ASSESSMENT OF INFLAMMATORY MARKERS AND PERIODONTAL OUTCOMES IN CKD PATIENTS WITH PERIODONTITIS

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ASSESSMENT OF INFLAMMATORY MARKERS AND PERIODONTAL OUTCOMES IN CKD PATIENTS WITH PERIODONTITIS

by

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LIST OF ABBREVIATIONS

%	Percentage
µL	Micro-liter
ACR	Albumin to creatinine ratio
ANOVA	Analysis of Variance
APR	Acute Phase Protein
BMI	Body Mass Index
BOP	Bleeding on Probe
BUSE	Blood Urea Serum Electrolyte
CAL	Clinical Attachment Loss
CEJ	Cementoenamel Junction
CHD	Coronary Heart Disease
CKD	Chronic kidney disease
CKD-MBD	Chronic-kidney disease-Mineral and Bone-Disorder
CLSI	Clinical and Laboratory Standard Institute
CRIC	Chronic renal Insuffiency Cohort
CRP	C-reactive protein
CVD	Cardiovascular disease
DALYs	Disability-adjusted life-years
DM	Diabetes Mellitus
EGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-linked immunosorbent assay
EP	Eppendorf Tube
Epo	Erythropoietin
ESRD	End-Stage Renal Disease
GCF	Gingival Crevicular Fluid
GBI	Gingival Bleeding Index
HbA1c	Hemoglobin A1c
HD	Hemodialysis
HRP	Avidin-Horseradish Peroxidase
ICC	Intraclass Correlation Coefficient
IFN-α	Interferon Neuron Alpha

IFN-β	Interferon Neuron Beta
IFN-γ	Interferon Neuron Lambda
IL-1	Interleukin-1
IL-10	Interleukin-10
IL-10	Interleukin-10
IL-12	Interleukin-12
IL-18	Interleukin-18
IL-19	Interleukin-19
IL-1R	Interleukin-1 Receptor
IL-1RA	IL-1 Receptor Antagonist
IL-20	Interleukin-20
IL-22	Interleukin-22
IL-24	Interleukin-24
IL-26	Interleukin-26
IL-33	Interleukin-33
IL-36	Interleukin-36
IL-37	Interleukin-37
IL-38	Interleukin-38
IL-4	Interleukin-4
IL-5	Interleukin-5
IL-6	Interleukin-6
Il-8	Interleukin-8
JAK1	Janus Tyrosine Kinase
JEPeM	Jawantkuasa Etika Penyelidikan Manusia
KDIGO	Kindey Disease Improving Guideline Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KPP	Klinik Pakar Perubatan
LAF	Lymphocyte Activating Study
LPS	Lipopolysaccharides
Ml	Milliliter
Mm	Millimeter
MYR	Ringgt Malaysia
NHANES	The National Health and Nutrition Examination Survey
NSPT	Non-surgical Periodontal Therapy

OD	Optical Density
Pg/ml	Pictogram/milliliter
PS	Plaque Score
SD	Standard Deviation
SPSS	Statistical Package for Social Sciences
SRP	Surgical Root Planing
SST	Serum Separator Tube
STAT1	Signal Transducer and Activator for Transcription 1
STAT3	Signal Transducer and Activator for Transcription 3
STAT5	Signal Transducer and Activator for Transcription 5
TGF-β	Transforming Growth Factor Beta (β)
Th1	T-helper Type a
Th17	T-helper Type 17
Th2	T-helper Type 2
TNF-α	Tumor Necrosis Factor
Tr1	Regulatory T Cells
TYK2	Tyrosine Kinase 2
WHO	World Organization Health
PDL	Periodontal Ligament

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Appendix A Ethical Approval

Appendix B Experimental and Clinical Preparation

PENILAIAN PENANDA KERADANGAN DAN HASIL PEMERIKSAAN PERIODONTIUM DALAM KALANGAN PESAKIT BUAH PINGGANG KRONIK DENGAN PERIODONTITIS

ABSTRAK

Penyakit buah pinggang kronik (PBPK) dan periodontitis tanpa PBPK mempunyai kesan ke atas morbiditi dan kematian pesakit. Periodontitis meningkatkan beban keradangan, dan boleh mengganggu fungsi buah pinggang dengan mengubah tahap keradangan penanda inflamasi dan berpotensi memburukkan lagi kerosakan buah pinggang . Interleukin-1 (IL-1) adalah pro-penanda inflamasi dan Interleukin-10 (IL-10) adalah anti-penanda inflamasi yang mempunyai sifat imunomodulator yang mengawal tindak balas imun sistem. Hanya sedikit maklumat yang diketahui tentang perubahan dalam penanda inflamasi serum IL-1 dan IL-10 selepas terapi periodontium dalam pesakit PBPK dalam populasi kita. Oleh itu, kajian ini bertujuan untuk menilai dan membandingkan tahap penanda inflamasi Interleukin-1 (IL-1) dan Interleukin-10 (IL-10) serta parameter periodontum sebelum dan selepas menerima Terapi periodontium tanpa pembedahan (TPTP). Dua puluh pesakit PBPK (Tahap 3 dan Tahap 4) dengan periodontitis (Kumpulan 1), dua puluh pesakit periodontitis tanpa PGK(Kumpulan 2) dan dua puluh subjek sihat (Kumpulan 3) telah dipilih. Parameter periodontium klinikal seperti Kedalaman Probing Periodontal (PPD), Kehilangan Pelekatan Klinikal (KPK), Indeks Pendarahan Gingiva (IPG) dan Indeks Plak (IP) diukur dalam setiap pesakit semasa lawatan pertama dan enam minggu kemudian (lawatan kedua). Sampel darah dikumpul semasa setiap lawatan dan serum dianalisis untuk kepekatan IL-1 dan IL-10 menggunakan Enzyme-Linked Immunosorbent Assay. Penemuan kami menunjukkan bahawa tahap IL-1 dan IL-10 didapati jauh lebih tinggi ($p<0.05$) dalam pesakit PBPK dengan periodontitis (Kumpulan 1) berbanding pesakit

periodontitis tanpa PBPK (Kumpulan 2) dan subjek sihat (Kumpulan 3). Jika dibandingkan dengan kumpulan lain, parameter periodontium klinikal (PPD, PI dan GBI dalam Kumpulan 1 adalah lebih tinggi ($p<0.05$). Selepas rawatan TPTP, terdapat pengurangan ketara ($p<0.05$) dalam penanda keradangan dan parameter periodontal klinikal dalam Kumpulan 1 dan Kumpulan 2.

Kajian ini menunjukkan pesakit PBPK dan periodontitis mempunyai keradangan sistematik yang lebih teruk dan status periodontal yang lebih lemah daripada pesakit periodontitis bukan PBPK. TPTP menunjukkan perubahan yang baik bagi penanda keradangan dan parameter pergigian serta melambatkan kadar kemerosotan buah pinggang. IL-1 dan IL-10 adalah penanda keradangan yang mampu menunjukkan nilai perkembangan buah pinggang kronik. Oleh itu, kajian dari pelbagai penyelidikan dan sampel saiz yang lebih besar diperlukan pada masa hadapan.

ASSESSMENT OF INFLAMMATORY MARKERS AND PERIODONTAL OUTCOMES IN CKD PATIENTS WITH PERIODONTITIS

ABSTRACT

Chronic kidney disease (CKD) and periodontitis have an impact on patient's morbidity and mortality. The prevalence of comorbid CKD and periodontitis is shown to be frequent. Periodontitis increases the inflammatory burden, which has been shown to disrupt renal function by altering serum inflammatory levels, and potentially worsening CKD. Pro-inflammatory Interleukin-1 (IL-1) and anti-inflammatory Interleukin-10 (IL-10) have immunomodulatory properties that regulates host immune responses. Little is known about changes in the serum inflammatory markers of IL-1 and IL-10 following the periodontal therapy in CKD patients in our populations. Therefore, this study was aimed to assess and compare the levels of inflammatory markers IL-1 and IL-10 as well as periodontal parameters at baseline and afterreceiving NSPT. Twenty CKD patients (stage 3 and stage 4) with periodontitis (Group1), twenty non-CKD patients with periodontitis (Group 2) and twenty healthy patients(Group 3) were selected. The dental parameters such as Periodontal Probing Depth (PPD), Clinical Attachment Loss (CAL), Gingival Bleeding Index (GI) and Plaque Score (PS) were measured in each patient during first visit (baseline) and six weeks later (second visit). Blood sample was collected during each visit and analysed for serum IL-1 and IL-10 concentration using Enzyme-Linked Immunosorbent Assay. Ourfindings shows that IL-1 and IL-10 levels were found significantly higher ($p<0.05$) inCKD patients with periodontitis (Group 1) as compared to non-CKD patients with periodontitis (Group 2) and healthy subjects (Group 3). When compared to other

groups, the levels of dental parameters (PPD, PS and GBI in Group 1 were significantly higher ($p<0.05$). Following NSPT, there was significant reduction ($p<0.05$) in inflammatory markers and clinical periodontal parameters in Group 1 andGroup 2.

This study demonstrates that patients with CKD and periodontitis had a more severe systemic inflammatory response and poorer periodontal status than non-CKD. NSPT shown improvement in both inflammatory markers and dental parameters as well as delay the progression of CKD. IL-1 and IL-10 is a promising inflammatory marker to assess CKD progression. Therefore, multicentre and larger sample size studies are needed in the future.

CHAPTER 1

INTRODUCTION

1.1 Preview of Chapter

This introduction chapter summarizes the entire research study. The second section explains the study's background. The third section discussed the research problem and primary focus of the study. Meanwhile, section four explains the rationale of study. Section five focuses on conceptual framework of the study. Sections six and seven clarify the research question and study hypothesis. Section eight described general and specific objectives that related to the research problem. Section nine explains the study's scopes.

1.2 Background of the Study

CKD is a major cause of morbidity and mortality (Abraham et al., 2016) worldwide, and a serious public health issue. It is rapidly growing and affects more than 75 million people globally (Deng et al., 2021). In fact, in 2017 CKD claimed 1.2 million lives and was the world's 12th leading cause of death (Carney, 2020). Furthermore, in 2013, CKD was identified as one of the of the top ten causes of decreased life expectancy or disability-adjusted life-years (DALYs) in 2013(Deng et al., 2021). The burden of CKD in South Asia is extremely high with 3.0% of all deaths (Misra et al., 2017). Meanwhile, in Malaysia, the number of people receiving dialysis for end-stage renal disease has increased from 96 per million in 2002 to 182 per million in 2011. West Malaysia alone has a prevalence of 9.07% (Hooi et al., 2013).

The Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation defining CKD as the presence of kidney damage or a glomerular filtration rate (GFR <60 ml/min per 1.73m2) for ≥3 months, regardless of causes (Levey et al., 2011). CKD was divided into five stages indicated by the level of

Glomerular Filtration Rate (GFR) which it is equivalent to the total amount of fluid filtered by all the functional nephrons per unit of time.

Table 1.1 CKD stages and description

GFR Stages	GFR (mL/min/1.73m$^{2)}$	Description
G1	≥90	Kidney damage (protein in the urine) and normal GFR
G2	60-89	Kidney damage and mildly decreased GFR
G3a	45-59	Mildly to moderately decreased GFR
G3b	30-44	Moderately to severely decreased GFR
G4	15-29	Severely decreased GFR
G5	<15	Kidney failure

The well-known traditional risk factors for CKD are diabetes mellitus, hypertension (Abraham et al., 2016), glomerulonephritis, cystic kidney disease (Kalantar-Zadeh et al., 2021) poor glycaemic control, smoking and physical inactivity (Uhlig et al., 2003). Another established risk-factor for CKD in South Asian developing countries is lower socioeconomic level and environmental conditions (Abraham et al., 2016). However, periodontitis is now knowns as non-traditional risk factor for CKD because CKD and periodontitis both have risk factors in common.

Kidneys play a critical role in the regulation of body fluids, electrolytes and acid-base balance, therefore renal dysfunction are known to cause many derangements such as hyperkalaemia, metabolic acidosis and hyperphosphatemia (Dhondup & Qian, 2017). Stage 3 and stage 4 are pre-dialysis stage in which half of the kidney function is lost. Other consequences, such as high blood pressure or bone disease, may arise as

a result of this problem. Treatments are required to slow down the progression of the diseases. According to prior research by Baek et al. (2012), 51.9% of Stage 3 patients progress to Stage 4 or Stage 5 over 10 years due to CKD mismanagement or missing follow up appointment. There are only two choices of treatments for Stage 5 or end stage renal disease (ESRD) either kidney replacement therapy (dialysis or transplantation) or conservative care (Webster et al., 2017). The major complications include anaemia, cardiovascular disease, and chronic-kidney disease-mineral andbone-disorder (CKD-MBD) (Murabito & Hallmark, 2018). As highlighted in study by Akchurin & Kaskel, (2015), dialysis patients have a higher risk of death. However,the progression of kidney damage may be prevented if all the treatment plans were followed (Lorenz et al., 2008). As a result, detecting and managing CKD early is crucial in order to prevent decrease renal function and progression to end-stage renal disease (Baek et al., 2012).

Inflammation is the biological response of tissue to harmful stimuli such as pathogens or irritants. Inflammation has been discovered as a significant component of CKD, and one of the major contributors to anaemia and erythropoietin (Epo) resistance since the production of cytokines causes restriction of erythropoiesis and shortening the lifespan of red blood cells (Nemeth & Ganz, 2019). Therefore, due to inflammation, the body is unable to use stored iron to produce enough red blood cells(Nemeth & Ganz, 2014). Previous study has shown that inflammation in CKD can becontributed by variety of causes (Akchurin & Kaskel, 2015) including hypoalbuminemia/malnutrition, atherosclerosis and cytokines (Silverstein, 2009). However, higher levels of circulating cytokines are explained by decreased renal clearance (Akchurin & Kaskel, 2015). CKD patients are in uremic conditions; therefore, this uremic environment causes oxidative and carbonyl stress, both of whichare highly pro-inflammatory markers.

Patients with CKD are more prone to have frequent infections and thrombotic events, which trigger additional inflammatory responses. It has also been postulated that uremic toxins contribute to intestinal dysbiosis in CKD by increasing translocation of gut bacteria and bacterial components into the circulation, which can activate systemic inflammation (Akchurin & Kaskel, 2015).

Inflammatory markers are produced not only limited to a local process, but they can also be systemic process, as they are mediated by a variety of factors such as acute phase proteins (APR), cytokines, complement, adhesion molecules, and white blood cells (Filiopoulos & Vlassopoulos, 2009). APR was produced in order to respond and fight the infections, injuries, ischemic necrosis and malignancy, APR contain both pro-inflammatory and anti-inflammatory markers. Pro-inflammatory markers are positive mediators that are released to fight the infection (Dyrla et al., 2017). Meanwhile anti-inflammatory markers are produced in response to the production of pro-inflammatory markers (Bozkurt et al., 2006). This systemic reaction aids in the elimination of pathogens and noxious substances, as well as the removal of damaged tissue and the healing of the afflicted tissue or organ.

The activation of pro inflammatory markers (IL-1) and anti-inflammatory markers (IL-10) pathways inside the kidneys, as well as the migration of inflammatory cells to the injury site are early responses to kidney damage. IL-1 is a significant proinflammatory markers that has been shown to be a superior marker in renal patients and has been extensively studied in the orchestration of the inflammatory response to acute renal injury. Meanwhile, IL-10 is a prototypical anti-inflammatory cytokine that regulates and suppresses inflammation, acting as a counterbalance to the actions of IL-1(Zhang & Parikh, 2019). In the Chronic Renal Insuffiency Cohort (CRIC) study, inflammatory markers (IL-1, IL-1R antagonist, IL-6) were found to be inversely related to kidney function measures and positively related to albuminuria (Akchurin &

Kaskel, 2015).

Periodontitis is a chronic, non-communicable (Preshaw & Bissett, 2019) and multifactorial disease with various etiologic and contributing factors (Slots, 2017). This is a bacterially-induced, host-mediated condition (Kitamura et al., 2019) characterised by the inflammation of the teeth's supporting tissues, progressive attachment loss (CAL ≥1 mm) (Cardoso et al., 2018) and bone loss, as well as the formation of a pocket around the teeth and/or gum recession (>3 mm) (Ibrahim et al., 2020). According to Deshampt-Lendhardt et al., 2019, severe periodontitis affects about 11% of the global population, and its frequency increases with age, reaching a plateau at 50–60 years of age (Deschamps-Lenhardt et al., 2019) Therefore, periodontitis is the most common oral disease worldwide (Lertpimonchai et al., 2017).

The traditional risk factors for periodontitis are poor and inadequate oral hygiene, diabetes mellitus (DM), cardiovascular disease, obesity (Saminathan et al., 2020) as well as poor lifestyle factors such as high sugar intake (Chapple et al., 2017) and smoking (Lertpimonchai et al., 2017). According to a study by Saminathan et al., the prevalence of periodontitis was about 74% among Malaysians who were obese (Saminathan et al., 2020). Additionally, a recent study discovered that, when comparing male and female participants, the prevalence of periodontitis was substantially greater in female's participants, (Saminathan et al., 2020).

Nonetheless, numerous investigations have revealed that CKD is now recognised as non-traditional risk factor of periodontitis. Several possible explanations for these findings in CKD patients have been proposed. Most notably, uraemia is common in patients with CKD because the kidneys are unable to filter properly, resulting in an increase in the level of toxic substances in the circulation (Ibrahim et al., 2020). In addition, T- and B-lymphocyte dysfunction, as well as monocyte and macrophage dysfunction, all contribute to the weakened immune system. As a result, the

host's immune response to subgingival Gram-negative microbials is reduced (Ismail, et al., 2013). Furthermore, periodontitis is triggered in CKD patients due to the malnutrition and local inflammation, in addition to dry mouth as reported by Ruspo et al. (2014). The inability of CKD patients to produce saliva to fight infection thus increases the inflammation (Ruospo et al., 2014).

The inflammation of periodontitis is triggered by the presence *P.gingivalis*. This dysbiotic oral microbiota has evolved to thrive in an inflammatory environment and is abundant in virulence factors (Hajishengallis, 2015). The pathobiant outgrowth (known as *P.Ginigivalis*) on the other hand , can an exacerbate and aggravate host inflammatory responses (Loos & Van Dyke, 2020). Chronic periodontal inflammation has been associated to an increase in inflammatory response in HD patients, which has a deleterious impact on their lifespan (Akchurin & Kaskel, 2015). Periodontal health is worse and more severe in pre-dialysis patients (Joseph et al., 2009) increasing the frequency of CKD patients experiencing periodontitis in Asia. This is because CKD patients have a dry mouth, which makes them susceptible to oral bacteria (Ruospo et al., 2014).

Several researched have discussed the hypothesis of a bidirectional relationship between CKD and periodontitis. Periodontal disease, is a source of systemic inflammation, is biologically plausible as a risk factor for CKD (Monica et al., 2011). According to a study reported by Bouchard et al. (2017), the present of oral biofilm is required for the development of periodontal diseases, dental caries and gingival inflammation (Kitamura et al., 2019). As a result, the periodontal infections cause an inflammatory response in the host which frequently result in connective tissue damage and bone resorption (Stadler et al., 2016). Other than that, the hectic lifestyles may have unintentionally contributed to stress, which may have increased the burden of inflammation (Khan et al., 2015).