ASSOCIATION BETWEEN CHRONIC PERIODONTITIS AND HYPERTENSION AMONG THAI ADULTS

Miss Ploysiri Rassamee

A Thesis Submitted in Partial Fulfillment of the Requirements

for the Degree of Master of Science in Periodontics

Department of Periodontology

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ความสัมพันธ์ระหว่างโรคปริทันต์อักเสบชนิดเรื้อรังกับโรคความดันโลหิตสูงในกลุ่มผู้ใหญ่ไทย

น.ส.พลอยศิริ รัศมี

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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By	Miss Ploysiri Rassamee
Field of Study	Periodontics
Thesis Advisor	Professor RANGSINI MAHANONDA, Ph.D.
Thesis Co Advisor	Associate Professor KITTI TORRUNGRUANG, Ph.D.

Accepted by the Faculty of Dentistry, Chulalongkorn University in Partial Fulfillment of the Requirement for the Master of Science

.....Dean of the Faculty of Dentistry

(Assistant Professor SUCHIT POOLTHONG, Ph.D.)

THESIS COMMITTEE

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(Assistant Professor CHANTRAKORN CHAMPAIBOON, Ph.D.)

.....Thesis Advisor

(Professor RANGSINI MAHANONDA, Ph.D.)

.....Thesis Co-Advisor

(Associate Professor KITTI TORRUNGRUANG, Ph.D.)

.....External Examiner

(Associate Professor THOSAPHOL LIMPIJANKIT)

พลอยศิริ รัศมี : ความสัมพันธ์ระหว่างโรคปริทันต์อักเสบชนิดเรื้อรังกับโรคความดันโลหิตสูงในกลุ่มผู้ใหญ่ไทย. (ASSOCIATION BETWEEN CHRONIC PERIODONTITIS AND HYPERTENSION AMONG THAI ADULTS) อ.ที่ปรึกษาหลัก : ศ. ทญ. ดร.รังสินี มหานนท์, อ.ที่ปรึกษาร่วม : รศ. ทพ. ดร.กิตติ ต.รุ่งเรือง

เนื่องจากมีการศึกษาพบว่าโรคปริทันต์อักเสบอาจส่งผลเพิ่มความเสี่ยงต่อการเกิดโรคความดันโลหิตสูง แต่ยังขาดข้อมูลสนับสนุนจากการศึกษาทางระบาดวิทยาในกลุ่มประชากรขนาดใหญ่ งานวิจัยครั้งนี้ศึกษาความสัมพันธ์ระหว่างโรคปริทันต์อักเสบและโรคความดันโลหิตสูงในกลุ่มพนักงานการไฟฟ้าฝ่ายผลิตแห่งประเทศไทย (EGAT) จำนวน 1,378 คน ช่วงอายุ 53-73 ปี จากการตรวจสภาวะปริทันต์สามารถแบ่งเป็น 3 กลุ่มตามระดับความรุนแรงของโรคปริทันต์คือระดับน้อย ระดับปานกลางและระดับรุนแรง ส่วนโรคความดันโลหิตสูงใช้เกณฑ์ค่าเฉลี่ยความดันโลหิตซีสโตลิคตั้งแต่ 140 มิลลิเมตรปรอทขึ้นไป หรือมีค่าเฉลี่ยความดันโลหิตไดแอสโตลิตตั้งแต่ 90 มิลลิเมตรปรอทขึ้นไป หรือได้รับยารักษาโรคความดันโลหิตสูง ผลการวิเคราะห์ข้อมูลพบว่าโรคปริทันต์อักเสบระดับรุนแรงมีความสัมพันธ์กับการเพิ่มความเสี่ยงโรคความดันโลหิตสูงอย่างมีนัยสำคัญทางสถิติ โดยมีค่า odds ratio เป็น 1.55 (95% CI: 1.03-2.33, $P = 0.035$) ภายหลังการควบคุมปัจจัยที่ส่งผลต่อโรคความดันโลหิตสูงได้แก่ อายุ เพศ ระดับการศึกษา โรคเบาหวาน การสูบบุหรี่ การบริโภคเครื่องดื่มที่มีแอลกอฮอล์ ความถี่การออกกำลังกาย โรคอ้วน ไตรกลีเซอไรด์ในเลือดสูงและคลอเรสเตอรอลในเลือดสูง ข้อสรุปจากการศึกษาประชากรไทยวัยผู้ใหญ่กลุ่มนี้พบว่าโรคปริทันต์อักเสบระดับรุนแรงสัมพันธ์กับการเพิ่มความเสี่ยงต่อโรคความดันโลหิตสูง อย่างไรก็ตามยังคงต้องการข้อมูลเพิ่มเติมจากการศึกษาระบาดวิทยาระยะยาว

สาขาวิชา ปริทันตศาสตร์ ลายมือชื่อนิสิต .....

ปีการศึกษา 2561 ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

ลายมือชื่อ อ.ที่ปรึกษาร่วม .....

5975830132 : MAJOR PERIODONTICS

KEYWORD: Periodontitis, hypertension, high blood pressure, Thai adults, epidemiological study, cross-sectional study

Ploysiri Rassamee : ASSOCIATION BETWEEN CHRONIC PERIODONTITIS AND HYPERTENSION AMONG THAI ADULTS . Advisor: Prof. RANGSINI MAHANONDA, Ph.D. Co-advisor: Assoc. Prof. KITTI TORRUNGRUANG, Ph.D.

Previous studies suggest that periodontitis may be associated with an increasing risk of hypertension. However, data from large epidemiological studies are limited. The aim of this cross-sectional study was to examine the association between periodontitis and hypertension using data from a cohort study in a Thai population. The study population comprised of 1,378 employees of the Electricity Generating Authority of Thailand (EGAT), aged 53 to 73 years old, were categorized into no/mild, moderate, or severe periodontitis groups. Hypertension was determined as having systolic blood pressure 140 mmHg or more or diastolic blood pressure 90 mmHg or more, or taking antihypertensive medication. The results of multivariate analysis, after adjusting confounders including age, gender, education level, diabetes mellitus, smoking status, alcohol consumption, frequency of exercise, obesity, hypertriglyceridemia, and hypercholesterolemia, there was a significant association between severe periodontitis and hypertension with an odds ratio of 1.55 (95% CI: 1.03-2.33; *P* = 0.035). In conclusion, severe periodontitis was associated with an increasing risk of hypertension in this group of Thai adults. However, further longitudinal epidemiological studies are needed.

Field of Study: Periodontics

Academic Year: 2018

Student's Signature .....

Advisor's Signature .....

Co-advisor's Signature .....

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Ploysiri Rassamee

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LIST OF ABBREVIATIONS

A. actinomycetemcomitans	*Aggregatibacter actinomycetemcomitans*
AAP	American Academy of Periodontology
AME	Apparent mineralocorticoid excess
BMI	Body mass index
BOP	Bleeding on probing
CAL	Clinical attachment level
CD	Cluster of differentiation
CDC/AAP	Centers for Disease Control and Prevention/ American Academy of Periodontology
CEJ	Cemento-enamel junction
cm	Centimeter
CNS	Central nervous system
CPI	Community Periodontal Index
CPITN	Community Periodontal Index of Treatment Needs
CRP	C-reactive protein
CVDs	Cardiovascular diseases
DBP	Diastolic blood pressure
EGAT	Electricity Generating Authority of Thailand
EGFR	Estimated glomerular filtration rate
ET	Endothelin receptor
FMD	Flow mediated dilation
GRA	Glucocorticoid-remediable aldosteronism
GTR	Guided tissue regeneration
HDL	High-density lipoprotein
HT	Hypertension

IFN-γ	Interferon gamma
IL	Interleukin
kg/m^2	Kilogram per square meter
L	Liter
LDL	Low-density lipoprotein
LPS	Lipopolysaccharide
mg/dl	Milligram per deciliter
mg/L	Milligram per Liter
mm	Millimeter
mmol/L	Millimoles per Liter
Mo	Mobility
NADPH	Nicotinamide adenine dinucleotide phosphate
NO	Nitric oxide
P. gingivalis	*Porphyromonas gingivalis*
PD	Probing depth
PDSI	Periodontal severity index
PI	Plaque index
PSD	Polymicrobial Synergy and Dysbiosis
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SD	Standard deviation
S-OHI	Simplified oral hygiene index
T. forsythia	*Tanerella forsythia*
TNF-α	Tumor necrosis factor alpha
WBC	White blood cell
WC	Waist circumference
WHO	World Health Organization

CHAPTER I

INTRODUCTION

1. Background and rationale

Hypertension is a major risk factor for cardiovascular diseases (CVDs), leading to premature death and disability (Chobanian et al., 2003). The prevalence of hypertension has been rising worldwide (Kearney et al., 2005). In Thailand, one out of four adults or around 10 million people have hypertension and almost half of these individuals are unaware of their conditions (World Health Organization Thailand, 2017). Hypertension is a multifactorial disease (Oparil, Zaman, and Calhoun, 2003). Several dietary and lifestyle factors, as well as chronic inflammation, have been implicated as risk factors for hypertension (De Miguel et al., 2015).

Periodontitis is a disease of the tooth supporting tissues, caused by host immuno-inflammatory response to subgingival plaque (Kornman, 2008). The disease is characterized by chronic inflammation and destruction of the periodontal connective tissue and alveolar bone. It has been hypothesized that periodontitis may be associated with an increased risk for hypertension (Tonetti and Van Dyke, 2013). This may be partly attributed to the fact that periodontitis is associated with elevated levels of systemic inflammatory markers such as C-reactive proteins (CRP), fibrinogen, and white blood cells (Tsioufis et al., 2011). These inflammatory markers are known to be related to endothelial dysfunction and dysregulation of blood pressure control (Amar et al., 2003). However, results from epidemiological studies of the association between periodontitis and hypertension remain inconclusive. The majority of studies supported a positive association (Iwashima et al., 2014; Rivas-Tumanyan et al., 2013) whereas others failed to observe the association (Nesse et al., 2010; Ollikainen et al., 2014). Moreover, there are limited data from large scale epidemiological studies, particularly in Asian

populations (Choi et al., 2015; Kawabata et al., 2016). Most of these large scale studies also have methodological flaws such as inadequate adjustment for potential confounders (Choi et al., 2015) or the use of the community periodontal index (CPI) (Choi et al., 2015; Iwashima et al., 2014; Kawabata et al., 2016; Nesse et al., 2010), which has been shown to underestimate the prevalence of periodontitis (Nesse et al., 2010). To date, there have not been any epidemiological studies that examine the association between these two diseases in Thai population.

2. Objective

To examine the association between periodontitis and hypertension using data from a cohort study in a Thai population.

3. Hypothesis

Moderate or severe chronic periodontitis is related to diagnosis of hypertension.

4. Field of research

Epidemiological study/Cross-sectional study

5. Inclusion criteria

Employees of the Electricity Generating Authority of Thailand (EGAT) who worked at the EGAT headquarters in Nontaburi were included in this study. Participants who were at risk from bacterial endocarditis or hematogenous total joint infection, or were undergoing hemodialysis were excluded (Torrungruang et al., 2005). These individuals had to take antibiotic prophylaxis before periodontal examinations.

6. Application and expectation of research

This will be the first study that provides a link for the association between chronic periodontitis and hypertension in Thai adults. The better awareness of periodontal health in hypertensive patients will be achieved public health goals.

7. Keywords

Periodontitis, hypertension, high blood pressure, Thai adults, epidemiological study, cross-sectional study

CHAPTER II

REVIEW LITERATURE

1. Chronic periodontitis

1.1. Periodontitis and its impact on global health

The Global Burden of Disease Study in 2010 ranked severe periodontitis as the sixth-most prevalent disease in the world, affecting 11.2% (743 million people) worldwide (Kassebaum et al., 2014). In Thailand, severe periodontitis has been recognized as the main oral health problem among adults (age 35-59) and, in particular, elderly people (age 60 and over). The number of elderly Thais has been expected to grow from 16% in 2015 to 37% in 2050 (สำนักทันตสาธารณสุข กรมอนามัย กระทรวงสาธารณสุข, 2013). Importantly, recent epidemiology data suggest that periodontitis may associate with the major non-communicable diseases such as cardiovascular disease, cancer, chronic respiratory disease, diabetes and autoimmune disorders, all of which have become the leading cause of death in global population (Linden and Herzberg, 2013). In addition, patient with severe form of periodontitis can suffer from teeth loss that negatively affect their quality of life (Petersen and Ogawa, 2012). Therefore, the need of global action in prevention, detection and care is necessary in promoting periodontal health and general wellbeing worldwide (Tonetti et al., 2017).

1.2. Dental plaque bacteria and chronic immune responses

Etiology of periodontal disease is dental plaque biofilm, adhering to tooth and root surfaces and the majority of which are the bacteria. The disease mechanisms involve host immune response to dental plaque bacteria and their products. Periodontal disease begins with gingivitis (mild form), the localized inflammation of the gingiva with no bone loss. A severe form called periodontitis occurs when untreated gingivitis progresses to the loss of the gingiva, bone and ligament, which creates the deep

periodontal 'pockets' and bone resorption that are a hallmark of periodontitis and can eventually lead to tooth loss (Kornman, 2008; Page and Schroeder, 1976).

Progression from health/gingivitis to periodontitis are associated with the shift of microbial plaque component from Gram-positive commensal bacteria to Gram-negative pathogenic bacteria. Commensal bacterial colonization prevents the pathogenic bacterial colonization which keep steady/healthy state of gingiva. Whereas the specific group of Gram-negative bacteria with virulent factors: *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, and *Tanerella forsythia* were proposed in the 1996 international workshop of the American Academy of Periodontology (AAP) as 2 key periodontal pathogens causing human periodontitis. This traditional concept has recently challenged by a new paradigm of periodontitis progression: a theory of "Polymicrobial Synergy and Dysbiosis (PSD)" (Lamont and Hajishengallis, 2015). This theory proposes that bacterial dysbiosis (imbalance of microbial biofilm) could disrupt homeostasis of the periodontal tissue. Keystone pathogen(s) such as *P. gingivalis* and *T. forsythia* could impede the host's immune response and boost the pathogenic potent of the whole bacterial plaque community, therefore promoting inflammation and destruction of periodontal tissues.

Like other infectious diseases, periodontitis is multi-factorial in nature. Genetics and environmental factors such as smoking and stress can influence disease initiation and severity (AlJehani, 2014).

Periodontitis inflammation is associated with large infiltration of plasma cells and memory T cells and secretion of inflammatory cytokines (Kinane, Stathopoulou, and Papapanou, 2017; Mahanonda et al., 2016). Expression of IL-17 and IFN-γ has been detected in CD4+ T cells isolated from periodontitis tissue (Dutzan et al., 2016). Recent findings suggest that healthy gingiva contains two memory T cell populations; a CD69- recirculating population and a CD69+ gingiva-resident memory T cell population.

Interestingly, a significant increase in the proportion of CD4+CD69+ CD103- memory T cells was observed in periodontitis tissues compared with healthy gingiva (Mahanonda et al., 2018). Cytokine production from this subset of memory T cells may be responsible for tissue damage and bone loss in periodontitis. Further investigation to characterize memory T cell antigen specificity, the role of subgingival plaque bacteria, and specific tissue signals that promote the localization of recirculating and gingiva-resident memory T cells will provide insights into how the gingival immune response operates in health and disease.

1.3. Treatment of periodontitis

Periodontal treatment involves removal of etiologic agent-dental plaque biofilm by non-surgical debridement (scaling and root planning) and/or access periodontal surgery in order to stop the disease progression and prevent tooth loss. While these treatments can result in elimination of periodontal inflammation, however regeneration of lost periodontal tissue does not occur. The ultimate goal of periodontal treatment continues to be regeneration of the attachment structures of teeth including bone, periodontal ligament and cementum, which have been destroyed by periodontal diseases. Attempts to regenerate the bone and adjacent structures in periodontal defects by various surgical techniques such as guided tissue regeneration (GTR) and bone grafts have historically met with only modest and unpredictable success (Bartold et al., 2016; Chen and Jin, 2010).

1.4. Assessment of periodontal conditions

Periodontal conditions can be assessed routinely by determining the quality and quantity of attachment level of periodontal supporting tissues including gingival connective tissues, periodontal ligament and alveolar bone. The information can be collected by both clinical and radiographic examinations. In normal periodontal condition, the gingival tissue is absence of inflammation, the margin is approximately

located at the level of cemento-enamel junction (CEJ), the gingival sulcus depth is less than 3 mm, and the alveolar bone crest is intact and located average 2 mm from CEJ (Lang and Bartold, 2018). As disease progresses from normal to gingivitis, the gingival margin becomes thicken and turns into redness, which are the signs of inflammation. In more severe form of periodontal diseases, the inflammation extends beyond gingival tissues and results in connective tissue and bone destruction. The gingival sulcus is pathologically deepened and become periodontal pocket (figure 1). The formation of periodontal pocket is clinically measured as probing depth (PD) using instrument called periodontal probe (figure 2: left).

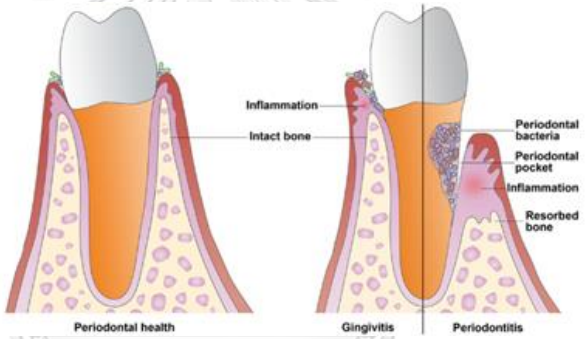

Figure 1: Normal periodontal condition (periodontal health), gingivitis and periodontitis; modified from (Ren and Du, 2017).

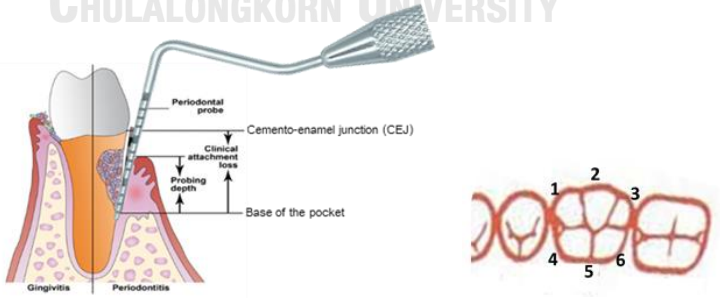

Figure 2: (Left) Periodontal probe, and the measurements of probing depth and clinical attachment loss; modified from (Ren and Du, 2017). (Right) The six sites of periodontal recording: 1 = mesio-buccal; 2 = mid-buccal; 3 = disto-buccal; 4 = mesio-lingual; 5 = mid-lingual; and 6 = disto-lingual.

PD is the distance between the gingival margin and the base of the periodontal pocket (figure 2). The depth of penetration of the probe can reflect the amount inflammation and destruction of tissues underneath (Greenstein, 2005). The measurement of PD is performed by gently inserting periodontal probe into gingival sulcus, positioned parallel to the long axis of the tooth surface, moved circumferentially and recorded at six sites per tooth (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual and disto-lingual) (Preshaw, 2015) (figure 2: right). The deeper PD sites are related to the greater connective tissue and bone destruction. The deeper PD sites (>5 mm) are related to higher levels of periodontal bacteria such as *P. gingivalis*, A. *actinomycetemcomitans* compared to PD sites <3 mm (Wolff, Dahlen, and Aeppli, 1994). The limitation of PD is that PD may change over time as the result of changes in the position of the gingival margin rather than the true alteration of the existing periodontal attachment. Therefore, CAL measurement has been suggested and used along with PD as a gold standard across the studies since it is better related to past disease activity, or history of periodontal destruction (AAP, 2003). Clinically, CAL is the distance between CEJ (the fixed point on the tooth) and the base of the pocket (figure 2: left).

There is no solid case definition to classify the severity of periodontitis for the purpose of epidemiological study. Many population-based studies used Community Periodontal Index (CPI) or Community Periodontal Index of Treatment Needs (CPITN), which was developed by World Health Organization (WHO) (Ainamo et al., 1982). This index has the advantages of less time consuming for data collection and easy to perform. However, this index also has limitations include that it assesses PD only and does not provide any information on loss of attachment. Furthermore, it only records the most severe score in each sextant and therefore does not provide full information about disease extent and severity in advanced cases (Baelum and Papapanou, 1996). To

overcome this problem, the Center for Disease Control and Prevention and the American Academy of Periodontology (CDC/AAP) proposed the case definitions which use PD along with CAL and classify severity of periodontitis into no/mild or moderate or severe form (Table1) (Page and Eke, 2007). This classification defines the disease by determining the thresholds of PD and CAL, and the number of affected sites which provide suitable estimates of the prevalence of periodontitis (Page and Eke, 2007).

Table 1: Case definitions proposed for population-based surveillance of periodontitis by CDC/AAP; CAL = Clinical Attachment Level, PD = Probing Depth, and mm = millimeter (Page and Eke, 2007).

Disease Category	Clinical Definition		
	CAL		PD
Severe periodontitis	≥2 interproximal sites with CAL ≥6 mm (not on same tooth)	and	≥1 interproximal site with PD ≥5 mm
Moderate periodontitis	≥2 interproximal sites with CAL ≥4 mm (not on same tooth)	or	≥2 interproximal site with PD ≥5 mm (not on same tooth)
No/mild periodontitis	Neither "moderate" nor "severe" periodontitis		

1.5. Possible link between periodontitis and systemic inflammation

A relationship between oral diseases, including periodontitis, and systemic diseases has been studied for many years (Hunter, 1921; Scannapieco, 1998). In addition to Diabetes which is well accepted as a true risk factor for periodontitis and vice versa (Preshaw et al., 2012), the association between periodontitis and a number of other systemic diseases including respiratory disease (Garcia, Nunn, and Vokonas, 2001; Scannapieco, Bush, and Paju, 2003), chronic kidney disease (Iwasaki et al., 2012), rheumatoid arthritis (de Pablo et al., 2009), cognitive impairment (Kaye et al., 2010), obesity (Chaffee and Weston, 2010), metabolic syndrome (Morita et al., 2010) and cancer (Arora et al., 2010) has been suggested. However, the actual biological

mechanisms linking between periodontitis and remote organs are unclear. Two possible pathogenic mechanisms have been described to explain how periodontitis could contribute to systemic diseases:

1.5.1. Direct mechanism

As chronic periodontitis progresses, the pocket epithelium becomes ulcerated providing a direct entry point for periodontal bacteria or their by-products, especially Gram-negative bacteria into the systemic circulation. Then circulating bacteria could have direct effects on certain organ tissues. As seen in patients with acute myocardial infarction, periodontal bacteria such as *A. actinomycetemcomitans, P. gingivalis*, and *Treponema denticola* were detected in their thrombi. This raises the possibility that these bacteria might have a role in atheromatous plaque inflammation and instability (Ohki et al., 2012). Moreover, the incidence of bacteremia after periodontal probing and periodontal treatments including scaling, root planing, subgingival irrigation, and periodontal surgery has been documented (Daly et al., 2001; Kinane et al., 2005; Lineberger and De Marco, 1973; Lofthus et al., 1991). The data from systematic review demonstrated that 49.4% patients had positive bacteremia after these periodontal procedures. The bacteria that frequently found in blood circulation were *Streptococcus viridans*, *A. actinomycetemcomitans*, *P. gingivalis*, *Micromonas micros*, *Streptococcus* species and *Actinomyces* species (Horliana et al., 2014)

1.5.2. Indirect mechanism

The inflammatory response to periodontal bacteria or their by-products may have indirect systemic effects. It is well recognized that chronic periodontitis represents a source of chronic inflammation that may be a significant contributing factor in the pathogenesis of other inflammatory based diseases. Systemic inflammation and increased circulating proinflammatory mediators and cytokines have been found in patients with periodontitis (D'Aiuto et al., 2004)). The level of C-reactive protein (CRP), an accepted parameter for measuring systemic inflammation in individuals, for example, is elevated in periodontitis subjects (Pepys and Hirschfield, 2003). A meta-analysis of 18

case-control studies has reported that subjects with periodontitis have higher serum CRP concentrations by 1.56 mg/L compared to controls (Paraskevas, Huizinga, and Loos, 2008). In addition, serum levels of other inflammatory markers such as IL-6, IL-10 and TNF-α are elevated in patients with periodontitis, when compared to healthy controls (Loos et al., 2000).

2. Hypertension

Hypertension is a chronic medical condition which the blood pressure in the arteries is elevated in excess of normal range for a person's age and sex. It is a major risk factor for cardiovascular disease (CVD), leading to premature death and disability (Chobanian et al., 2003). The prevalence of hypertension has been rising worldwide (Kearney et al., 2005). In Thailand, one out of four adults or around 10 million people have hypertension and almost half of these individuals are unaware of their conditions (World Health Organization Thailand, 2017). Hypertension is a multifactorial disease (Oparil, Zaman, and Calhoun, 2003). Several dietary and lifestyle factors, as well as chronic inflammation, have been implicated as risk factors for hypertension (De Miguel et al., 2015).

2.1. Blood pressure classification/hypertension criteria

The classification of blood pressure from the guideline of the Seventh Joint National Committee (JNC7) report for adults 18 years and older are in following Table 2. The classification is based on the average of two or more properly measured, seated, and blood pressure readings on each of two or more office visits (Chobanian et al., 2003).

Table 2: Classification of blood pressure for adults; SBP = systolic blood pressure, DBP = diastolic blood pressure (JNC7) (Chobanian et al., 2003).

Blood pressure classification	SBP (mmHg)		DBP (mmHg)
Normal	<120	and	<80
Prehypertension	120-139	or	80-89
Stage1 Hypertension	140-159	or	90-99
Stage2 Hypertension	≥160	or	≥100

The JNC7 has introduced a new classification that includes the term prehypertension for those with blood pressures ranging from 120-139 mmHg systolic and/or 80-89 mmHg diastolic. Prehypertension is not a disease category. Rather, it is a designation chosen to identify individuals at high risk of developing hypertension. Patients who are altered to this risk, they will be encouraged to intervene and prevent or delay the disease from developing. Individual who are prehypertensive are not candidates for drug therapy based on their level of blood pressure and should be firmly and unambiguously advised to practice lifestyle modification in order to reduce their risk of developing hypertension in the future. Moreover, this report suggests that all people with hypertension (stage1 and 2) need to be treated. The treatment goal for individuals with hypertension and no other compelling conditions is less than 140/90 mmHg. The goal for individuals with prehypertension and no compelling indications is to lower blood pressure to normal levels with lifestyle changes, and prevent the progressive rise in blood pressure using the recommended lifestyle modifications (Chobanian et al., 2003).

2.2. Blood pressure measurement methods

The arterial blood pressure in humans is routinely measured by the auscultatory method. A mercury sphygmomanometer is preferred and an acceptable alternatives include a recently calibrated aneroid manometer or a validated electronic device

attached to an arm cuff (Carretero and Oparil, 2000). The guideline of the JNC7 report suggests that patients should be seated quietly at least 5 minutes in a chair (rather than on an examination table), with feet on the floor, and arm supported at heart level. Caffeine, exercise, and smoking should be avoided at least 30 minutes prior to measurement. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. At least 2 measurements should be made and the average record. For manual determinations which palpated radial pulse obliteration pressure should be used to estimate systolic blood pressure. The cuff should then be inflated 20 to 30 mmHg above this level for the auscultatory determinations and the cuff deflation rate for auscultatory readings should be 2 mmHg per second. Systolic blood pressure is the point at which the first of two or more Korotkoff sounds is heard, and the disappearance of Korotkoff sound is used to define diastolic blood pressure (Chobanian et al., 2003).

2.3. Pathogenesis of hypertension

Like periodontitis, hypertension is a multifactorial disease. It is resulted from a complex interaction of genetic, environmental, and demographic factors. Many pathophysiologic factors (Figure 3) have been implicated in the genesis of essential hypertension. However, a major pathophysiologic mechnisms of hypertension include activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (Oparil, Zaman, and Calhoun, 2003).

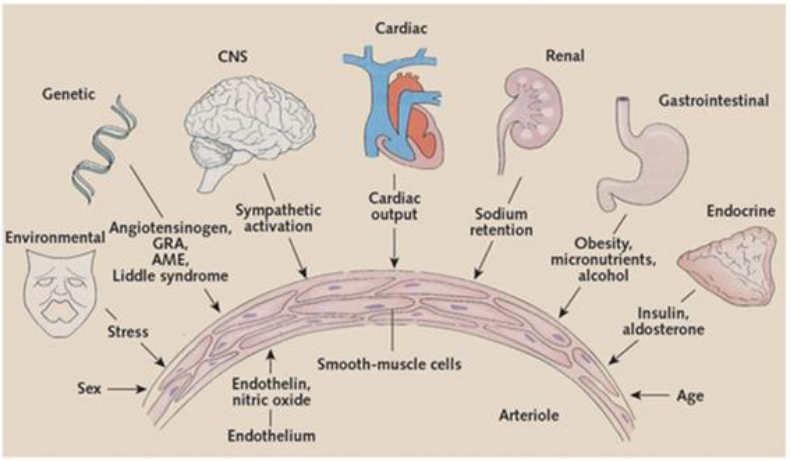

Figure 3: Pathophysiologic mechanisms of hypertension; AME = apparent mineralocorticoid excess, CNS= central nervous system, GRA= glucorticoid-remediable aldosteronism) (Calhoun, Bakir, and Oparil, 2000).

Moreover, the structural and functional abnormalities in the vasculature, which decreasing vascular compliance, including endothelial dysfunction, increased oxidative stress and arterial stiffness, may predispose to hypertension and contribute to its pathogenesis (Oparil, Zaman, and Calhoun, 2003).

- **Endothelial dysfunction**

Function of normal endothelial cells in response to various stimuli, including changes in blood pressure, shear stress, and pulsatile stretch, is releasing nitric oxide (NO). NO is a potent *vasodilator, inhibitor* of platelet adhesion and aggregation, and *suppressor* of migration and proliferation of vascular smooth-muscle cells. It also plays an important role in blood pressure regulation, thrombosis, and atherosclerosis (Cai and Harrison, 2000). The cardiovascular system in healthy persons is exposed to continuous NO-dependent vasodilator tone, but NO-related vascular relaxation is diminished in hypertensive persons (Figure 4) (Panza, 2001).

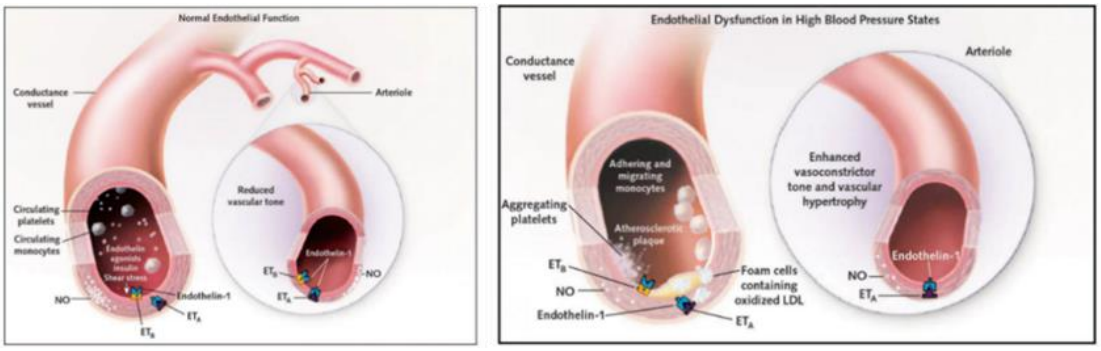

Figure 4: Endothelial function in the normal vasculature (left) and in the hypertensive vasculature (right) (Panza, 2001).

In normal conductive arteries platelets and monocytes circulate freely, and oxidation of low-density lipoprotein is prevented by NO formation. At the level of sm all arterioles, reduces vascular tone is maintained by constant release of NO. Endothelin-1, a potent vasoactive peptide produced by endothelial cells, normally induces no or only minimal vasoconstriction through stimulation of type A endothelin receptor (ET_A) located on smooth-muscle cells and contributes to basal NO release by stimulating type B endothelin receptors (ET_B) on endothelial cells (Figure 4: left). In the hypertensive microvasculature, decreased activity of NO and enhanced ET_A-mediated vasoconstrictor activity of endothelin-1 result in increased vascular tone and medial hypertrophy, with a consequent increase in systemic vascular resistance (Figure 4: right) (Panza, 2001).

- **Increased oxidative stress**

Long-term infusion of angiotensin II is linked to the upregulation of vascular p22phox messenger RNA, a component of the oxidative enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Fukui et al., 1997). The angiotensin II receptor-dependent activation of NADPH oxidase is associated with enhanced formation of the oxidant superoxide anion ($\cdot O_2^-$). Superoxide readily reacts with NO to

form the oxidant peroxynitrite ($ONOO^-$). Leading a reduction in NO bioactivity which enhances vasoconstrictor response in hypertension (Rajagopalan et al., 1996).

- **Arterial stiffness**

Systolic blood pressure and pulse pressure increase with age mainly because of reduced elasticity of the large conduit arteries. Atherosclerosis in these arteries resulted from collagen deposition and changes of smooth-muscle cells such as hypertrophy, thinning, fragmenting, and fracture of elastin fibers (O'Rourke, Hayward, and Lehmann, 2000). Increasing wall thickness relates to loss of endothelial function , which may reduce NO synthesis or releasing, which can increase systolic blood pressure (Safar, 1999).

3. The association between chronic periodontitis and hypertension

The association between periodontitis and hypertension has been suggested for many years. However, the results remain inconclusive. The example of 14 association studies have been summarized in Table 3. Most of these studies are cross-sectional design and used CPI/CPITN or a percentage of sites of PD and/or CAL for periodontal status criteria. The recent data from the systematic review and meta-analysis revealed that periodontitis is associated with a higher risk of hypertension especially in severe form of disease (OR = 1.64: 95%CI, 1.23-2.19) (Martin-Cabezas et al., 2016). This analysis included mostly cross-sectional studies, 3 case-control studies, and 2 longitudinal studies. Regarding their limitations, there were the lack of prospective study, the heterogeneity among studies populations, and the difference of the diagnosis criteria of periodontitis and hypertension (Martin-Cabezas et al., 2016).

A potential influence of periodontitis on hypertension may be explained by common risk factors such as common susceptibility (genetic factors), smoking, stress,

Table 3: Previous studies of association between periodontitis and hypertension

Study	Type	Population	N	Age (years)	Periodontal Assessment	Hypertension Assessment	Adjustment	Main findings
(Ogawa et al., 1998)	Cross-sectional	Male, Japanese factory workers	2,000	>18	CPITN	- Measurement - HT treatment	-	- Higher CPITN in subjects with HT (P <0.005) - In regression analysis, SBP associated with CPTIN in non-smoking without HT.
(Angeli et al., 2003)	Cross-sectional	Untreated hypertension	104	57	CPITN	SBP ≥140 or DBP ≥90 mmHg in 3 different visits over 1 month, echocardiography	-	- Increasing BP with increased periodontal severity (P <0.01 for DBP, P <0.01 for SBP) - In multiple logistic regression, only left ventricular mass showed association with moderate to severe periodontitis (P <0.0001).
(Buhlin et al., 2003)	Cross-sectional (case-control)	Severe Periodontitis (N = 50) Control (N = 47)	96	52.7 50.2	PD, BOP, PI, x-ray	- Measurement	-	- No difference of BP between groups with and without periodontitis. - Severe periodontitis (≥7 sites of PD ≥6mm) ; associated with lower HDL (P = 0.007), higher total cholesterol /HDL (P = 0.03), elevated monocytes count (0.56/0.44 x10^9/L, P = 0.002), higher CRP levels (low correlation with BOP (R = 0.26, P = 0.02), number of PD (R = 0.27, P = 0.01) ; associated with HDL (OR = 2.15 for 0.5 mmol/l, P = 0.02), with BMI (OR = 4.54, P = 0.005)

Study	Type	Population	N	Age (years)	Periodontal Assessment	Hypertension Assessment	Adjustment	Main findings
(Inoue et al., 2005)	Cross-sectional at 2 times point (2002, 2003)	Japanese manufacturing workers (apparently healthy)	424	20-59 39.8	PD, BOP, CPTIN	- Measurement - HT treatment	Gender, age, BMI, smoking, drinking, HT, DM, WBC count	- **No significantly difference** in HT prevalence (P = 0.28). - Higher SBP of 6 mmHg (P = 0.003), higher DBP of 3.4 mmHg (P = 0.017) in the periodontitis group compared to controls (at baseline) - Higher WBC counts ($0.6x10^3$/ml, P = 0.005)
(Holmlund, Holm, and Lind, 2006)	Retrospective cross-sectional	Periodontal pt. and dental health survey participants	4,254	53	PI, PD, BOP, Mo, bone loss, PDSI	HT treatment	Age, gender, smoking, number of teeth	OR = 1.32; 95% CI 1.13-1.54 for HT with increasing severity of periodontitis (P <0.0005)
(D'Aiuto et al., 2006)	Prospective interventional RCT	Severe PD; ≥50% dentition with PD >4 mm, bone level (x-ray)	40	48	BOP, PD, x-ray, severe periodontitis case definition	Measurement at baseline and 2, 6 months after treatment	-	Decreasing SBP by 7 ± 3 mmHg with intensive (local minocycline 80 mg at treatment session) compared to standard PD treatment after 2 months (P = 0.02)
(Engstrom et al., 2007)	Cross-sectional	HT and matched controls (age, gender, tobacco used)	1,239	35-65	PD	SBP ≥140 or DBP ≥90 mmHg or HT treatment	Age, gender, tobacco, number of teeth,	DBP associated with prevalence of deep PD (PD ≥5 mm)

Study	Type	Population	N	Age (years)	Periodontal Assessment	Hypertension Assessment	Adjustment	Main findings
(Desvarieux et al., 2010)	Cross-sectional Data (INVEST)	General, HT 62%	653	>55	Subgingival plaque, samples-quantification of etiologic, putative and health associated bacteria, PD, CAL	SBP ≥140 or DBP ≥90 mmHg or HT treatment	Age, gender, ethnicity, education, BMI, smoking, DM, LDL-, HDL-cholesterol	- There was an association between levels of subgingival periodontal bacteria and increasing BP and prevalence of HT. - By increasing SBP 9 mmHg or increasing DBP 5 mmHg (P <0.001). - OR for prevalence of HT = 3.13 (95% CI: 1.62-6.03, P <0.001)
(Tsakos et al., 2010)	Cross-sectional	USA, general	13,994	>17	Page and Eke, 2007	SBP ≥140 or DBP ≥90 mm Hg or HT treatment	Age, gender, ethnicity, CRP, creatinine, Na^+/K^+ ratio, chronic conditions, smoking, alcohol, BMI, education level, income	- Increasing SBP by 0.5 mmHg (95% CI: 0.3-0.6, P <0.001) - Only 10% increasing of BOP had 1.1 times higher odds in having HT (95% CI: 1.0-1.1, P <0.05).

Study	Type	Population	N	Age (years)	Periodontal Assessment	Hypertension Assessment	Adjustment	Main findings
(Morita et al., 2010)	Cohort study (2002-2006)	Japanese adult employees	1,023	20-56 (37.3)	CPI score 3-4 (periodontal pockets ≥4 mm	SBP ≥130 or DBP ≥85 mmHg (criteria for metabolic syndrome in Japan)	Age, gender, smoking habit, exercise, eating between meals, healthy body weight	In subjects with periodontal pockets in 2002 had 1.5 times higher odd of having HT in 4 years than subjects without periodontal pockets (95% CI: 1.0-2.3, *P* <0.05).
(Rivas-Tumanyan et al., 2013)	Cross-sectional	Participants in Puerto Rican Elderly Dental Health Study (PREDHS), 63% HT	182	≥60 (78)	Page and Eke, 2007	- Self-reported, - SBP ≥140 or DBP ≥90 mmHg	(Age, gender, smoking status, alcohol drinking), DM, physical activity, BMI ≥25 kg/m^2, consumption of fruits and vegetables, whole wheat bread, and high-fiber cereal, use of preventive	- Severe periodontitis had 2.93 times higher odds of high BP (95% CI: 1.25-6.84, *P* = 0.05) - (In subgroup; the association was stronger to subjects with HT diagnosis or taking antihypertensive medications: OR = 4.20; 95% CI: 1.28-3.80, *P* = 0.05)

Study	Type	Population	N	Age (years)	Periodontal Assessment	Hypertension Assessment	Adjustment	Main findings
							dental services and daily flossing	
(Ollikainen et al., 2014)	Cross-sectional	National Health 2000 survey in Finland, non-smoking	1,296	30-49 (40.0)	Number and % of teeth with PPD ≥4 mm or ≥6 mm	SBP ≥140 or DBP ≥90 mmHg or HT treatment	Age, gender, BMI, educational level, physical activity, alcohol consumption (gram/week) and serum lipid (triglycerides, HDL-, LDL-cholesterol)	**No consistent associations** between the number of teeth with deepened PD (≥4 mm with OR = 0.98, 95% CI: 0.95-1.01) or (≥6 mm with OR = 1.00, 95% CI: 0.97-1.04) or sextants with gingival bleeding (OR = 0.8, 95% CI: 0.5-1.1) with HT.
(Iwashima et al., 2014)	Cross-sectional	Urban Japanese	1,643	30-79 (66.6)	CPITN	SBP ≥140 or DBP ≥90 mmHg or HT treatment	Age, gender, BMI, DM, dyslipidemia, EGFR, smoking status, daily alcohol intake, daily fruit	**- No individual oral health markers were significantly associated with HT.** - Subjects with ≥3 disorders (CPITN stage 4, presence of gingival bleeding, remaining tooth number ≤18 for male and ≤21 for female or no opposing tooth) had 1.82 times higher odds of HT (95%CI: 1.23-2.72, *P* = 0.003) and they had

Study	Type	Population	N	Age (years)	Periodontal Assessment	Hypertension Assessment	Adjustment	Main findings
							intake, physical activity, daily sugar-sweetened soft drink intake, nocturnal sleep duration	highest SBP (130 ± 2 mmHg) compared to those with no components.
(Kawabata et al., 2016)	Longitudinal prospective	Japanese university students	2,588	18-27 (18.2)	CPI score 3-4 or PPD ≥4 mm ± BOP ≥30%	SBP ≥140 or DBP ≥90 mmHg	Age, gender, BMI, fatty foods consuming, number of present teeth, S-OHI, presence of PPD ≥4 mm and BOP ≥30%	The risk of having HT in prehypertension group after 3 years was associated with PD, when PD defined as PD ≥4 mm with BOP ≥30 % at baseline (OR = 2.74, 95%CI: 1.19-6.29, *P* = 0.02).

increased age and socioeconomic factors, which may confound the association between periodontitis and hypertension (Leong et al., 2014) or by dissemination of infectious and/or inflammatory components from periodontal lesions through blood stream, and affect the regulation of blood pressure (Tsioufis et al., 2011). The data from a longitudinal population-based study, the Oral Infections and Vascular Disease Epidemiology Study (INVEST), revealed a strong positive association between increased subgingival colonization by *A. actinomycetemcomitans*, *P. gingivalis*, *T. forsythia* and *T. denticola*, and more than a 3-fold increase in the odds of prevalence of hypertension. Moreover, there was an increasing of systolic blood pressure by 9 mmHg and increasing of diastolic blood pressure by 5 mmHg compared to non-hypertensive participants. The participants of this study were age 55 years and older, had no baseline history of stroke, myocardial infarction, or chronic inflammatory conditions (Desvarieux et al., 2010). However, there were some studies which showed no association between periodontitis and hypertension, such as in the national Health 2000 Survey in Finland of dentate, non-diabetic, non-smoking and 30-49-year-old, there were no relation between periodontal pocketing or extent of bleeding on probing and hypertension (Ollikainen et al., 2014) there was no difference of blood pressure between groups with and without PD (Buhlin et al., 2003) and the other study was a longitudinal study (Rivas-Tumanyan et al., 2012).

Regarding the effect of periodontitis on blood vessel properties and blood pressure regulation, increasing serum levels of CRP in severe periodontitis was found to be related to endothelial dysfunction. The individuals with severe periodontitis had decreasing flow-mediated dilation (FMD) of brachial artery compared to individuals with healthy periodontal status (Amar et al., 2003). The study of endothelial function in patients with coronary artery disease who had periodontitis also revealed the higher serum levels of CRP and IL-6 but lower FMD when compared to non-periodontitis group

(Higashi et al., 2009). The other inflammatory markers, which have been suggesting an increased procoagulant state such as plasminogen-activator-inhibitor1 (Bizzarro et al., 2007), fibrinogen (Schwahn et al., 2004), E-selectin, myeloperoxidase, and soluble intercellular adhesion molecule-1 (Ramirez et al., 2014) have been observed higher levels in periodontitis patients compared to control. In animal study, the evidence has been provided the strong immune response to lipopolysaccharide (LPS: endotoxin from gram-negative bacteria) via intraperitoneal injection can lead to systemic inflammation in rats. LPS-induced increases in serum levels of CRP, TNF-α, and IL-1β associated with an increased in blood pressure (Wu, Chan, and Chan, 2012). Chronic inflammation caused by periodontitis may contribute to endothelial disfunction through a decrease in NO bioaviability, decrease in NO production and/or increase in NO inactivation. A production of inflammatory cytokines results in activation of endothelial cells, leading to excessive induction of adhesion molecules, cytokines, growth factors and vasoconstrictors (Huang and Vita, 2006; Verma et al., 2002) (Figure 4) (Panza, 2001). Moreover, many studies demonstrated that periodontal treatment significantly reduced serum levels of CRP, IL-6 and fibrinogen in patients having refractory hypertension and severe periodontitis (Vidal et al., 2009). Intensive periodontal treatment including subgingival scaling and root planning, can improve endothelial function by significantly increase flow-mediated dilation of brachial artery after 6 months following. The degree of improvement was associated with improvement of periodontal status (Tonetti et al., 2007).

As above mentioned, chronic periodontitis is a local infection which leads to increased systemic inflammation caused by increasing both bacteremia and systemic cytokines such as IL-1β, IL-6 and TNF-α. Increasing serum levels of these cytokines in severe chronic periodontitis have been reported to be associated with endothelial dysfunction, leading to increasing blood pressure or hypertension (Tsioufis et al., 2011). Recent epidemiological studies showed the association between chronic periodontitis and hypertension, even with some of them showed conflicting results. In addition, there

are not many studies have been conducted in Asia, also in Thailand. Therefore, we conducted the study to determine the association between chronic periodontitis and hypertension among these Thai population, to support the epidemiological result.

CHAPTER III

MATERIALS AND METHODS

This cross-sectional study was conducted in year 2002 among the employees and retired personnel of the Electricity Generating Authority of Thailand (EGAT). Individuals with complete data on all variables were included in the present investigation. The study was approved by the Ethics Review Committee of the Faculty of Medicine at Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. All participants signed an inform consent prior to the study.

1. Assessment of periodontal status

Periodontal examinations were carried out by four experienced periodontists and three postgraduate students from the Department of Periodontology, Faculty of Dentistry, Chulalongkorn University as previously described (Torrungruang et al., 2005). One maxillary quadrant and one contralateral mandibular quadrant were randomly selected. All teeth in these quadrants were examined except third molars and retained roots. Individuals who were at risk from bacterial endocarditis or hematogenous total joint infection, or were undergoing hemodialysis, and those with fewer than six teeth in the selected two quadrants were excluded from periodontal examinations.

The examinations included the number of missing teeth, probing depth (PD) and gingival recession (RE). PD and RE were measured using a PCP-UNC 15 probe on six sites per tooth (mesiobuccal, mid-buccal, distobuccal, mesiolingual, mid-lingual and distolingual). Clinical attachment level (CAL) was calculated as the sum of PD and RE. Calibration for periodontal measurements was carried out among seven examiners before the study. The weighted kappa coefficient (within $\pm$ 1 mm) between each pair of examiners ranged from 0.72-0.90 for PD and 0.69-0.79 for CAL. The weighted kappa

coefficient (within ± 1 mm) within each examiner range from 0.85-0.96 for PD and 0.80-0.97 for CAL.

2. Assessment of hypertension

Mean blood pressure was calculated. Blood pressure was conducted twice after a 5-minute rest, using auscultatory method and seated measurement at brachial artery with a validated automatic device. Participants were diagnosed as hypertension if mean systolic blood pressure was ≥140 mmHg or mean diastolic blood pressure was ≥90 mmHg or both or if they were currently taking prescribed antihypertensive medication (Vathesatogkit et al., 2012).

3. Assessment of potential confounders

Variables known to be associated with hypertension were assessed using questionnaire, interview, anthropometric measurements, and blood examinations. Age and educational attainment were self-reported. Smoking status, alcohol consumption, and physical activities were assessed by using questionnaire. Measures of weight, height, and waist circumference (wc) were made through the examination of the participants dressed in light clothing, but without shoes. Blood examinations of fasting blood sugar, triglyceride level, and total cholesterol level were collected using standard protocols (Sritara et al., 2003). Then all variables were stratified as followed: **Age** was dichotomized into two groups: <60 years and ≥60 years; **Education level** was stratified as ≤high school and >high school; **Diabetes mellitus** was diagnosed if an individual had fasting blood sugar ≥126 mg/dl or had been taking anti-diabetic drugs during the past 2 weeks (Expert committee on the diagnosis and classification of diabetes mellitus, 2003); **Smoking status** was classified as non-smokers, former smokers, and current smokers. Smokers were defined as persons who had smoked at least 100 cigarettes in their lifetime; **Alcohol consumption** was classified as non-drinkers, former drinkers, and

current drinkers ('drinkers' were defined as persons who had consumed any types of alcoholic beverage at least 12 drinks in a one-year period); **Exercise** was dichotomized into two groups: 1-2 and ≥3 sessions/week (Vathesatogkit et al., 2012); **Body mass index (BMI)** was calculated from weight in kilograms divided by square height in meters and divided into two categories: <30 and ≥30 kg/m^2 (WHO International Association for the Study of Obesity and International Obesity Task Force, 2000); **WC** was measured at the level of umbilicus in centimeters and divided into two categories using cutoff point of ≤88 cm for female and ≤102 cm for male; **Hypertriglyceridemia** was diagnosed if an individual had triglyceride ≥150 mg/dl; **Hypercholesterolemia** was diagnosed if an individual had total cholesterol ≥240 mg/dl or had been taking lipid-lowering drugs (NCEP III, 2002).

4. Data analyses

The participants were categorized into three groups: no/mild, moderate, and severe periodontitis, according to the Center for Disease Control and Prevention and the American Academy of Periodontology (CDC/AAP) case definition (Page and Eke, 2007). No/mild periodontitis (was defined as having <2 interproximal sites with CAL ≥4 mm and <2 interproximal sites with PD ≥5 mm), Moderate periodontitis (was defined as having ≥2 interproximal sites with CAL ≥4 mm (not on the same tooth), or ≥2 interproximal sites with PD ≥5 mm (not on the same tooth)), Severe periodontitis (was defined as having ≥2 interproximal sites with CAL ≥6 mm (not on the same tooth), and ≥1 interproximal site with PD ≥5 mm).

SPSS software program (SPSS version 22.0; IBM Corp., Chicago, IL, USA) was for statistical analysis. Statistical significance was determined at α = 0.05. Pearson chi-square was used to test the association between hypertension and each categorical variable. Independent t-test was used to determine the periodontal parameters of

participants diagnosed with hypertension compared to those with normal blood pressure. The logistic regression model was used to investigate the degree of association between periodontal disease severity and hypertension, adjusting for potential confounders as described above. Wald statistic was used to determine statistical significance. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated for each independent variable.

CHAPTER IV

RESULTS

The study population comprised 1,378 individuals with a mean ± SD age of 59 ± 5 years (age range 53 to 73 years) and 77.10% were men. There were 661 participants (48.00%) who were diagnosed with hypertension, and their mean SBP ± SD and mean DBP ± SD were 142.30 ± 15.65 and 91.16 ± 9.20 mmHg, respectively. For participants who had normal blood pressure, their mean SBP ± SD and mean DBP ± SD were 116.62 ± 10.55 and 76.00 ± 7.50 mmHg, respectively. The demographic and clinical characteristics of normotensive and hypertensive participants are presented in Table 4. The hypertensive participants had higher proportions of age ≥60 years, male sex, ≤high school education, diabetes mellitus, former smokers, current or occasional drinkers, BMI ≥30 kg/m^2, waist circumference >88 cm in female or >102 cm in male, triglyceride ≥150 mg/dl, hypercholesterolemia and severe periodontitis, compared to normotensive participants (P <0.05).

Table 4: Demographic and clinical characteristics of participants diagnosed with hypertension compared to those with normal blood pressure

Variables	Total N (%)	No hypertension (N = 717) N (%)	Hypertension (N = 661) N (%)
Age (years)*			
<60	791 (57.40)	447 (62.30)	344 (52.00)
≥60	587 (42.60)	270 (37.70)	317 (48.00)
Gender*			
Female	315 (22.90)	210 (29.30)	105 (15.90)
Male	1,063 (77.10)	507 (70.70)	556 (84.10)
Education level*			
≤High school	324 (23.50)	133 (18.50)	191 (28.90)
>High school	1,054 (76.50)	584 (81.50)	470 (71.10)

Variables	Total N (%)	No hypertension (N = 717) N (%)	Hypertension (N = 661) N (%)
Diabetes mellitus*			
No	1,160 (84.20)	632 (88.10)	528 (79.90)
Yes	218 (15.80)	85 (11.90)	133 (20.10)
Smoking status*			
Non-smoker	655 (47.53)	363 (50.60)	292 (44.20)
Former smoker	535 (38.82)	243 (33.90)	292 (44.20)
Current smoker	188 (13.65)	111 (15.50)	77 (11.60)
Alcohol consumption*			
Non-drinker	406 (29.46)	239 (33.30)	167 (25.30)
Former drinker	336 (24.38)	188 (26.26)	148 (22.40)
Current/occasional drinker†	636 (46.16)	290 (40.44)	346 (52.30)
Exercise (sessions/week)			
1-2	338 (24.50)	189 (26.40)	149 (22.50)
≥3	1,040 (75.50)	528 (73.60)	512 (77.50)
BMI (kg/m^2)*			
<30.0	1,302 (94.50)	699 (97.50)	603 (91.20)
≥30.0	76 (5.50)	18 (2.50)	58 (8.80)
WC (cm)*			
≤88 in female or ≤102 in male	1,204 (87.40)	645 (90.00)	559 (84.60)
>88 in female or >102 in male	174 (12.60)	72 (10.00)	102 (15.40)
Triglyceride (mg/dl)*			
<150	891 (64.70)	496 (69.20)	395 (36.90)
≥150	487 (35.30)	221 (30.80)	417 (63.10)
Hypercholesterolemia (total cholesterol ≥240 mg/dl or taking medication)			
No	541 (39.30)	297 (41.40)	244 (36.90)
Yes	839 (60.70)	420 (58.60)	417 (63.10)
Periodontitis severity (Page and Eke, 2007)*			
No/mild	157 (11.40)	101 (14.10)	56 (8.50)
Moderate	740 (53.70)	392 (54.70)	348 (52.60)
Severe	481 (34.90)	224 (31.20)	257 (38.90)

* *P* <0.005., † Occasional drinker = less than once per month.

Moreover, the proportion of participants who had hypertension was assessed according to periodontitis severity (Figure 5). The no/mild periodontitis group had the highest proportion of normotensive individuals and the lowest proportion of hypertensive individuals. In contrast, the severe periodontitis groups had the lowest proportion of normotensive individuals and the highest proportion of hypertensive individuals. The differences between groups were statistically significance (P <0.05).

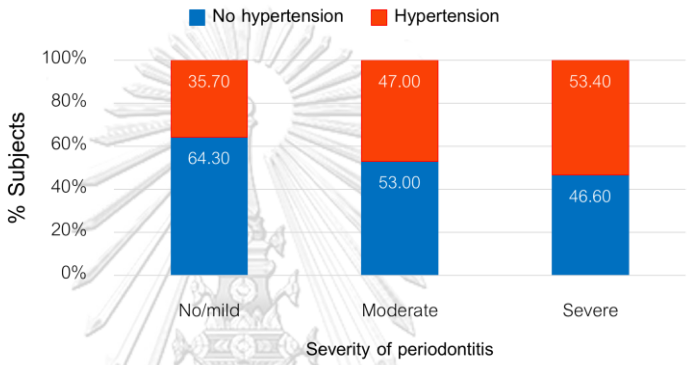

Figure 5: Proportion of subjects with diagnosis of hypertension according to the severity of periodontitis

Differences in periodontal parameters according to diagnosis of hypertension are presented in Table 5. Hypertensive participants had a significantly higher number of sites with PD ≥5 mm and CAL ≥4 mm (P <0.005), compared to normotensive participants. However, plaque scores, which reflected oral hygiene practice, were not different between groups (P = 0.086).

Table 5: Periodontal parameters of participants diagnosed with hypertension compared to those with normal blood pressure

Parameters	No hypertension (N = 717)	Hypertension (N = 661)
	mean ± SD	mean ± SD
Mean probing depth (mm)[NS]	2.45 ± 0.69	2.39 ± 0.94
PD ≥5 mm (sites)[*]	1.52 ± 2.34	1.95 ±2.49

Parameters	No hypertension (N = 717)	Hypertension (N = 661)
	mean ± SD	mean ± SD
Mean clinical attachment level (mm)[NS]	3.13 ± 1.14	3.08 ± 1.06
CAL ≥4 mm (sites)[*]	5.50 ± 3.34	6.06 ± 3.24
CAL ≥6 mm (sites)[NS]	1.71 ± 2.40	1.94 ± 2.34
Plaque score (%)[NS]	59.26 ± 23.85	61.45 ± 23.46

[NS] Not significant and * P <0.005.

Logistic regression analysis was used to assess the magnitude of associations between periodontitis severity and hypertension (Table 6). In univariable analysis, both moderate and severe periodontitis groups were associated with an increased risk for hypertension, with odds ratios of 1.60 (95% CI; 1.12-2.29, P = 0.010) and 2.07 (95% CI; 1.43-3.00, P = 0.001), respectively. After adjustment for potential confounding factors, there was a significantly increased risk of hypertension in the severe periodontitis group, with an odds ratio of 1.55 (95% CI; 1.03-2.33, P = 0.035). For the moderate periodontitis group, there was a trend for an increased risk of hypertension, with an odds ratio of 1.35 (95% CI; 0.92-1.98); however, the association did not reach statistically significant (P = 0.123). Besides severe periodontitis, other confounders including age, sex, education, diabetes, smoking, hypertriglyceridemia were significantly associated with hypertension (P <0.05).

Table 6*:* Logistic regression analysis of the association between periodontitis severity and hypertension

Variables	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Moderate periodontitis	1.60 (1.12-2.29)	0.010	1.35 (0.92 - 1.98)	0.123
Severe periodontitis	2.07 (1.43-3.00)	0.001	1.55 (1.03 - 2.33)	0.035
Age ≥60 years	1.53 (1.23-1.89)	0.001	1.51 (1.20 - 1.90)	0.001
Male	2.19 (1.69-2.85)	0.001	2.75 (1.85 - 4.10)	0.001
≤High school	1.78 (1.39-2.30)	0.001	1.53 (1.17 - 1.20)	0.002
Diabetes mellitus	1.87 (1.39-2.52)	0.001	1.45 (1.06 - 1.98)	0.020

Variables	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Smoking status				
Former smoker	1.49 (1.19-1.88)	0.001	0.86 (0.65 - 1.16)	0.339
Current smoker	0.86 (0.62-1.20)	0.378	0.52 (0.35 - 0.76)	0.030
Alcohol consumption				
Former drinker	1.13 (0.84-1.51)	0.424	0.78 (0.55 - 1.11)	0.169
Current/occasional drinker	1.71 (1.33-2.20)	0.001	1.15 (0.82 - 1.61)	0.412
Exercise 1-2 sessions/week	0.81 (0.64-1.04)	0.100	0.88 (0.67 -1.14)	0.333
BMI $\geq$30 kg/m^2	3.74 (2.18-6.41)	0.001	2.59 (1.40-4.77)	0.002
WC >88 cm (F) or >102 cm (M)*	1.64 (1.18-2.26)	0.003	1.85 (1.22 -2.80)	0.004
Triglyceride $\geq$150 mg/dl	1.51 (1.21-1.89)	0.001	1.30 (1.03 - 1.66)	0.030
Hypercholesterolemia (Total cholesterol $\geq$240 mg/dl or taking medication)	1.21 (0.97-1.50)	0.087	1.26 (1.00 - 1.60)	0.051

* F = Female, M = Male.

CHAPTER V

DISCUSSION AND CONCLUSION

The results from the present study demonstrated, for the first time, that severe periodontitis was associated with an increased risk of hypertension among this group of Thai adults. The association remained significant after controlling for potential confounders including age, gender, educational level, diabetes mellitus, smoking status, alcohol consumption, frequency of exercise, obesity, hypertriglyceridemia, and hypercholesterolemia.

Epidemiological studies have reported the inconsistent results regarding the association between periodontitis and hypertension. Most studies supported positivity between these two diseases (Iwashima et al., 2014; Rivas-Tumanyan et al., 2013) whereas the others did not (Nesse et al., 2010; Ollikainen et al., 2014). These may be due to demographic variables such as age, gender, and population size, or difference in methodology and research design among studies. In Asian region, limited large scale population was conducted for the association study (Choi et al., 2015; Kawabata et al., 2016) while the majority from western countries (Chrysanthakopoulos and Chrysanthakopoulos, 2016; Darnaud et al., 2015; Holmlund, Holm, and Lind, 2006; Rivas-Tumanyan et al., 2012; Tsakos et al., 2010). Moreover, there were differences in diagnostic criteria of periodontitis and hypertension among studies. Regarding a variety of periodontal criteria, the use of CPI (Choi et al., 2015; Kawabata et al., 2016), CDC/AAP case definition (Rivas-Tumanyan et al., 2013; Tsakos et al., 2010), a percentage of sites of PD and/or CAL (Chrysanthakopoulos and Chrysanthakopoulos, 2016; Holmlund, Holm, and Lind, 2006), or other periodontal indices (Darnaud et al., 2015), was observed. Regarding hypertension criteria, the used of self-reporting

(Chrysanthakopoulos and Chrysanthakopoulos, 2016; Rivas-Tumanyan et al., 2012), blood pressure measurement (Kawabata et al., 2016), and/or current prescribed antihypertensive medication (Choi et al., 2015; Tsakos et al., 2010) were observed.

The results of this study revealed the significant association between severe periodontitis and hypertension which confirmed the previous study in Puerto Rico (Rivas-Tumanyan et al., 2013). It should be noted that both used the same periodontal criteria (CDC/AAP), shared similar population characteristics (all adults), and used similar confounding factors (age, sex, smoking, and alcohol consumption). Interestingly, their study comprised a smaller scale of 182 participants, and they found high OR of 4.20 (95% CI; 1.28-13.80, P <0.05) as compared to this study which incorporated large-scale data. 1,378 participants with the OR of 1.55 (95% CI; 1.03-2.33, P = 0.035). Meanwhile, a much larger-scale study of the Third National Health and Nutrition Examination Survey (approximately 14,000 participants), which used the same periodontal diagnosis criteria, did not report a significant association between severe periodontitis and hypertension after adjusting of confounders such as ethnicity, age and sex (OR = 1.3, 95% CI; 0.8-2.2) (Tsakos et al., 2010). The association could be considerably modified by these demographic variables.

Interestingly, most association studies of these two diseases in the past used hypertension criteria as followed by the JNC7 report (Chobanian et al., 2003). In 2017, the latest hypertension criteria has been purposed that individuals are diagnosed with hypertension if the systolic blood pressure ≥130 mmHg or mean diastolic blood pressure ≥80 mmHg (Whelton and Carey, 2017). When this blood pressure criteria or currently taking prescribed antihypertensive medication were used as the outcome variable in examining the association instead, we found the association between severe periodontitis and increased risk of hypertension with crude OR of 1.72 (95% CI; 1.23-2.40, P = 0.002), meanwhile crude OR of moderate periodontitis was 1.32 (95% CI; 0.96-

1.80) but there was not statistically significant (*P* = 0.091). After controlling confounding factors, we found that both moderate and severe periodontitis had a trend of an increased risk of hypertension but the association did not reach statistically significant with ORs of 1.13 (95% CI; 0.77-1.66, *P* = 0.545) and 1.46 (95% CI; 0.95-2.25, *P* = 0.083), respectively (not showed in results). The results revealed the same trend of increased risk of hypertension by periodontal severity, although the association did not reach the statistically significant. These may be implied that the criteria of hypertension could affect the association and also the magnitude by increasing number of subjects who had hypertension.

Due to the inflammatory process caused by periodontitis may be probable mechanisms related to hypertension. There was a study found that the extents of gingival bleeding, markers of current active periodontal inflammation, provided stronger association with current measurement of blood pressure than lifetime experience of periodontal disease, which measured by CAL (Tsakos et al., 2010). Interestingly, this study found that hypertensive participants were related to having higher sites of PD ≥5 mm compared to normotensive group. Our study concurred with the results of study by Vidal and coworkers (Vidal et al., 2011) who reported that hypertensive patients had a higher proportion of sites with dental plaque, gingival bleeding, number and proportion of sites with clinical attachment loss (CAL ≥4 mm and CAL ≥6 mm), and number of sites with PD ≥5 mm than did non-hypertensive patients. The site with deep PD related to the more complex of subgingival microbial (Socransky et al., 1991) and higher risk of disease progression (Matuliene et al., 2008). The results by the oral infections and vascular disease epidemiology study also supported the association between subgingival periodontal bacteria and those elevated blood pressure, and prevalence of hypertension (OR = 3.05, 95% CI: 1.60-5.82, *P* <0.001) (Desvarieux et al., 2010).

In relation to strengths of this study, the sample size of Thai adults was large enough to allow meaningful analyses with good statistical power. Second, periodontal status was clinically evaluated through PD and CAL measurement, and the severity was precisely classified by CDC/AAP case definition. This classification defines the disease by determining the thresholds of PD and CAL and the number of affected sites which provide suitable estimates of the prevalence of periodontitis (Page and Eke, 2007). There are only a few studies which used these criteria for periodontal status (Rivas-Tumanyan et al., 2013; Tsakos et al., 2010). Due to the collection of our periodontal data, a half-mouth six-sites periodontal examination was used which may result in low estimates. However, recent systematic review (Tran et al., 2013) suggested that like full-mouth examination, half-mouth examination is acceptable in estimating prevalence and severity of periodontal disease in large population-based study.

Third, regarding the diagnosis of hypertension, this study classified the participants by blood pressure measurement, and currently prescribed antihypertensive medication, which are required in studying hypertension prevalence (Ong et al., 2007). Several studies used these hypertension diagnosis criteria (Choi et al., 2015; Iwashima et al., 2014; Rivas-Tumanyan et al., 2013; Tsakos et al., 2010). The questionnaire or self-reporting method may have resulted in under-diagnosis of hypertension and underestimation of the magnitude of the association between periodontitis and hypertension (Martin-Cabezas et al., 2016).

It should be noted that white coat hypertension may contribute to hypertension data of the study group. This phenomenon has been commonly observed in office setting or medical care environment, approximately 15-30% prevalence (O'Brien et al., 2000; O'Brien et al., 2013). In order to obtain precise blood pressure measurement, ambulatory blood pressure monitoring (day time and night time monitoring) is necessary and needs strict compliance (Chobanian et al., 2003).

However, this study also has limitation. The cross-sectional design couldn't establish the clear direction of the association between periodontitis and hypertension. The prospective design is needed to confirm the true relationship between these two diseases.

In conclusion, severe periodontitis was independently associated with an increased risk of hypertension in this group of Thai adults. Our findings, if confirmed in further prospective studies, suggest that regular periodontal check-up and maintaining healthy periodontal status may help reduce the risk of hypertension, which is connected to many serious cardiovascular conditions.

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VITA

NAME	พลอยศิริ รัศมี
DATE OF BIRTH	24 ตุลาคม 2528
PLACE OF BIRTH	กรุงเทพฯ
INSTITUTIONS ATTENDED	ภาควิชาปริทันตวิทยา คณะทันตแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
HOME ADDRESS	เลขที่ 76/48 หมู่ 5 หมู่บ้านเกื้อกูลนิเวศน์ ถนนติวานนท์ ตำบลปากเกร็ด อำเภอปากเกร็ด จังหวัดนนทบุรี 11120
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