ISBN: 978-602-9461-16-9

To Commemorate The 64th Anniversary of The Faculty of Dentistry
Universitas Gadjah Mada, Yogyakarta, Indonesia

The 2nd International Joint Symposium on Oral and Dental Sciences

In Conjunction with Dental Specialists Seminar

March 1-3, 2012
Hotel Inna Garuda Yogyakarta, Indonesia

http://ijm2012.ugm.ac.id

Proceeding Book

Proceeding Book
The 2nd International Joint Symposium on Oral and Dental Sciences
March 1-3, 2012

PERIODONTAL INFECTION AND DIABETES : MAKING THE CONNECTIONS IN TWO WAYS

Yoifah Rizka[1], Widyastuti[1]

[1] Periodontics Departement, Faculty of Dentistry, Hang Tuah University, Surabaya Indonesia 60282

* Corresponding Author: yoi.riez@yahoo.co.id

Abstract

Recent attention has been focused on our understanding of the negative influences of oral chronic inflammation on systemic health. There is growing evidence that periodontal diseases may affect general health. Periodontal diseases have powerful and multiple influences on the occurence and severity of systemic conditions and disesases, such a diabetes mellitus, cardiovascular diseases, respiratory diseases, and pregnancy complications. The relationship of periodontitis and diabetes has been supported by sufficent evidences in the past twenty years and has long been discussed with conflicting conclusions. Both of these diseases have a relatively high incidence globally in the general population with a number of common pathways in their pathogenesis. Their relationship appears bi-directional insofar that the presence of one condition tends to promote the other, and that the appropriate management of either may assist treatment of the other. However, the converse possibility that periodontal disease either predisposes or exacerbates the diabetic condition has received little attention, and it is only less known about the impact of periodontal diseases on the diabetes-related inflammatory state. Although type 2 diabetes is a multiple risk-factor syndrome, lowered insulin sensitivity, called insulin resistance, is essential in developing the disease. Pro-inflammatory cytokine produced from chronic inflammation subjects as periodontitis, is known to play a predominant role in inducing insulin resistance.

This review attempts to explain the immunobiological connection between periodontal disease and diabetes mellitus type 2, exploring the mechanisms through which periodontal infection can contribute to the low-grade general inflammation associated with diabetes (thus worsening insulin resistance) and discussing the impact of periodontal treatment on glycemic control in people living with both diabetes and periodontal disease.

Keywords : Periodontal diseases, diabetes mellitus, insulin resistance, chronic inflammation

Introduction

The understanding of the etiology and pathogenesis of periodontal diseases and their chronic, inflammatory and infectious nature necessitates admitting the possibility that these infections may influence events elsewhere in the body. At the sametime, recognition of the interaction between oral diseases and some systemic conditions entails that dentists and periodontists should direct their practice and knowledge not only to events strictly related to the oral cavity but also consider systemic conditions and diseases which may change or interfere with established preventive and therapeutic approaches.

The concept that oral diseases could influence distant structures is, to a certain extent, a return to the theory of focal infection. The evidence supporting this theory dates from around 1900 and it was based on the expert opinion and personal clinical experience of a few physicians and dentists. Some reports of questionable scientific merit have also supported the influence of dental sepsis on systemic health. The return of this concept since the end of the 80's has been investigated in a quite different scenario. Advances in the methods of scientific investigation were undoubtedly decisive in this context. The development of epidemiological studies and statistical analysis, the enhanced understanding of biological plausibility by means of advances in molecular biology, microbiology, immunology and genetics, the possibility of successfully treating periodontal diseases, caries and endodontic infections and retaining teeth instead of

extracting them, all these factors have led dental and medical researchers and clinicians to resume the study of the relationship between oral diseases and systemic conditions with a more scientific approach.[1]

Diabetes mellitus, or DM, is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both.[2] The disease is characterized by an increased susceptibility to infection, poor wound healing, and increased morbidity and mortality associated with disease progression. Diabetes is also recognized as an important risk factor for more severe and progressive periodontitis, infection or lesions resulting in the destruction of tissues and supporting bone that form the attachment around the tooth.

Periodontal diseases is a group of chronic, progressive bacterial infection resulting in inflammation and destruction of tooth supporting tissue. Both diabetes mellitus and periodontitis are chronic diseases affecting large number of population worldwide. Both diseases are thought to share a common pathogenesis that involves an enhanced inflammatory response that can be observed at the local and systemic level. The inflammatory response is mainly caused by the chronic effects of hyperglycemia and specifically the formation of biologically active glycated proteins and lipids that promote inflammatory responses.[3]

The purpose of this review is to make the connection between periodontal disease and diabetes based on information in the literature and to discuss proper management.

Epidemiological Consideration

The prevalence of type 2 diabetes worldwide, which is increasing rapidly, represent a significant burden to human health because of its numerous and often complications. As per WHO estimate, the number of incidence of adults with diabetes will rinse fron 171 million in 2000 to 366 million in the year 2030 over the world.[4] Most predominantly, India is declare as the capital of diabetes because approximately 41 million Indians have diabetes till date and every fifth diabetic in the world is an Indian.[5] Hyperglycemia, polydypsia, polyuria,polyphagia, ketoacidosis, are the characteristic symptoms of diabetes mellitus. The long-term effect may include development of nephropathy, neuropathy, retinopathy, cardiovascular, peripheral, vascular, and cerebrovascular disease.[6]

Periodontal disease is a silent devastating condition and initially may not be taken as muchseriously by the patient because early symptoms are less alarming. It is a group of inflammatory disease that affect the periodontal attachment apparatus. Out of this group of disease, gingivitis, and chronic periodontitis are most commonlyseen clinically. According to one U.S survey, 50% adults are affected by gingivitis, whereas chronic periodontitis is estimated to affect approximately 35% of the adult population where as moderate to advanced forms of the disease is estimated to effect 13% to 15% of adult.[7]

Periodontitis is much more than a localized oral infection. The interrelationship between the periodontitis and diabetes suggests the predisposition of systemic disease to oral infection and vice versa. In order to understand the cellular/molecular mechanisms responsible for such a cyclical association, common changes associated with diabetes and periodontitis that produce a synergy when the conditions coexist are being studied.

Effect of periodontal disease on diabetes

Diabetic patients with periodontitis disease may have increased risk of diabetic complication. In a separate analysis including over 600 subjects periodontal disease is suggested as a significant risk faktor for myocardial infarction and stroke as well as diabetes. The patient with severe periodontitis have 2,3 times high death rate from ischemic heart disease compared to rate in the subjects with or no mild periodontitis. In the subjects with severe periodontitis , the death rate from diabetic nephropathy was 8,5 mm higher subjects with no or mild periodontitis. The overall mortality rate from cardio renal disease was 3,5–fold higher in subjects with severe periodontitis, suggesting that the presence of the periodontal disease poses a risk for cardiovascular and renal mortality.[8] A case controlled study at baseline reported that diabetic patient with severe periodontitis have a greater prevalence of proteinuria, stroke, transient ischemic attack, angina, myocardial infarction, and heart failure than in diabetic patients with mild periodontitis.[9] These findings strongly suggest that with increasing diabetes-related complication, periodontal patients are more likely to develop additional long-term complication.

Effect of diabetes on periodontitis

Till date, influence of diabetes on oral health is extensively studied. Several studies revealed that the degree glycemic control is an important variable in a relationship between diabetes and periodontitis. A large scale analysis showed that individual with type 1 diabetes manifested advanced periodontal diseases with a higher prevalence and severity of gingival inflammation and periodontal destruction being seen in those with a higher glycemic index. Significantly more periodontal attachment loss and alveolar bone was lost in type 1 diabetic patients who had poor glycemic control than those who were well controlled or non-diabetic patient.[10] Similarly in a longitudinal study of

362 subjects, poorly controlled type 2 diabetic subjects showed an 11-fold increased in risk for alveolar bone loss over a two year period compared to non diabetic control subjects.[11] Tooth loss in Pima Indians with type 2 diabetes was reported to be 15 times higher than In those without diabetes. This finding has been confirmed in meta analysis of studies in various diabetics populations. However, no significant risk of longitudinal bone loss has found in well controlled type 2 diabetic patients as compared to non-diabetic controls. Same phenomenon has been pointed out by other reseachers. Significantly higher values of glycosylated hemoglobin, or HbA are reported in children and adolescents with periodontitis.[12]

Large number of investigations has provided the evidence that type 1 and type 2 diabetes increase the risk and severity of periodontitis, and vice versa periodontitis has been shown to have impact on diabetic status by using rodent studies although the underlying mechanism has not been discussed.[13] The assosciation between diabetes mellitus and peridontal disease is therefore, considered to be bidirectional diabetes as a risk factor for periodontitis and perriodontitis as a possible severity for diabetes. In fact, that periodontitis should be considered the sixth "classic" complication of diabetes.[14]

Mechanisms by Which Periodontitis May Influence Diabetes-Related Inflammatory State and Insulin Resistance

That diabetes is a risk factor for increased severity of gingivitis and periodontitis. Evidence has consistently indicated. Conversely, periodontitis may be a risk factor for worsening glycemic control among patients with diabetes and may increase the risk of diabetic complications. Periodontitis may initiate or propagate insulin resistance in a manner similar to that of obesity, by enhancing activation of the overall systemic immune response initiated by cytokines

Findings from the Third National Health and Nutrition Examination Survey (NHANES III) in the United States showed that the prevalence of diabetes among people with periodontal disease (n = 1293) was 12.5%, whereas only 6.3% of periodontally healthy participants (n = 12178) reported that they had diabetes, a 2-fold difference. Other studies have shown an association between the severity of periodontitis and glucose intolerance, signs of metabolic syndrome and additional diabetes-related complications, such as cardiovascular problems.[15]

There is limited knowledge about the mechanisms through which periodontal diseases may influence the diabetic state. In untreated severe periodontal disease, the cumulative surface area of ulcerated pocket epithelium has been estimated to range from 8 to 20 cm2, which approximates the size of the palm of an adult hand.[16] Bacteremia and endotoxemia can be induced by dental procedures, as well as by usual daily activities (such as chewing), leading to an elevated inflammatory state and stimulating increases in the levels of serum inflammatory markers. Thus, locally produced proinflammatory mediators, such as interleukin-1 (IL-1), IL-6, tumour necrosis factor alpha (TNF-α) and prostaglandin E2 (PGE2), move into the systemic circulation and may subsequently exert effects on distant organ systems, as would be the case with other chronic infections or inflammatory processes and resulting in an acute-phase response. Elevated levels of these serum markers and mediators of inflammation have been observed in individuals with periodontitis. Moreover, patients with periodontitis, particularly those with gram-negative organisms such as *Porphyromonas gingivalis*, *Tannerella forsythia* and *Prevotella intermedia*, have significantly higher levels of C-reactive protein (CRP) and fibrinogen than those without periodontitis. Periodontal treatment not only reduces clinically evidentinflammation, but also has been associated with decreases in IL-6, TNF-α and CRP, indicating that periodontal diseases have systemic effects extending beyond the local periodontal environment.

Chronic inflammation through the action of inflammatory mediators is mainly associated with the developmentof insulin resistance, which is influenced by genetically modified environmental factors, including decreased physical activity, poor nutrition, obesity and infection. In the obesity-related model of the development of insulin resistance, activated adipocytes release abnormal levels of bioactive molecules, such as lipids, fatty acids, monocyte chemoattractant protein-1 andvarious inflammatory mediators (e.g., CRP, plasminogen activator inhibitor-1, TNF-α and IL-6). The release of these cytokines and other mediators results in the local recruitment of monocytes within the adipose tissues. With differentiation of the monocytes into macrophages comes an increase in the release of inflammatory factors and chemokines locally within the adipose tissue but also systemically, such that the inflammatory response is propagated to various tissues, especially to insulinsensitive organs such as the liver and skeletal muscle, thus contributing to overall insulin resistance. One of the earliest studies to link the release of inflammatory substances from adipose tissues to insulin resistance in type 2 diabetes showed that TNF-α mRNA and protein were induced locally within adipose tissue and systemically in the plasma. When the expression of TNF-α was inhibited in a rodent model (fa/fa) by use of a recombinant TNF-α receptor– immunoglobulin G chimeric protein, insulin sensitivityimproved, which suggested that this cytokine has a direct role in the

development of insulin resistance. Thus, a mechanism was proposed that links the expression ofTNF-α and other inflammatory mediators to the development of insulin resistance in obesity and type 2 diabetes. In this model, receptor ligands, such as inflammatory cytokines, bacterial lipopolysaccharides, lipids, free fatty acids, other microbial products and advanced glycation end products, activate the intracellular pathways, such as the I-kappa-B (IκB), I-kappa-B kinase-β (IKKβ), nuclear factor-kappa B (NF-κβ) and the protein c-Jun *N*-terminal kinase (JNK) axes. JNK has been shown to promote insulin resistance through the phosphorylation of serine residues in the insulin receptor substrate-1. Insulin receptor signalling, which normally occurs through a tyrosine kinase cascade, is inhibited by counter-regulatory phosphorylation of serine and threonine. Unlike JNK, IKKβ causes insulin resistance through transcriptional activation of NF κB. This protein transcription factor is known to initiate the transcription of a variety of genes for compounds involved in insulin resistance, such as the genes for cytokines (TNF-α, IL-1, IL-6 and IL-8), growth factors, adhesion molecules and acute phase proteins. Activation of IKKβ leads to the phosphorylation of IκB, a cytosolic inhibitor of NF-κB. Phosphorylation targets IκB for ubiquitination and proteasomal degradation, freeing NF-κB to translocate to the nucleus where it regulates the transcription of target genes promoting insulin resistance. Other cellular stressors may activate these pathways, such as proteinkinase C activators and oxidants. Once activated in the tissues, especially in the adipose tissue and associated immune cells, these processes may become self-perpetuating through a positive feedback loop created by theproinflammatory cytokines.

Given these mechanisms promoting insulin resistance, it seems that in individuals with type 2 diabetes and periodontitis, an elevated chronic systemic inflammatory state induced by periodontal disease may contribute to insulin resistance through a "feed-forward" mechanism, worsening glycemic control. This might explainwhy periodontitis increases the risk of poor glycemic control among patients with type 2 diabetes. Periodontitis may also contribute to the elevation of serum inflammation mediators through enhanced in vitro production of TNF-α, IL-1β and PGE2 by monocytes, as has been shown in patients with both diabetes and periodontitis. This may indicate an innate hyperresponsiveness of these monocytes to periodontal bacterial challenge. Periodontitis may also play a role through the translocation of gram-negative species and their products from the periodontal biofilm into the circulation and through direct cytokinemia from the gingival crevicular fluid (i.e., translocation of cytokines from the periodontalspace into the circulation). With regard to the last of these mechanisms, poorer glycemic control was associated with increased levels of cytokines, especially IL-1β, in the gingival crevicular fluid. In individuals with type 2 diabetes and periodontitis, serum levels of TNF-α were significantly correlated with the severity of periodontal destruction, plasma endotoxin and IL-1β levels in the gingival crevicular fluid, but not with body massindex (BMI), serum glucose or hemoglobin A1c (HbA1c) levels. Furthermore, there was a dose–response relationship between the severity of periodontitis and serum TNF-α levels, which suggested that periodontal disease may play a major role in elevating levels of this cytokine,which is closely linked to insulin resistance. An examination of NHANES III data from participants without diabetes revealed a positive association between BMI and clinical attachment loss. Moreover, those in the highest quartile of body mass (BMI ≥ 30.8 kg/m2) had significantly higher serum levels of TNF-α and soluble TNF-α receptors than those in the lowest quartile of body mass (BMI < 24.6 kg/m2). These data suggest that obesity is associated with both systemic inflammation and periodontal disease and that insulin resistance may mediate this relationship.[17]

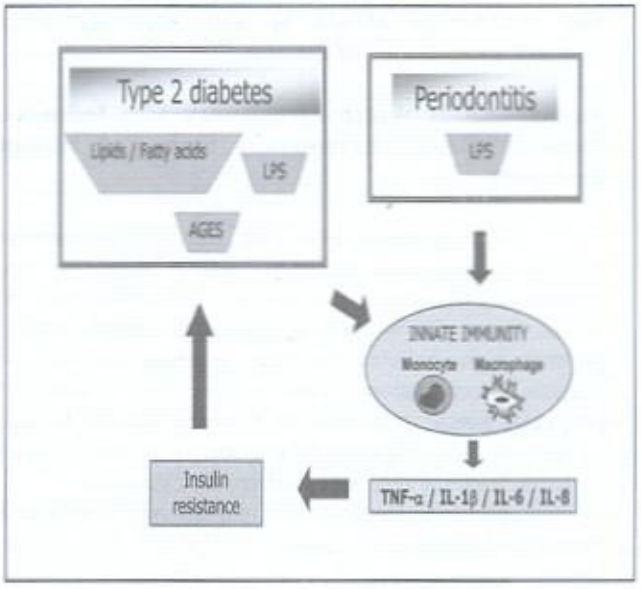

Figure 1 : Innate immunity, periodontitis and type 2 diabetes mellitus. Periodontal diseases also involve activation of the broad axis of innateimmunity through upregulation of proinflammatory cytokines from monocytes and polymorphonuclear leucocytes, including interleukin(IL)-1β, IL-6, IL-8, tumour necrosis factor alpha (TNF-α) and prostaglandin E2. Inappropriate secretion of these cytokines, in terms of either type or quantity, characterizes a dysregulated immune response that leads to destruction of periodontal tissues in the presence of gramnegative bacterial biofilm. These locally produced cytokines move into the systemic circulation, where they may perpetuate an elevated inflammatory state, worsening the patient's diabetes through increasing insulin resistance and glucose levels.[17]
AGES = advanced glycation end products, LPS = lipopolysaccharide

Impact of Periodontal Treatment on Systemic Inflammatory State and Glycemic Control

Periodontal treatment that reduces periodontal inflammation may help to restore insulin sensitivity, thereby improving glycemic control.[18] Intervention studiesshowing a decrease in the level of systemic inflammatory markers and improved glycemic control following periodontaltherapy would support such a hypothesis. Studies of patients with both diabetes and periodontitis have shown that nonsurgical periodontal therapy with adjunctive local delivery of minocycline reduced circulating levels of TNF-α.[19,20] In one of those studies, the reduction in serum levels of TNF-α was accompanied by, and strongly correlated with, a significant decrease in mean HbA1c values (from 8% to 7.1%).[19] Conversely, a pilot studyshowed that serum levels of TNF-α were not significantly affected 4 weeks after mechanical periodontal therapy. In the same study, systemic levels of mediators such as CRP and soluble E-selectin were significantly reduced following nonsurgical periodontal debridement.[21]

Outcomes of a meta-analysis of 10 intervention trials involving 456 patients with diabetes (type 1 or type 2) showed that following mechanical periodontal debridement, HbA1c levels decreased by an average of 0.38% over all studies, by 0.66% among patients with type 2 diabetes and by 0.71% among cases in which antibioticswere administered. However, none of these changes were statistically significant.[22] Other studies have shown significant improvements in glycemic control with periodontal therapy.[23] These conflicting data are difficult to interpret because of the wide range of medical treatment regimens used in study populations, inadequate sample sizes, combined enrolment of patients with type 1 and type 2 diabetes, confounding by smoking and BMI, and study design (e.g., studies examining only short-term outcomes or pilot studies). Although the 0.7% improvement in HbA1c levels attributed to mechanical periodontal debridement and antibiotic therapy reportedin the meta-analysis was not statistically significant, its clinical significance should not be minimized, given that the less potent class of oral glucose-lowering agents, the α-glucosidase inhibitors, reduces HbA1c level by 0.5% to 1%. Other classes of oral agents, such as insulin secretagogues, biguanides and thiazolidinediones, as well as nutritionaltherapy and physical activity, improve glycemic control to a similar degree, with 1% to 2% reduction inHbA1c.[24] Therefore, since periodontal treatment appears to have the same power to lower HbA1c as other glucoselowering therapies, it may represent an alternative or adjunctive therapy for improving insulin sensitivity and glycemic control in patients with both type 2 diabetes and periodontitis.

Final Considerations

As this literature review has indicated, the cytokine induced inflammatory state in periodontitis can contribute to the overall low-grade inflammation that occurs in diabetes. This low-grade inflammation is characterized by chronic activation of the patient's innate immunity and, consequently, may aggravate insulin resistance and adversely affect glycemic control. Current evidence is conflicting, but does support, to some extent, the hypothesis that periodontal treatment may restore insulin sensitivity and improve glycemic control by reducing periodontal inflammation and serum levels of cytokines and inflammatory markers. Further research is requiredto clarify this aspect of how periodontal diseases influence diabetes. As scientific knowledge in this area accumulates, the clinician must determine its relevance
to patient care. Nonetheless, information about host responses and modulation factors in diabetes, periodontitis and diabetes-associated periodontitis may be used for therapeutic purposes. As our understanding of these diseases deepens, the focus is shifting from diagnosis and treatment to prevention and health promotion. Many cases of diabetes may remain undiagnosed, and opportunistic screening for diabetes in the dental office, based on self-reported data and clinical periodontal parameters, might be effective in identifying some of these cases. Active and supportive therapy to improve insulin sensitivity and glycemic control, such as preventing the recurrence of periodontal disease and tooth mortality in patients with diabetes, should be considered important components of treatment. As evidence of the close link between inflammatory periodontal diseases and diabetes continues to accumulate, physicians and oral health professionals should interact to a greater extent, to improve general health care and glycemic control and to prevent complications among patients with diabetes.

References

[1] Weidlich P, Cimões R, Pannuti CM, Oppermann RV (2008) : Association between periodontal diseases and systemic diseases. Braz Oral Res 2008;22 (Spec Iss 1):32-43
[2] Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2000; 23: S4-S19.
[3] Southerland JH, Taylor GW, Offenbacher S (2005): Diabetes and Periodontal Infection: Making the Connection. Clinical Diabetes; 23 : 4
[4] Wild S, Roglic G, Green A, Sicree R, King H (2004) : Global prevalence of diabetes: estimates for the year 2000 and projections for 2030.Diabetes

Care; 27, pp. 1047-53
[5] Joshi SR, Parikh RM (2007) : India-Diabetes capital of the world now heading towards hypertension. J Assoc Physicians India , 55, pp.323-4
[6] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004 ; 27 : Suppl 1, S5-S10
[7] Albander JM, Brunelle JA, Kingman A (1999) : Destructive periodontal disease in adults 30 years of age a and older in United States. J Periodontol ; 70, pp.13-29
[8] Saremi A, Nelson RG, Tulloch-Reid M, Hanson RL, Sievers ML, Taylor GW et al (2005) : Periodontal disease and mortality in type 2 diabetes. Diabetes Care ; 28, pp. 27-32
[9] Thortensson H, Kuylenstierna J, Hugoson A(1996): Medical status and complication in relation to periodontal disease in insulin dependent diabetics. J Clinical Periodontol ; 23, pp.194-202
[10]Tervonen T, Karjalainen K, Knuuttila M, Huumonen S (2000) : Alveolar bone loss in type 1 diabetic subject. J Clinical Periodontol ; 27, pp. 567-71
[11]Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, et al (1998) : Non-insulin dependent diabetes mellitus and alveolar bone loss progression over 2 years. J Periodontol ; 69, pp. 76-83
[12] Karjalainen K, Tervonen T, Kuksa T (1996) : Collagen glycosylation in palatal mucosa in type I diabetic patients and in healthy controls. J Dent Res ; 75, pp. 215
[13] Pontes Anderson CC, Flyvbjerg A, Buschard K, Holmsrtup P (2007) : Relationship between periodontitis and diabetes : Lessons from rodent studies. J Periodontol; 78, pp.1264-75
[14] Loe H. (1993) : Periodontal disease. The sixth complication of diabetes mellitus. Diabetes Care; 16(1), pp. 329-34
[15] Soskolne WA, Klinger A (2001) : The relationship between periodontal diseases and diabetes: an overview. Ann of Periodontol.;6(1), pp. 91-8.
[16] Hujoel PP, White BA, García RI, Listgarten MA (2001) : The dentogingival epithelial surface area revisited. J Periodontal Res.;36(1), pp. 48-55.
[17] Tunes RS,Foss-Freitas MC, Nogueira-Filho G (2010) : Impact of Periodontitis on the Diabetes-Related Inflammatory Status. J Can Dent Assoc; 76: a35
[18] Mealey BL, Rose LF (2008) : Diabetes mellitus and inflammatory periodontal diseases. Curr Opin Endocrinol Diabetes Obes.;15(2), pp. 135-41
[19] Iwamoto Y, Nishimura F, Nakagawa M, Sugimoto H, Shikata K, Makino H, et al (2001) : The effect of antimicrobial periodontal treatment on circulating tumor necrosis factor-alpha and glycated hemoglobin level in patients with type 2 diabetes. J Periodontol.;72(6), pp. 774-8.
[20] Nishimura F, Iwamoto Y, Mineshiba J, Shimizu A, Soga Y, Murayama Y (2003) : Periodontal disease and diabetes mellitus: the role of tumor necrosis factor -alpha in a 2- way relationship. J Periodontol; 74(1), pp.97-102.
[21] Lalla E, Kaplan S, Yang J, Roth GA, Papapanou PN, Greenberg S (2007) : Effects of periodontal therapy on serum C-reactive protein, sE-selectin and tumor necrosis factor-alpha secretion by peripheral blood-derived macrophages in diabetes. A pilot study. J Periodontal Res.;42(3), pp. 274-82.
[22] Jones JA, Miller DR, Wehler CJ, Rich SE, Krall-Kaye EA, McCoy LC, et al (2007) : Does periodontal care improve glycemic control? The Department of Veterans Affairs Dental Diabetes Study. J Clin Periodontol ;34(1), pp. 46-52. Epub 2006 Oct 13.
[23] Faria-Almeida R, Navarro A, Bascones A.(2006) : Clinical and metabolic changes after conventional treatment of type 2 diabetic patients with chronic periodontitis. J Periodontol ; 77, pp. 591-8.
[24] Powers AC (2006) Diabetes mellitus. In: Jameson JL, Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, editors. Harrison's endocrinology & metabolism, 16th ed. Philadelphia [PA]: The McGraw-Hill Companies, Inc. pp. 283-331.

Widyastuti

To Commemorate The 64th Anniversary of The Faculty of Dentistry
Universitas Gadjah Mada, Yogyakarta, Indonesia

The 2nd International Joint Symposium on Oral and Dental Sciences

In Conjunction with Dental Specialists Seminar

Hotel Inna Garuda Yogyakarta, March 1 - 3, 2012

This is to certify that :

Widyastuti , drg., Sp.Perio

has participated in

The 2nd International Joint Symposium on Oral and Dental Sciences as:

POSTER PRESENTER

Given this day, March 3, 2012
in Yogyakarta, Indonesia

SKP PDGI: SKP-N/172/PB PDGI/II/2012

Symposium participant	: 6 SKP
Speaker	: 4 SKP
Hands-on participant	: 3 SKP
Hands-on supervisor	: 5 SKP
Moderator	: 3 SKP
Committee	: 3 SKP
Poster presenter	: 3 SKP
Poster examiner	: 3 SKP

Prof. Dr. drg. Iwa Sutardjo RS., SU, SpKGA(K)
Dean

64th
Panitia Dies FKG UGM

Prof. Dr. drg. Haryo M. Dipoyono, M.S., Sp.Pros(K)
Chairperson of the Anniversary Committee