibility,body composition and cardiorespiratory endurance (Caspersen *et al*. 1985).

Assessment and measurement of physical activity

While measuring physical activity, its dimensions and domains should be considered. The dimensions include mode, intensity, frequency and duration, and domains include domestic, occupational, transportation and leisure time. Mode can be explained on the basis of physiological mechanism involved such as aerobic vs anaerobic activity. Frequency is the bout of physical activity in a day or a week. Duration on the other hand is minutes or hours of bout of activity within a certain time frame. Intensity is the rate of energy expended during physical activity (Strath *et al*. 2013).

Over the years, more than 30 different methods has been used for the assessment and measurement of physical activity (LaPorte *et al*. 1985). These methods can be broadly classified as objective and subjective measurements (Bauman *et al*. 2006). Objective methods used in epidemiological studies assess physiological or biomechanical parameters (heart rate, body movements) expressed during physical activity and include calorimetry, mechanical and electronic monitors, physiological biomarkers and dietary measurements. These methods though very precise are costly and impractical for large population based studies (LaPorte *et al*. 1985). Subjective methods include self-reported questionnaires, surveys (dairy, recall, general) and behavioral observations (LaPorte *et al*. 1985, Bauman *et al*. 2006), and assess physical activity via estimation of energy expenditure (EE). These methods are inexpensive

and can be employed for large scale epidemiological research (Bauman *et al*. 2006). The limitation of questionnaires is difficulty in accurately recalling physical activity performed in the past and hence the imprecise calculation of intensity and duration of physical activity (Ekelund *et al*. 2011). Yet, self-reported questionnaires are more valid for population based assessment (Loney *et al*. 2011). The choice of physical activity assessment method depends on its practicality, suitability, cost-effectiveness and the type of epidemiological study being done (Strath *et al*. 2013).

Recommendations of physical activity

"Global Recommendations on Physical Activity for Health" are improvised by WHO with the intention of guiding policy makers towards the dose dependent relationship of different dimensions of physical activity essential in preventing chronic diseases. These guidelines are meant for three age-groups: 5–17 years old; 18–64 years old; and 65 years old and above, and are as follows;

1. “60 minutes of moderate- to vigorous-intensity physical activity daily is necessary for children and youth aged 5-17 years. Additional health benefits ensue if the physical activity amount to greater than 60 minutes. At least 3 times per week, high intensity strenuous physical activities should be a part of daily regimen to strengthen muscle and bone. Most of the daily physical activity should primarily be aerobic.
2. Moderate-intensity aerobic physical activity for at least 150 minutes throughout the week or at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity is imperative for adults aged 18-64. Aerobic activity should be done in intervals of at least 10 minutes duration. Adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week, or engage in 150 minutes of high-intensity aerobic physical activity per week, or an equivalent combination of moderate- and high-intensity activity for additional health benefits. Muscle-strengthening activities should be performed targeting major muscle groups on 2 or more days a week.
3. 150 minutes of moderate-intensity aerobic physical activity throughout the week or at least 75 minutes of high-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and high-intensity activity should be done by older adults. Aerobic activity should be performed in intervals of at least 10 minutes duration. Older adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week, or engage in 150 minutes of vigorous-intensity

aerobic physical activity per week, or an equivalent combination of moderate-and vigorous-intensity activity for additional health benefits. Older adults, with poor mobility, should perform physical activity for 3 or more days per week to enhance balance and prevent falls. Muscle-strengthening activities, involving major muscle groups, should be done on 2 or more days a week. Older individuals should be as physically active as their abilities and conditions allow even if their health doesn't allow the recommended physical activity" (WHO 2018).

3.2.2 Physical activity and chronic diseases

Cardiovascular disease

Exercise, a type of physical activity, has therapeutic effects for cardiovascular patients. It has been implicated in the treatment planning of both established coronary heart disease cases and high risk cases to avoid the ensuing complications. Combined with proper diet, aerobic exercise has shown to decrease the changeable cardiovascular risk factors (hypercholesterolemia, hypertension and hyperglycemia). Studies have demonstrated that subjects doing physical activity have lesser concentrations of total cholesterol and low density lipoprotein (LDL) in comparison to sedentary subjects. Besides triglyceride levels were also lower in physically active individuals.

Physical activity is strongly associated with decreased incidence of high blood pressure, its effects manifested after an acute phase of activity and even at rest. The major mechanism that explains the asscociation between reduction in hypertension and exercise is decrease in peripheral vascular resistance caused by autonomic response and structural changes in endothelium. The neurohumoral response downregulates the sympathetic activity and in effect causes peripheral vasoconstriction, releasing endothelin 1 (a vasoactive agent causing strong vasoconstriction) and nitric oxide (causing vasodilation). The adaptations in the endothelial structure caused by exercise are expansion of luminal size of blood vessels, effectuating a decrease in peripheral resistance. Physical activity also prevents the progression of hyperglycemia related complications. It causes production of slow muscle fibres, with greater insulin sensitivity and growth of muscle capillaries. Therefore, regular physical activity and healthy diet are therapeutically recommended for managing and preventing metabolic syndrome as well (Ganzit & Stefanini 2012).

Diabetes mellitus type 2

Besides pharmacological interventions, physical activity has also been regularly recommended in the treatment planning of diabetes mellitus type 2. The pathophysiological process which health enhancing physical activity affects positively is insulin signaling and glucose metabolism in skeletal musculature. The major site of glucose uptake and disposal associated with insulin is skeletal muscle (70% of ingested glucose). Exercise acutely increases the insulin sensitivity of muscle cells and facilitates glucose uptake. Insulin sensitivity is improved because physical activity mediates active expression of proteins known for insulin signaling. These include glycogen synthase and glucose transporter isoform 4 (GLUT 4). The increased muscle concentration of glycogen synthase disposes glucose as glycogen via non-oxidative pathways. Insulin activates GLUT 4 translocation to cell surface mediating glucose transport from blood into skeletal muscle against its concentration gradient. The transportation of glucose is dependent on the amount of GLUT 4 in muscle cells (Kilpelainen 2009). Another process that takes place as a result of contracting muscle is increased inflow of glucose into the cells independent of insulin. This contraction associated uptake of glucose by skeletal muscle is not affected by insulin resistance and hence contributes to the positive effects of regular physical activity in diabetic patients (Wadén 2010).

Exercise accentuates the oxidative ability of skeletal musculature, which causes an increased rate of fat oxidation in entire body. Sedentary lifestyle is associated with deposits of triglycerides within muscle cells, inducing insulin resistance. Not only triglycerides but their metabolic end-products also increases insulin resistance. Exercise makes skeletal muscles more insulin sensitive, one mechanism of which can be through facilitation of lipid oxidation and fatty acid turnover thus preventing its intramuscular deposition. Exercise decreases the amount of free fatty acids (FFAs) in circulating blood, because of lipid oxidation. This decreases the delivery of FFA to liver increasing its insulin sensitivity. Hence, exercise also prevents liver insulin resistance (Kilpelainen 2009).

The delivery of insulin and related substances to muscle is mediated by perfused capillaries, which are in fact increased by insulin itself, increasing glucose and insulin entry into muscles. The abnormality in microvascular functioning can downregulate insulin effect of increasing muscle capillary perfusion and thereby causing a reduction in insulin sensitivity. Physical

activity can correct this endothelial malfunctioning by dilation of muscle vasculature. The capillaries dilate as a result of increased production of nitric oxide. The improved perfusion of capillaries enhances the amount of glucose and insulin uptake (Kilpelainen 2009).

Obesity

Regular physical activity tends to decrease the total excess adipose tissue of the body (Ballor & Keesey 1991). Exercise training targets the reduction of total, abdominal and subcutaneous fat without weight control in normal weight and obese subjects, as shown by trial studies (Kilpelainen 2009). Exercise affects both white and brown adipose tissues (Dewal & Stanford 2019). It improves the function of white adipose tissue. Animal studies have shown that physical activity causes mitochondrial activity and alters gene expression in fat tissue and stimulates browning of white adipose tissue (Stinkens *et al*. 2018).

Cancer

Sedentary lifestyle increases the risk of many types of cancer such as colon, prostate, breast and pancreatic cancer. Regular physical activity is implicated in decreasing the risk of lung cancer. Physical activity is known to reduce inflammation which is protective against developing lung cancer. It also upregulates immune function, thereby increasing natural killer cells and suppressing tumor growth (Pletnikoff 2017). Physical activity also decreases the incidence of prostate cancer, as it affects various biological pathways (hormonal, insulin, and immune system) likely involved in the causation of prostate cancer (Pernar *et al*. 2018).

Psychological disorders

Physical activity has been associated with better mood and mental health (Chan *et al*. 2018, Pascoe & Parker 2018), and reducing the incidence of mood disorders. A recent review has implicated a bidirectional relationship between physical activity and mental health in younger adults (Pascoe & Parker 2018). Physical activity protects against depression, a disease contributing to one of the greatest burden of global diseases (McDowell *et al*. 2018), and has repeatedly shown its efficacy as an interventional treatment of the disease (Hess *et al*. 2018). The pathophysiology of depression is rather complex and involves dysfunctional molecular processes within the brain via interaction of immune system, energy metabolism and neuroprotective elements. Physical activity is neuroprotective, the central and peripheral effects of which are exhibited through multiple pathways. It affects immune system

positively, encouraging an anti-inflammatory response. It maximizes stress response by directly and indirectly modulating the noradrenergic system (neurotransmitter amount and function), which is crucial in creating a pro or anti-inflammatory environment. It improves hippocampal health by increasing neurotrophic growth factors such as brain-derived neurotrophic factor, thereby upgrading cortisol (stress hormone) regulation. The contraction of muscles during physical activity leads to the expression of myokines (IL-6). These myokines multiply the production of transcription factors and coassociates and down regulate the production of pro-inflammatory cytokines (Phillips C & Fahimi 2018).

Inflammation

Inflammatory process has been consistently linked with the pathogenesis of various chronic diseases such as coronary heart disease (Abramson & Vaccarino 2002, Ford 2002, Lunde *et al*. 2017), atherosclerosis (Mury *et al*. 2018), metabolic syndrome, insulin resistance, diabetes mellitus type 2 and cancer. Studies have shown that physical activity has been associated linearly with anti-inflammatory markers and inversely with pro-inflammatory markers (Tir *et al* 2017). IL-6, a pro-inflammatory cytokine, is a biomarker of inflammation released in the beginning of inflammatory response. Whereas, fibrinogen and C reactive protein (CRP), are biomarkers of acute phase of inflammation (Graham *et al*. 2018). Regular physical activity tends to decrease the concentrations of fibrinogen, CRP (Abramson & Vaccarino 2002, Lunde *et al*. 2017) and IL-6 (Lunde *et al*. 2017) and effectuates long term anti-inflammatory effects (Lunde *et al*. 2017, Graham *et al*. 2018). The effects of physical activity on inflammatory mediators are as effective as pharmacological intervention (Tir *et al* 2017).

3.2.3 Periodontitis and chronic diseases

Oral health has direct or indirect relationship with systemic health. It has been suggested that there is link between periodontitis and different systemic diseases. Periodontitis is caused by long standing poor oral hygiene and an increase in bacterial count therefore, these are also a constant source of infection to other body parts and systems. Systemic diseases, for instance, circulatory issues, where oral infectious processes can be a risk factor, range from cardiovascular diseases, cerebrovascular diseases, and peripheral arterial diseases. Evidences have also been found which suggest the association between oral health and respiratory diseases (Arigbede *et al*. 2012).

Numerous studies have been conducted to find association between gingivitis and periodontitis and cardiovascular diseases. A cohort study was conducted in Stockholm to find association between long standing gingivitis and risk of stroke. It was concluded that not only periodontitis but also long standing gingivitis can lead to cerebral infarctions, illustrating the importance of maintaining good oral hygiene in order to reduce chronic inflammatory burden to body which can lead to poor outcomes such as stroke (Söder *et al*. 2015).

Another Swedish cohort study was conducted to find association between calculus score and incidence of angina pectoris. The presence of higher amount of calculus in mouth shows poor oral hygiene and it is a clear risk factor for gingivitis and periodontitis. In calculus microorganisms are encapsulated and if remain there for long time, can cause local periodontitis as well as can spread systemically through hematogenous spread and can cause systemic diseases. The result of the study proved the association between high calculus index score and incidence of angina pectoris (Soder *et al*. 2016).

Studies suggest that diabetes mellitus is a major risk factor for periodontitis and it has been determined that risk of periodontitis increased three folds among patient with diabetes as compared to non-diabetic individuals. According to US National Health and Nutrition Examination Survey (NHANES) III, severe periodontitis was prevalent in individuals with HbA1c > 9% than those without diabetes (Preshaw *et al*. 2012). The mechanism by which diabetes can affect periodontal health is mainly related to impaired immune system. Patients with diabetes have impaired immune cells that are unable to eliminate periodontal pathogens and have decreased ability to renew the lost periodontal tissues. There is more secretion of pro-inflammatory cytokines in diabetics which lead to destruction of periodontal tissues (Weinspach *et al*. 2013).

3.2.4 Link between periodontitis and physical activity

It is now a well-established phenomenon that physical activity plays a vital role in maintaining and improving general health and preventing body against various diseases (Karacabey 2005). There is strong evidence that the risk of many non-communicable chronic diseases such as cardiovascular disease, type 2 diabetes, obesity, cancers (colon and breast cancers), osteoporosis and others is inversely associated with regular physical activity (CDC 1996). According to WHO (2012), non-communicable diseases and oral diseases share some

common risk factors. As physical activity and non-communicable diseases have inverse relationship, therefore, studies on both humans and animals are ongoing to establish a relationship between physical activity and oral diseases.

Andrade *et al*. (2017) determined the association of exercise with alveolar bone loss in Wistar rats with periodontitis. According to the trial, physical training decreased alveolar bone loss and periodontal attachment loss among rats with periodontitis. The possible mechanism can be due to decrease in the ratio of tumor necrosis factor alpha (TNF-α) and IL-10 in rats who were present in physical training group. IL-10 is a strong anti-inflammatory cytokine that can decrease bone resorption by inhibiting osteoclastic bone resorption and regulating osteoblastic bone formation. In addition, IL-10 may also decrease TNF-α, that can increase osteoclastic bone resorption and play an important role in development of periodontitis (Zhang *et al*. 2014).

Studies indicate that healthy lifestyle which include physical activity can decrease the incidence as well as progression of periodontitis (Iwasaki *et al*. 2018). In a longitudinal study by Merchant *et al*. (2003) an inverse and linear relationship between sustained physical activity and periodontitis among men aged 40-75 years was found. Similarly, Al-Zahrani *et al* (2005) concluded that physical activity according to the recommended levels can decrease risk of periodontitis among non/smokers and former smokers (Merchant *et al* 2003, Al-Zahrani *et al*. 2005).

The microorganisms in oral cavity are divided into six complexes, of which bacteria in blue, purple and yellow complexes are more commonly linked with healthy periodontium (Anderson *et al*. 2018). Anderson *et al*. (2018) conducted a study to assess the relationship between IgG antibodies against 19 periodontal bacteria and physical activity. They clustered the antibody titers into four groups and found that antibodies in Orange-Blue cluster, indicative of healthy periodontal status, has a positive association with physical activity.

The mechanism through which physical activity is associated with periodontitis is still not fully understood. However, one mechanism can be excessive inflammatory response in pathogenesis of periodontitis. In response to periodontal pathogens, pro-inflammatory cytokines are released in periodontal tissue. IL-1β is one of such pro-inflammatory cytokine which is responsible for periodontal attachment loss and alveolar bone loss (Masada *et al.* 1990). When acute phase is unable to restrict disease progression, these cytokines signal liver

cells to secrete CRP (Medzhitov 2007). Based on this mechanism, a study conducted by Sanders *et al*. (2009) found that people who were engaged in daily physical activity of thirty minutes or more had lower levels of pro-inflammatory cytokine IL-1β and CRP in gingival crevicular fluid as compared to less active individuals. Study concluded that leisure time physical activity may play a protective role against excessive inflammatory response in periodontitis (Sanders *et al.* 2009).

A number of environmental factors and chronic diseases such as tobacco usage, diabetes, obesity and stress are known to increase the risk of developing periodontitis (Merchant *et al*. 2003, Al-Zahrani *et al*. 2005). In diabetes, there is impairment of immune system due to constant hyperglycemia, leading to alveolar bone resorption and attachment loss. Similarly, obesity which causes insulin resistance as well as hyperglycemia, also increases the risk of periodontitis (Merchant *et al*. 2003). Physical activity is associated with improving insulin sensitivity and glucose metabolism (Merchant *et al*. 2003). It has been suggested that individuals engaged in higher levels of physical activity on a daily basis may have lower incidence of periodontitis (Bawadi *et al*. 2011). It improves overall health of an individual and enhances quality of life (Al-Zahrani *et al*. 2005).

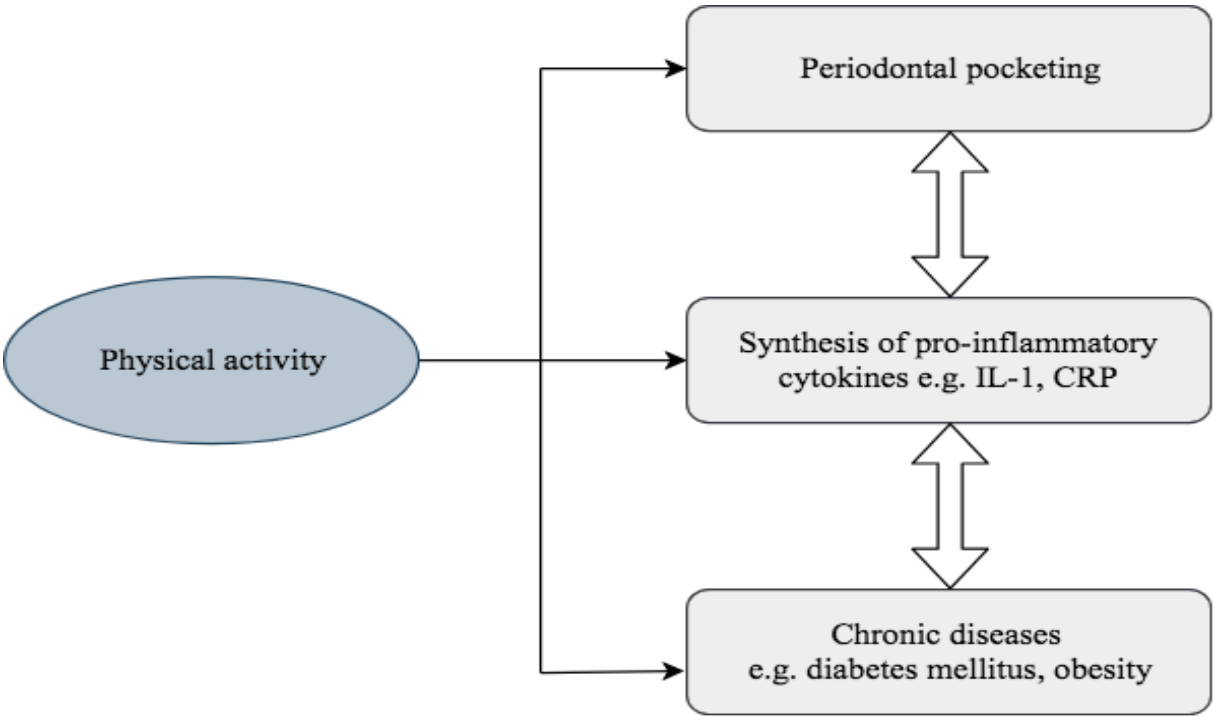

Figure 2. Proposed mechanism of association between physical activity and periodontitis.

Table 4 Cross-sectional and longitudinal studies associating physical activity and periodontitis.

AUTHOR	DESCRIPTION OF PARTICIPANTS	EXPOSURE ASSESSMENT	OUTCOME ASSESSMENT	CONFOUNDERS	RESULTS
Anderson *et al.* (2018)	N= 5,611 Age ≥ 40 Design= Cross sectional	Physical activity classified on the basis of METs* 3 categories of participants; sufficiently active, insufficiently active and inactive	Periodontal antibody titres against 19 periodontal bacteria	Age, gender, ethnicity, smoking, alcohol intake, waist circumference, education, poverty-income ratio. Effect modifiers: sex, age, smoking, periodontal disease, and diabetes status	Antibodies against Orange-blue cluster correlated with healthy periodontium, has a positive association with physical activity
Iwasaki *et al*. (2018)	N= 374 Age= 70 Design= Longitudinal	Healthy lifestyle score based on smoking status, physical activity levels, BMI*, diet (DVS) *	CAL* ≥ 3mm at one or more site of tooth, or progression if present at baseline Tooth loss	Sex, regular dental checkups, tooth brushing frequency, use of interdental cleaning devices, income, education and living status, hypoalbuminemia, fasting blood glucose level. Tooth-based factors included tooth status, tooth type, tooth position, use as an abutment, and the greatest baseline CAL* among the six sites per tooth	The highest healthy lifestyle score (4; most healthy) has significant association with lower incidence or progression of periodontitis and tooth loss in old aged individuals
Andrade *et al*. (2017)	N= 24 rats Design= Randomized control trial	With and without exercise, with and without periodontal disease (induced by ligation protocol)	bone loss, periodontal inflammatory status and anxiety-like behaviour	-	Exercise is shown to decrease alveolar bone loss, anxiety like behaviour and expression of inflammatory proteins in rats with periodontal disease

Singla *et al*. (2016)	N= 800 Age= 20-50 Design= Cross-sectional	Health Practice Index (HPI) measured by smoking, alcohol, breakfast, sleep/night, work/day, exercise, diet, stress	Periodontal status assessed by clinical attachment loss measured using CPI*	Age, gender, location, marital status, income/month, education, occupation, religion, frequency of dental visits, device of cleaning, frequency of cleaning, method of cleaning, tobacco and paan chewing	Periodontitis is associated with lifestyle factors including physical activity
Bawadi *et al*. (2011)	N= 340 Males= 168 Females= 172 Mean age= 36.4 ± 14.9 Design= Cross-sectional	Physical activity classified as low, moderate and high based on scoring protocol of IPAQ*, Healthy eating index score (good, fair, poor) determined by FFQ*	Plaque index, gingival index, clinical attachment loss, probing pocket depth, number of decayed, filled and missing teeth	Age, gender, BMI*, marital status, income, years of education, diabetes, hypertension, dyslipidemia, smoking status, brushing frequency	Lower amount of physical activity and poor diet has significant association with greater odds of periodontitis
Shimazaki *et al*. (2010)	N= 1160 Age= 20-77 Design= Cross-sectional	Indicators of obesity= BMI* and body fat percentage, Indicator of physical fitness= maximal oxygen consumption during exercise	CPI* scoring	Age, gender, smoking, number of teeth, fasting plasma glucose, systolic blood pressure	Physical fitness and obesity may have an interactive role in periodontal health
Sanders *et al*. (2009)	N= 751 Cases= 359 Controls= 392 Age ≥ 18 Design= Cross-sectional	Physical activity divided into sufficient and insufficient based on leisure time physical activity questionnaire	Interleukin 1β , CPR*, periodontitis cases having moderate (2 or more interproximal site with clinical attachment level ≥ 4mm) or severe periodontitis	Age, gender, country of birth, diabetes status, smoking status, body mass index	Leisure time physical activity might be protective against an accentuated inflammatory response of periodontal disease
Al-Zahrani *et al*. (2005b)	N= 12,110 Age ≥ 18 Design= Cross-sectional	Health enhancing behaviours involving normal weight (body mass index of 18.5 to 24.9 kg/m2), physical exercises (≥ 5 episodes of moderate or ≥ 3 episodes of vigorous-intensity physical activity/week), and high-quality diet (healthy eating index > 80)	1 site with both a probing depth ≥ 4 mm and a clinical attachment loss ≥ 3 mm	age, gender, ethnicity, cigarette smoking, other tobacco products, education, diabetes, poverty index, census region, acculturation, vitamin use, frequency of dental checkups, calculus, gingival bleeding	Individuals keeping up with the health enhancing behaviours are 40% less prone to periodontitis compared to individuals without these practices

Al-Zahrani *et al*. (2005a)	N= 2521 Age ≥ 18 Design= Cross-sectional	Physical activity assessed by questionnaire is divided as inactive, partially active and active. Active are those meeting recommended level of ≥ 5 episodes of moderate or ≥ 3 episodes of vigorous-intensity physical activity/week	Periodontitis defined by attachment loss ≥ 3 mm and probing depth ≥ 4 mm on one site of tooth.	age, gender, race, education, smoking, body mass index, poverty index, vitamin use, healthy eating index, time since last dental visit, gingival bleeding, calculus.	Physical activity according to the recommended level can decrease risk of periodontitis among non/smokers and former smokers
Merchant *et al*. (2003)	N= 39,461 males Age= 40-75 Design= Longitudinal	Physical activity (self reported questionnaire and dairies) expressed as METs/week	Periodontitis diagnosed with bone loss in mm	Age, smoking, diabetes, BMI*, alcohol consumption and total calories	Sustained physical activity has an inverse linear association with periodontitis irrespective of the known risk factors
Wakai *et al*. (1999)	N= 630 Males= 517 Females= 113 Age= 23-83 Design= Cross-sectional	Physical fitness tests include maximum oxygen uptake, anaerobic threshold, grip strength, sit-ups or sit-and-reach tests, eye-closed test, one-foot balance test. Medical status variables; Hypertension, hematuria, leukocytosis or thrombocytosis, positive CRP*, serum alkaline phosphatase, high-density lipoprotein cholesterol, fasting plasma glucose	CPITN* scoring system	Age, smoking habits, and higher fasting plasma glucose and simplified debris index	Oral health is closely related to medical status and physical fitness
Shizukuishi *et al*. (1998)	N= 310 Males= 252 Females= 58 Age= 38.7 ± 11.0 Design= Cross-sectional	Questionnaire assessing lifestyle factors including physical exercise, cigarette smoking, alcohol consumption, sleeping hours, eating breakfast, snacking, working hours per day, mental stress, tooth brushing frequency,	Indicators of periodontal health status; 1.Modified Miller's CPI* score 2.Above and below the upper 25th percentile of	Age and gender	Physical activity, a lifestyle factor is not a predictor of periodontal disease

		toothbrushing methods, use of interdental cleaners, and dental visit	CPI* distribution		
Sakki *et al.* (1995)	N= 527 Age= 55 Design= Cross-sectional	Dietary habits, smoking habits, alcohol consumption and physical activity measured by questionnaire	Periodontal pocket deeper than 3mm	Age, gender, vocational education, family income, occupational status, tooth brushing frequency, time of last dental visit, frequency of dental visits	Physical activity is not significantly associated with periodontitis

* METs= metabolic equivalents, BMI= body mass index, DVS= dietary variety score, CAL= clinical attachment loss, CPI= community periodontal index, IPAQ= international physical activity questionnaire, FFQ= food frequency questionnaire, CPR= C reactive protein, CPITN= community periodontal index for treatment needs.

4 AIMS OF STUDY

The purpose of this study was to explore the relationship between physical activity and periodontal pocketing in Finnish adults.

5 METHODOLOGY

5.1 Study population

The data utilized in this study was from the Health 2000 and Health 2011 Surveys in Finland (Heistaro 2008, Lundqvist & Mäki-opas 2016). The Ethics Committee for Epidemiology and Public Health of the Hospital District of Helsinki and Uusimaa approved both the surveys. Furthermore, all the participants were asked to fill in the written informed consent.

5.1.1 The Health 2000 Survey

The Health 2000 Survey was performed in 2000 and 2001. The targeted population was individuals aged 18 or over, residing in mainland Finland. Study design was two-stage stratified cluster sampling. The total sample size was 9992, however main focus of the survey was on the sample of 8028, aged 30 years and above. The study of young adults included the remaining 1894 individuals. The modes of data collection were questionnaires, interviews, anthropometric and functioning measurements, blood samples and clinical examinations. The data on key characteristics of each individual was taken from the National Population Register. Furthermore, administrative register data was extracted after approval from the institutes responsible for corresponding registers. Major public health problems and functional capacity were the main objective of the study, with special emphasis on respiratory and cardiovascular diseases, musculoskeletal and mental disorders and oral health (Heistaro 2008).

Information regarding physical activity was collected by a set of questions assessing leisure time, commuting and occupational physical activity. These questions assessed the type and frequency of physical activity and were originally from the Gothenburg Study (Wilhelmsen *et al*. 1972). IPAQ scale (Craig *et al*. 2003) was used to assess physical activity during leisure time inclusive of household activities, sitting and walking.

Information regarding oral health status was gathered through questionnaires, interviews, clinical and radiological examinations. A detailed clinical examination and panoramic radiograph was performed on 6335 subjects. Participants were inquired about oral self-care, use of dental services and self-reported oral health in the interview. Clinical oral examination collecting information on number of teeth and use of removable denture was arranged at home for those people who were unable to attend the health examination (Heistaro 2008).

5.1.2 The Health 2011 Survey (Follow-up survey)

This survey which was both cross-sectional and longitudinal in design, was done to provide a general idea of health and functional capacity of the middle-aged and elderly Finnish population. The total sample size was 10129. All the subjects who participated in the Health 2000 Survey, were alive, living in Finland and did not refuse, were re-invited in 2011 to obtain a representative longitudinal data on adult Finnish population. In 2011, the sample of adults aged 30 years or above comprised of 7964 (Suominen *et al*. 2018). The modes of data collection were questionnaires, interviews, laboratory and clinical measurements. Subjects who were unable or unwilling to take part in health examination were offered phone interviews and health evaluation at home. The data on key characteristics of each individual was taken from the National Population Register. Furthermore, administrative register data was extracted after approval from the institutes responsible for corresponding registers (Lundqvist & Mäki-opas 2016).

In Health 2011 Survey, the questions pertaining to physical activity were developed by the UKK Institute with the purpose of measuring health-enhancing physical activity of subjects (UKK Institute 2009). Information on oral health status was gathered in the form of questionnaires and interviews from all the subjects, whereas, the clinical examination could only be performed in two parts of Finland covering only southern and northern areas (Helsinki and Oulu), and radiographic examination only in Helsinki. The number of subjects invited to take part in oral clinical examination was 3938 (Suominen *et al*. 2018). Participants were inquired about oral self-care, use of dental services and self-reported oral health in the interview (Lundqvist & Mäki-opas 2016).

5.2 Study design and participants

This was a longitudinal quantitative study. The data for physical activity was taken at baseline from The Health 2000 Survey and subjects were followed up to see the longitudinal association of physical activity with number of teeth with deepened periodontal pockets ≥ 4mm in 2011. The data on number of teeth with deepened periodontal pockets ≥ 4mm were taken from both The Health 2000 and The Health 2011 Surveys. Amongst the subjects who have undergone oral clinical examination in 2000 (n= 6335) and in 2011 (n= 1845) surveys, those who attended oral clinical examination in both surveys and had number of teeth ≥ zero were included in this study, hence the total number of subjects were 1225.

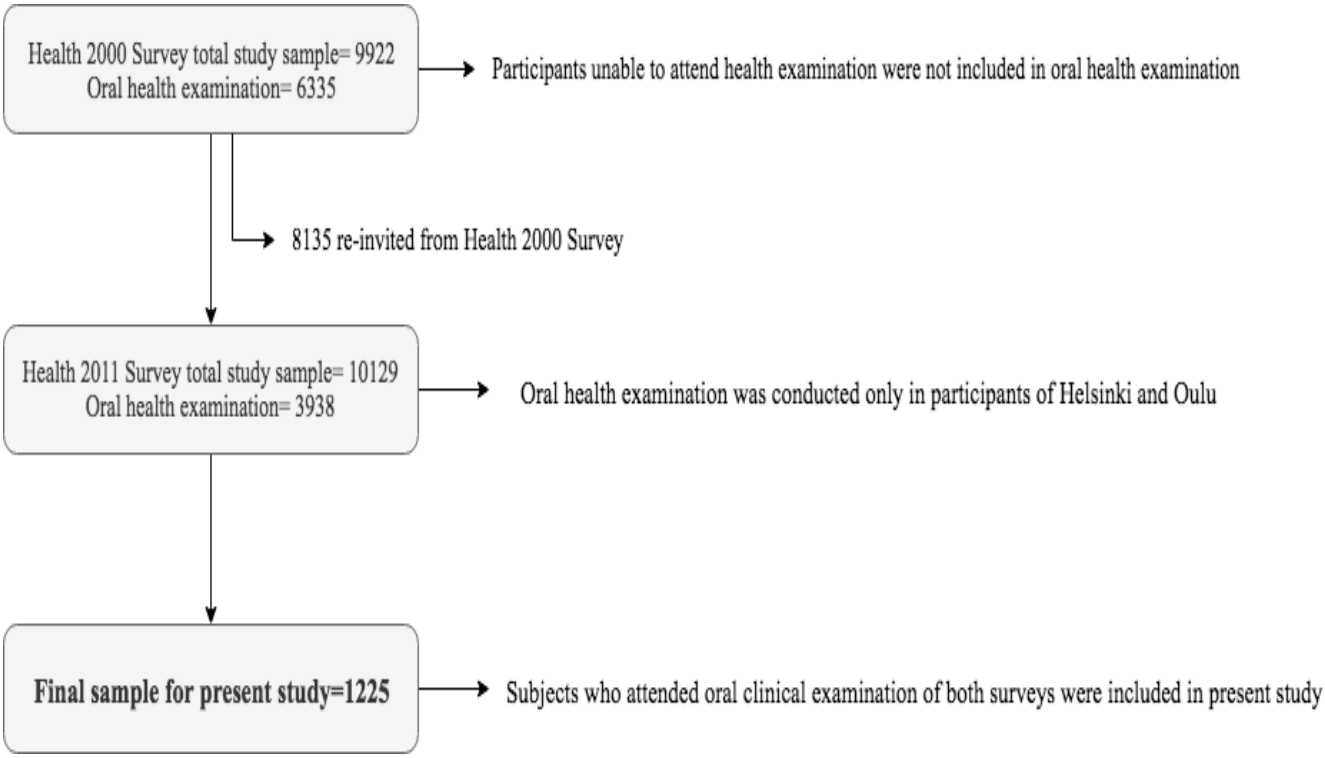

Figure 3. Subject selection for present study.

5.3 Periodontal health

The Health 2000 and Health 2011 Surveys, both followed the same protocol for clinical oral examination of subjects. A dentist and a dental nurse were responsible for the examination procedures (Heistaro 2008, Lundqvist & Mäki-opas 2016).

The status of periodontal health was evaluated by gauging the depth of periodontal pockets on all the teeth in the oral cavity excluding only third molars. Each tooth was probed with a WHO periodontal probe with ball end (20g force) at four sites which includes mesial corner and midpoint of lingual side, and distal corner and midpoint of buccal side. The measurement of periodontal pocket was done in millimeters and deepest pocket depth for each tooth was marked in categories of; : no periodontal pocket, "4–6mm periodontal pocket depth and 6mm or more periodontal pocket depth (Knuuttila & Suominen-Taipale 2008). In the analysis of this study, number of teeth with deepened periodontal pockets ≥ 4mm was used as an outcome variable. The variable was formed by calculating the number of teeth with deepened periodontal pockets ≥ 4mm per participant.

5.4 Physical activity

Physical activity was measured by asking participants questions pertaining to leisure time, commuting and occupational activity. One of the questions assessing frequency of leisure-time physical activity was "How often do you exercise at least 30 minutes so that you sweat and get out of breath?" The six answering choices were: daily, 4-6 times per week, 2-3 times per week, once a week, 2-3 times per month, few times per year or less frequently. "How many minutes do you walk or cycle to and from work daily?" was another question used to evaluate commuting physical activity. The seven answering choices were: I am not working or I work from home, using public transport or car during commuting, less than 15 minutes per day, 15-29 minutes per day, 30–59 minutes per day, 1-2 hours per day, over 2 hours per day. The physical activity variable used in the study was constructed by combining different options of above two questions to make four categories as illustrated in table 5.

Table 5 Physical activity variable.

Physical activity categories	Leisure time physical activity question		Commuting physical activity question
Ideal	I OR II	AND	V OR VI OR VII
Adequate	I OR II	OR	V OR VI OR VII
Moderately adequate	III	AND	I OR II OR III OR IV
Inadequate	IV OR V OR VI	AND	I OR II OR III OR IV

In addition, they were converted into three categories (adequate, moderately adequate and inadequate) by combining the first two categories, to have a larger reference category (i.e. subjects with the highest activity) in the analysis.

5.5 Other measurements

The socio-demograhic and socioeconomic factors included age, gender, level of education and marital status. Body mass index (BMI), alcohol consumption frequency, smoking, use of medications, diabetes mellitus, hypertension, rheumatoid arthritis, perceived general health, use of dental services, tooth brushing frequency, number of teeth with deepened periodontal pockets ≥ 4mm, and number of teeth with plaque were the other covariates.

Age was treated both as continuous and categorical variable. The four categories of age from 2000 survey were: 30-44, 45-54, 55-64 and 65+ years. From 2011 survey, accordingly these

categories were: 40-54, 55-64, 65-74, and 75+. The information about level of education was gathered through interview and was grouped into three categories: basic (who did not complete high school and with no formal vocational education), intermediate (who completed high school or formal vocational qualification) and higher (university or polytechnic graduates). Marital status was also inquired in the interview with following options: married, living with your partner, divorced or living apart, widowed and single. The answers one and two as well as three and four were combined to form three categories: married or cohabiting, divorced or widow and single were formed. BMI was utilized as a continuous variable. The readings of height and weight measured during clinical evaluation was mainly used for BMI. In some instances self-reporting, questionnaire and bio impedance also collected the information for BMI (Heistaro 2008).

Behavioral lifestyle factors in this study were smoking and alcohol consumption, the data for which was obtained through interview. Smoking was categorized into regular and non-regular use. The question assessing frequency of alcohol consumption was “how often have you drunk alcoholic drinks during the past 12 months?” The responses were: not once, 6-7 times a week, 4-5 times a week, 2-3 times a week, once a week, a couple of times a month, approximately once a month, approximately once every two months, 3-4 times a year and a couple of times a year. Answering options one, eight and nine were combined. Similarly, options six and seven, four and five as well as one and two were combined to make five categories: never, once a month or less, 2-4 times a month, 2-3 times a week and four times or more per week.

The data for perceived general health and use of medications was retrieved from interview. The question for perceived health was “What is your current health status?” The answering options were: good, rather good, moderate, rather poor and poor. Answers one and two as well as four and five were put together to form three categories: good or fairly good, average, fairly bad or poor. Use of lipid lowering drugs, systemic corticosteroids, anti-inflammatory drugs and multi analgesics NSAIDs were categorized into yes and no. The data on diabetes mellitus, hypertension and rheumatoid arthritis was also gathered through interview and categorized into yes and no.

Dental behaviour and hygiene covered presence of plaque, tooth brushing frequency and use of dental services. Oral clinical examination measured dental plaque with the help of modified scale of Silness and Löe (1946). One surface from three specific teeth was examined for

measuring plaque i.e. the lingual surface of the most posterior tooth on the lower left quadrant, the buccal surface of the most posterior tooth on the upper right quadrant and the buccal surface of the left lower canine. Each tooth was scored as one of the three: no plaque, marginal gingival plaque only, plaque also elsewhere.The plaque status of a subject was determined according to the tooth with greatest score. In Health 2011 survey, buccal aspect of all teeth excluding only third molars were assessed for presence of plaque and recorded in two categories: no plaque and any plaque.

The information related to tooth brushing frequency and use of dental services was retrieved from interview. The question assessing tooth brushing frequency was “how often do you usually brush your teeth”. The answers were: more often than twice a day, twice a day, once a day, less frequently than every day, and never. Answering options one and two as well as four and five were put together to give three categories: twice a day, once a day and occasionally. The question assessing the use of habitual dental services was “do you usually go to a dentist”. The answers were: regularly for checkup, only when you have toothache or some other trouble and never. These options were labelled as: regular, sometimes and never.

5.6 Statistical analysis

The statistical analysis was performed with the help of SPSS 25. The test used to analyze the association between exposure and outcome in this longitudinal design is Poisson regression. The predictor variable was physical activity at baseline and outcome variable was number of teeth with deepened periodontal pockets ≥ 4mm from the follow-up.

Kruskal-Wallis test was performed to compare the difference in mean number of teeth with deepened periodontal pockets ≥ 4mm according to the level of physical activity (Table 8). Poisson regression yielded results as incidence rate ratio (IRR) and 95% confidence interval (CI) which were shown in (Table 8). Number of teeth at follow-up was used as an offset variable in the analysis. Separate models were constructed to evaluate the effects of various covariates on the association between exposure and outcome variable. The following four models were used;

- Model 1: Adjusted for age and gender
- Model 2: Adjusted for age, gender, level of education and marital status
- Model 3: Model 2 + social and dental behavioral variables (smoking, alcohol consumption frequency, tooth brushing frequency, use of habitual dental services,

number of teeth with plaque), BMI, perceived health, use of medications (lipid lowering drugs, systemic corticosteroids, anti-inflammatory and NSAIDs), diabetes mellitus, hypertension, rheumatoid arthritis and number of teeth with deepened periodontal pockets ≥ 4mm in 2000

- Model 4: Model 3 excluding dental behavioral variables (tooth brushing frequency, use of habitual dental services, number of teeth with plaque).

6 RESULTS

The baseline charateristics of study population are given in table 6. There was slight increase in BMI among subjects during the 11 years' time period. The mean number of teeth decreased in 2011 from baseline. The average number of teeth with deepened periodontal pockets ≥ 4mm were slightly higher in 2011 than in 2000. The number of subjects with diabetes mellitus, hypertension and rheumatoid arthritis had increased in 11 years. Although, there was an improvement in oral hygiene behaviour, other detrimental behavioral aspects such as alcohol consumption also increased during this time period.

Table 6 Baseline characteristics of study population; The Health 2000 and Health 2011 Surveys (n=1225).

Baseline characteristics of study population	In 2000			In 2011	
Age (years) mean(SD)	47.9(11.3)		Age (years)	58.9(11.3)	
30-44 n(%)	529	(43.2)	40-54	491	(40.1)
45-54	359	(29.3)	55-64	363	(29.6)
55-64	232	(18.9)	65-74	251	(20.5)
65+	105	(8.6)	75+	120	(9.8)
total	*1225*			*1225*	
Gender n(%)					
Female	681	(55.1)		681	(55.1)
Male	544	(44.4)		544	(44.4)
total	*1225*			*1225*	
BMI* mean(SD)	26.3(4.4)			27.2(4.8)	
total	*1225*			*1225*	
Marital status n(%)					
Single	132	(10.8)		109	(9.0)
Widow/divorced	154	(12.6)		217	(17.9)
Married	934	(76.6)		889	(73.2)
total	*1220*			*1215*	
Level of education n(%)					
Basic	300	(24.6)		284	(23.4)
Intermediate	397	(32.5)		368	(30.3)
Higher	523	(42.9)		563	(46.3)
total	*1214*			*1215*	
Alcohol consumption frequency n(%)					
Never	290	(23.9)		188	(15.5)
Once a month or less	181	(14.9)		296	(24.4)
2 to 4 times a month	460	(37.9)		421	(34.7)
2 to 3 times a week	215	(17.7)		238	(19.6)
4 or more a week	69	(5.7)		70	(5.8)
total	*1215*			*1213*	
Smoking n(%)					
Regular use	238	(19.5)		166	(13.7)
Non-regular use	982	(80.5)		1048	(86.3)
total	*1220*			*1214*	
Perceived general health n(%)					
Fairly bad or poor	53	(4.4)		69	(5.7)
Average	265	(21.8)		209	(17.2)

Good or fairly good	899	(73.9)	937	(77.1)
total	*1217*		*1215*	
Systemic conditions n(%)				
Diabetes mellitus				
Yes	35	(2.9)	93	(7.7)
No	1185	(97.1)	1122	(92.3)
total	*1220*		*1215*	
Hypertension				
Yes	313	(25.7)	400	(32.9)
No	907	(74.3)	815	(67.1)
total	*1220*		*1215*	
Rheumatoid arthritis				
Yes	19	(1.6)	30	(2.5)
No	1201	(98.4)	1184	(97.5)
total	*1220*		*1214*	
Use of medications n(%)				
Systemic corticosteroids				
Yes	20	(1.8)	15	(1.2)
No	1109	(98.2)	1201	(98.8)
total	*1129*		*1216*	
Lipid lowering drugs				
Yes	59	(5.2)	223	(18.7)
No	1070	(94.8)	993	(81.7)
total	*1129*		*1216*	
Multi-analgesics NSAIDs*				
Yes	170	(15.1)	56	(4.6)
No	959	(84.9)	1160	(95.4)
total	*1129*		*1216*	
Anti-inflammatory				
Yes	455	(40.3)	106	(8.7)
No	674	(59.7)	1110	(91.3)
total	*1129*		*1216*	
Use of habitual dental services n(%)				
Never	7	(0.6)	47	(3.9)
Sometimes	391	(35.7)	395	(32.6)
Regular	697	(63.7)	770	(63.5)
total	*1095*		*1212*	
Tooth brushing frequency n(%)				
Twice a day	766	(70.0)	895	(73.8)
Once a day	290	(26.5)	284	(23.4)
Occasionally	39	(3.6)	34	(2.8)
total	*1095*		*1213*	
Number of teeth mean(SD)	22.8(9.1)		21.7(9.3)	
total	*1225*		*1225*	
Occurrence of plaque mean(SD)				
None n(%)	404	(36)	3.9(5.0)	
Marginal	604	(53.8)		
Elsewhere	114	(10.2)		
total	*1122*		*1124*	
Number of teeth with deepened periodontal pockets ≥ 4mm mean(SD)	4.2(5.6)		4.6(5.7)	
total	*1113*		*1091*	

*BMI= Body mass index, kg/m², NSAIDs= Non-steroidal anti-inflammatory drugs.

The subjects among the ideal, adequate, moderately adequate and inadequate categories of physical activity were evenly distributed (Table 7).

Table 7 Distribution of physical activity variable.

Levels of physical activity		In 2000		In 2011	
		n	%	n	%
4 categories	Ideal	39	3.4	55	4.5
	Adequate	322	27.8	343	28.3
	Moderately adequate	441	38.0	394	32.6
	Inadequate	358	30.9	418	34.5
3 categories	Adequate	361	31.1	398	32.9
	Moderately adequate	441	38.0	394	32.6
	Inadequate	358	30.9	418	34.5
	total	*1160*		*1210*	

There were no statistically significant differences in mean number of teeth with deepened periodontal pockets ≥ 4mm in 2000 and 2011 according to the level of physical activity performed by the subjects in 2000. However, the results were statistically significant for mean number of teeth with deepened periodontal pockets ≥ 4mm in 2011 according to the level of physical activity in 2011 ($P<0.02$). The difference between the mean number of teeth with deepened periodontal pockets ≥ 4mm in 2000 according to inadequate physical activity in 2000 and the mean number of teeth with deepened periodontal pockets ≥ 4mm in 2011 according to inadequate physical activity in 2011 was 1. Similarly, this difference for adequate physical activity subjects was 0.8 mean number of teeth with deepened periodontal pockets ≥ 4mm. Hence, the periodontal health status worsened slightly more in those performing inadequate physical activity as compared to those performing ideal physical activity during the 11 years' time period, however this difference was very small i.e. 0.2 mean number of teeth with deepened periodontal pockets ≥ 4mm (Table 8).

The average number of teeth with deepened periodontal pockets ≥ 4mm in 2000 according to the level of physical activity performed in 2000, were 3.35 in those belonging to ideal category, 4.33 in those performing adequate physical activity, 4.06 in those with moderately adequate physical activity and 4.41 in those with inadequate physical activity. The largest difference in average number of teeth with deepened periodontal pockets ≥ 4mm in 2000 was seen between ideal and inadequate physical activity, which was also statistically significant ($p= 0.035$) according to the Mann-Whitney test. At baseline, physical activity and number of teeth with deepened periodontal pockets ≥ 4mm showed a weak direct association according

to the Spearman's Correlation Coefficient (0.028) which was just statistically significant (p=0.042).

Table 8 Mean number of teeth with deepened periodontal pockets ≥ 4mm in 2000 and 2011 according to the level of physical activity in 2000 and 2011.

Levels of physical activity in 2000		Number of teeth with deepened periodontal pockets ≥ 4mm in 2000		in 2011	
		Mean	**SD**	**Mean**	**SD**
4 categories	Ideal	3.3	3.4	3.7	5.2
	Adequate	4.3	5.7	4.6	5.8
	Moderately adequate	4.1	5.4	4.4	5.6
	Inadequate	4.4	6.1	4.9	5.9
	p-value	**0.927**[1]		**0.480**[1]	
3 categories	Adequate	4.2	5.5	4.5	5.7
	Moderately adequate	4.1	5.4	4.4	5.6
	Inadequate	4.4	6.1	4.9	5.9
	p-value	**0.832**[1]		**0.508**[1]	
Levels of physical activity in 2011					
4 categories	Ideal			4.1	4.7
	Adequate			4.2	5.5
	Moderately adequate	N.A		4.2	5.4
	Inadequate			5.4	6.3
	p-value			**0.019**[1]	
3 categories	Adequate			4.2	5.4
	Moderately adequate	N.A		4.2	5.4
	Inadequate			5.4	6.3
	p-value			**0.009**[1]	

[1]Results of Kruskal Wallis test

In longitudinal analysis, statistically significant associations were seen in the level of physical activity and risk of deepened periodontal pockets ≥ 4mm (physical activity:4 categories, Model 1). In Model 2, the level of physical activity and number of teeth with deepened periodontal pockets ≥ 4mm showed a dose-response association such that decrease in physical activity increased the risk of deepened periodontal pockets ≥ 4mm. However, when slightly adjusted (Model 1) or more comprehensively adjusted (Model 3), there was no dose-dependent association. In Model 1 and Model 3, it was seen that participants engaging in other than ideal level of physical activity were at increased risk of deepened periodontal pockets ≥ 4mm. In Model 4, the risk of deepened periodontal pockets ≥ 4mm increased three times when dental behavioral factors (tooth brushing frequency, use of habitual dental services and number of teeth with plaque) were not taken into account (Table 9).

Statistically significant differences were seen in number of teeth with deepened periodontal pockets ≥ 4mm according to the level of physical activity (3 categories) of participants in slightly adjusted Poisson regression analysis. However, moderately adequate physical activity was found to be protective against risk of deepened periodontal pockets ≥ 4mm (Model 1, Table 9). The results remained statistically significant in model 2, showing increased risk of number of teeth with deepened periodontal pockets ≥ 4mm in those who were inadequately active. However, Model 3 and 4 showed decrease in the risk of deepened periodontal pockets ≥ 4mm in participants with inadequate physical activity (Table 9).

In order to understand the effect of tooth brushing frequency and regular dental checkup on periodontal pocketing, Poisson Regression Model slightly adjusted for age, gender and smoking were run separately. It showed that the risk of deepened periodontal pockets ≥ 4mm was 5 times more in subjects who brushed their teeth occasionally as compared to those who brushed twice a day (IRR= 5.9, 95% CI= 5.1- 6.9, $p<0.001$) . Similarly, the risk of deepened periodontal pockets ≥ 4mm was 6 times more in subjects who never used dental services compared to those who have used it regularly (IRR= 6.9 , 95% CI= 5.0- 9.5 , $p <0.001$).

Table 9 Association of physical activity in 2000 with number of teeth with deepened periodontal pockets ≥ 4mm in 2011.

Models	[1]Physical activity (4 categories)	IRR	95%CI	p-value	[2]Physical activity (3 categories)	IRR	95%CI	p-value
Model 1 n=1083	Ideal		(ref)		Adequate		(ref)	
	Adequate	1.4	1.2- 1.7	<0.001	Moderately adequate	0.9	0.7- 0.9	0.008
	Moderately adequate	1.1	1.0- 1.2	<0.423	Inadequate	1.1	1.0- 1.7	<0.001
	Inadequate	1.4	1.2- 1.6	<0.001				
Model 2 n=1079	Ideal		(ref)		Adequate		(ref)	
	Adequate	1.0	1.0- 1.2	0.432	Moderately adequate	1.3	1.2- 1.4	<0.001
	Moderately adequate	1.3	1.2- 1.6	<0.001	Inadequate	1.5	1.4- 1.7	<0.001
	Inadequate	1.6	1.4- 1.9	<0.001				
Model 3 n=935	Ideal		(ref)		Adequate		(ref)	
	Adequate	1.3	1.1- 1.6	<0.001	Moderately adequate	1.3	1.2- 1.4	<0.001
	Moderately adequate	1.7	1.4- 2.0	<0.001	Inadequate	1.1	1.0- 1.2	0.093
	Inadequate	1.4	1.1- 1.7	<0.001				
Model 4 n=971	Ideal		(ref)		Adequate		(ref)	
	Adequate	2.4	2.0- 2.9	<0.001	Moderately adequate	1.4	1.3- 1.5	<0.001
	Moderately adequate	3.0	2.5- 3.6	<0.001	Inadequate	1.3	1.2- 1.4	<0.001
	Inadequate	2.8	2.3- 3.4	<0.001				

[1]Physical activity (ideal=1(reference), adequate=2, moderately adequate=3, inadequate=4)
[2]Physical activity (ideal/adequate=1 (reference), moderately adequate=2, inadequate=3)

Model 1: Adjusted for age and gender in 2000
Model 2: Adjusted for age in 2000, gender, level of education in 2000, marital status in 2000
Model 3: Model 2 + smoking, alcohol consumption, tooth brushing frequency, use of habitual dental services, number of teeth with plaque, BMI, perceived health, use of medications (lipid lowering drugs, systemic corticosteroids, anti-inflammatory drugs and multi analgesics NSAIDs), diabetes mellitus, hypertension, rheumatoid arthritis and number of teeth with deepened periodontal pockets ≥ 4mm in 2000
Model 4: Model 3 excluding tooth brushing frequency, use of habitual dental services, number of teeth with plaque.

7 DISCUSSION

7.1 Principal findings

This study conducted on a sample of Finnish adult population found a statistically significant association between subjects performing other than ideal physical activity, having a higher risk of deepened periodontal pockets ≥ 4mm. Besides, cross-sectional analysis at baseline showed statistically significant difference in average number of teeth with deepened periodontal pockets ≥ 4mm between subjects with ideal and inadequate physical activity.

7.2 Findings relative to previous studies

Earlier, a longitudinal study conducted by Merchant *et al*. (2003) suggested that there was a reciprocal linear association between regular physical activity and risk of periodontitis, with men belonging to the highest quintile of physical activity had 13% less chances of developing periodontitis than those in the lowest quintile, irrespective of the known risk factors. However, that study included only men aged 40-75 years. The limitation of the study was that periodontitis was assessed on the basis of self-reported questionnaire as a dichotomous outcome. The result of another longitudinal study conducted by Iwasaki *et al*. (2018) on Japanese elderly subjects were also in agreement with current study. They reported that healthy lifestyle factors which included no smoking, sustained physical activity, healthy diet and BMI were associated with lowering the risk of periodontitis and tooth loss. But that study included only subjects who were 70 years of age and the predictor variables were not qualitatively assessed.

Over the past years, a few cross sectional studies have been done to find an association between physical activity and periodontitis indicating a positive association between enhanced physical activity and decreased prevalence of periodontitis (Wakai *et al*. 1999, Al-Zahrani *et al*. 2005a, Al-Zahrani *et al*. 2005b, Sanders *et al*. 2009, Bawadi *et al*. 2011). The findings of current study were consistent with a previous study by Bawadi *et al*. (2011) conducted on a random sample of 340 subjects who visited the medical center. The study suggested that lower level of physical activity and unhealthy diet played a significant role in the development of periodontitis.

There were also some cross-sectional studies that have suggested no association between physical activity and periodontitis (Sakki *et al*. 1995, Shizukuishi *et al*. 1998). One was

carried out in Finland, on 527 subjects aged 55 years, examining the relationship between periodontitis and lifestyle factors including physical activity (Sakki *et al*. 1995). The other study was done in Japan, on 310 factory workers, exploring the relationship between periodontitis and lifestyle (Shizukuishi *et al*. 1998). However, the sample size of both studies were small. In addition, the self reported questionnaire was unable to cover all the dimensions of physical activity.

Most of previous studies have examined physical activity as a component of lifestyle factors, considering dietary habits and BMI status as well. However, current study only examined risk of deepened periodontal pockets ≥ 4mm according to the level of physical activity performed by the subjects. Unlike most of previous studies, subjects who were physically active were taken as a reference group in this study. Both these factors might have impacted the observed results.

Current study found significant increase in risk of deepened periodontal pockets ≥ 4mm in 11 years time period. When ideal physical activity was taken as a cut-off point, all the subjects who did not belong to this category of physical activity had a higher risk of deepened periodontal pockets ≥ 4mm.

The inconsistent risk estimates might be a coincidental occurrence given the small sample size of the study. Moreover, the periodontal health was assessed on the basis of periodontal pocket depth measured at four sites, while only the deepest pockets were taken into account. This might have underestimated the true extent of periodontal disease. Besides, the information on physical activity was based on self-reported questionnaire. Misclassification could occur as a result of self-report of physical activity. The question on commuting physical activity could only distinguish between subjects physically active enroute to work than those physically inactive. A drawback of this would be underestimation of commuting physical activity. The question for leisure-time physical activity included in the analysis only measured the frequency of leisure-time physical activity. These might explain the fluctuating values of IRR seen in the result.

The dental behavioral determinants which included tooth brushing frequency, use of habitual dental services and number of teeth with plaque explained much of the association between physical activity and number of teeth with deepend periodontal pockets ≥ 4mm. When these

factors were not taken into account, then IRR increased to three times. This explained the positive role of regular tooth brushing, maintaining good oral hygiene and frequent dental checkups in decreasing the risk of periodontal pocketing.

Even though, previous studies have proposed the potential underlying mechanisms associating physical activity with periodontitis, however, they were not clearly understood. One of the probable pathophysiological mechanisms elucidating the protective action of physical activity against periodontitis was through enhancing insulin sensitivity and glucose metabolism. This ultimately manages diabetes mellitus type 2, which is an established risk factor of periodontitis. Secondly, the contraction of skeletal muscle during physical activity, works synergistically with insulin in mediating cellular uptake of glucose. This could be linked to better blood circulation as well as increased glucose transport into muscle cells, resulting in improved glucose homeostasis (Kilpelainen 2009, Wadén 2010).

Another underlying mechanism that might explain this association, was through the effective role of physical activity in reducing inflammation, a process involved in pathogenesis of periodontitis. Regular physical activity tends to decrease the concentrations of inflammatory biomarkers such as CRP, fibrinogen and IL-6 (Abramson & Vaccarino 2002, Lunde *et al*. 2017), hence protecting the periodontium.

7.3 Strengths and weaknesses

A unique strength of this study is its longitudinal design. This design is commonly used to investigate the causal association between exposure and occurrence of chronic diseases and to ascertain the temporality between exposure and outcome. This study explored the association between physical activity and status of periodontium over the course of time.

The previous two longitudinal studies have some restrictions with regards to gender and age, as one of the study included only men (Merchant *et al*. 2003) while the other was done on elderly subjects, aged 70 years (Iwasaki *et al*. 2018). However, the data for current study was taken from a survey of Finnish adult population, which was a representative sample adding to the strength of study.

The study evaluated sociodemographic, social and dental behavioral and other confounding variables used in past studies and have also adjusted for additional potential confounders in

data analysis, which reduced the risk of bias. Nonetheless, possibility of residual confounding that might happen due to unexplored confounding factors should not be ignored.

The participation rate in Health 2011 Survey was lower compared to Health 2000 Survey. In Health 2011 Survey, overall participation rate in oral clinical examination was 41% i.e. 38% in the southern and 45% in northern Finland. Since, oral clinical examination in follow-up survey was limited to southern and northern parts of Finland hence, the final sample size was small. This weakness in data collection might have impacted the results, giving conflicting risk estimates.

The data on physical activity was collected with the help of self-reported questionnaire. The reliability of self-reported physical activity was questionable due to recall bias, and potentially even social desirability bias. This might have resulted in misclassification among the categories of physical activity. However, it should be noted that this questionnaire on physical activity has strongly predicted morbidity and mortality in past studies.

7.4 Practical implications

The findings of this study pointed out that physical activity can be implicated in improving periodontal health. In order to prevent chronic oral diseases such as periodontitis and promote oral health, the dentists, public health community and policy makers should make a joint effort towards incorporating a holistic approach of promoting a healthy behaviour. A dentist can play his role by encouraging the patients to engage in recommended levels of physical activity, in addition to maintaining good oral hygiene. The benefits of this are not limited to improving periodontal health only, but are far reaching. This is because physical activity is a behavioral factor that has already been implemented as a preventive measure to address numerous chronic diseases including diabetes, heart conditions and obesity. Therefore, the risk factor for numerous outcomes can be targeted by promoting healthy physical activity.

7.5 Recommendations for future studies

On the basis of results of this study, it can be assumed that there is an association between unhealthy physical activity and increased risk of deepened periodontal pockets ≥ 4mm. Yet, because of the limitations of this study, it should be complemented with more longitudinal studies on a large sample and different population to demonstrate causality of association. Future studies can utilize the objective methods for measurement of physical activity. In

addition, more studies are required to investigate the underlying mechanism of association between physical activity and periodontitis.

8 CONCLUSION

This study investigated the association between level of physical activity and development of periodontal pocketing in a longitudinal setting among Finnish adults. Decreased levels of physical activity have statistically significant association with increased risk of of deepened periodontal pockets. This is consistent with the findings of many previous studies showing that less physical activity might be implicated in increasing the risk of periodontitis. The present study imparts to our interpretation of this association.

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