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RESEARCH ARTICLE

INTER-RELATIONSHIP BETWEEN PREDIABETES, GUTKA CHEWING AND PERIODONTAL INFLAMMATORY CONDITIONS IN PATIENTS WITH CHRONIC PERIODONTITIS

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ABSTRACT

Background: Pre-diabetes is the precursor stage to diabetes mellitus in which not all of the symptoms required to label a person as diabetic are present, but blood sugar is abnormally high. This stage is often referred to as the 'grey area'. Gutka, a smokeless tobacco; a mixture of powdered tobacco, areca nut and slaked lime is known to jeopardize periodontal health; however, severity of periodontal inflammation in gutka chewers with and without prediabetes remains unknown. The aim of this study is to investigate the **i**nter-relationship between pre-diabetes, gutka chewing and periodontal inflammatory conditions.

Methods: In this cross-sectional study, the effect of gutka use on periodontal health is investigated among 50 individuals with prediabetes and 50 without prediabetes. Demographic information regarding age, sex, duration of prediabetes, and gutka-chewing habits was collected using a questionnaire. Periodontal inflammatory conditions (plaque index [PI], bleeding on probing [BOP], probing depth [PD], clinical attachment level [CAL] and fasting blood glucose levels (FBGLs) were recorded.

Results: Periodontal inflammatory parameters (PI, BOP, PD and CAL) were significantly higher in individuals with prediabetes irrespective of gutka-chewing habit ($P < 0.05$). Periodontal inflammation in individuals with prediabetes were higher than in patients without prediabetes (<0.0001). Gutka chewing alone did not significantly increase the periodontal inflammatory conditions. Prediabetic patients were significantly more likely to have periodontal inflammation than individuals without prediabetes (<0.05).

Conclusion: In patients with chronic periodontitis, periodontal inflammatory conditions are worse in gutka chewers compared to non-chewers; in patients with both chronic periodontitis and prediabetes, hyperglycemia governs the severity of periodontal inflammation when compared to habitual gutka usage.

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INTRODUCTION

Periodontal disease is referred to as the sixth complication of diabetes mellitus. It is a group of inflammatory diseases that affect the periodontal attachment apparatus and initially be ignored by the patient because early symptoms are less alarming (Pucher, 1999). Out of this group of diseases, gingivitis and chronic periodontitis are most commonly seen clinically. According to 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 affect 13% to15% of adults (Albander, 1999).

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Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia with disturbances of carbohydrates, fat and protein metabolism resulting from the defects in insulin secretion, insulin action or both (Wild *et al*., 2004). Over the last century there has been a dramatic increase in the incidence of diabetes in the world owing to changes in human behavior and lifestyle. There is much evidence showing a link between type 1 and 2 diabetes mellitus and periodontitis. Diabetes has been associated with a number of oral complications, including gingivitis and periodontitis, dental caries, salivary gland dysfunction and xerostomia, burning mouth syndrome and increased susceptibility to oral infections. In patients with diabetes who are at an increased risk of developing periodontitis, host responses may be impaired, wound healing is delayed and collagenolytic activity may be enhanced. As a result, periodontitis may be a particular

problem in patients with diabetes, especially in those with uncontrolled disease (Vernillo, 2003). Diabetes may also contribute to the pathogenesis of periodontitis via associated vascular compromise, deficits in cell-mediated immunity and the presence of a high glucose content in the blood, enhancing bacterial growth. Furthermore, active inflammation characteristics of periodontitis generates compounds that may increase insulin resistance. Therefore, control of periodontal disease may help patients improve metabolic control. Prediabetes is a state of abnormal glucose homeostasis characterized by the presence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both. Prediabetes designations (IFG and IGT) have been defined by fasting blood glucose levels (FBGLs) of 100 to 125 mg/dL and post-glucose challenge levels of 140 to 199 mg/dL, respectively (Olson, 2010). Individuals with prediabetes might be more susceptible to periodontal inflammation than individuals with normal levels of serum glucose (Javed, 2013). The relationship of the smokeless tobacco and oral carcinoma, white oral mucosal lesions has been well documented (Wray, 1993). These lesions are commonly found in the areas of the mouth where smokeless tobacco products are placed and occur in 50-60% of smokeless tobacco users. In general, localized attachment loss in the form of gingival recession occurs in 25 to 30% of smokeless tobacco users (Robertson, 1990; Greer, 1983 and Poulson, 1984). This attachment loss is most prevalent adjacent to mandibular buccal areas where smokeless tobacco products are commonly placed (Robertson, 1990). *In vitro* studies have demonstrated that smokeless tobacco extracts affect monocyte and oral keratinocyte production of inflammatory mediators which may play a role in the development of these localized tissue alterations. Habitual gutka chewing has been associated with several oral mucosal disorders including periodontal inflammation, oral submucous fibrosis, and oral cancer (Javed, 2008; Javed, 2010; Warnakulasuriya, 2002 and Bathi, 2006). Areca nut, an essential component of gutka, has been associated with several disorders, including epilepsy, hepatocellular carcinoma, metabolic syndrome, impaired glucose tolerance (IGT), and diabetes (Javed, 2010). Slaked lime, areca nut, and powdered tobacco (the major constituents of gutka) are independent risk factors of periodontal inflammation and have known for suppressing the growth of cultured gingival keratinocytes and periodontal fibroblasts (Jeng, 1999 and Chang *et al*., 1998), Studies have also reported that arecoline has a diabetogenic effect and may result in insulin resistance by obstructing insulin signaling. The exact mechanism through which areca-nut chewing induces hyperglycemia remains debatable; however, it has been proposed that areca nut–derived nitrosamines may be diabetogenic in a way similar to streptozotocin, which targets and damages islet b-cell glucose receptors (Balkau, 1999). The aim of the present study is to investigate the severity of periodontal inflammatory conditions in gutka chewers and non chewers with and without prediabetes.

MATERIALS AND METHODS

Ethical Guidelines

The study was conducted from November 2015 to March 2017 and was approved by the ethical committee of GDCH, Ahmedabad. Informed consent was taken from all the participants.

Study Participants

The study group comprised of 100 patients with chronic periodontitis within the age group ranging from (20-45) years. Gutka chewers and non- chewers without prediabetes reporting to department of periodontia, GDCH Ahmedabad were recruited. Prediabetes patients were referred from PSM department, BJ Medical, Ahmedabad.

Interviewer-Administered Questionnaire

Information regarding age, sex, gutka usage (yes/ no), duration of gutka consumption, and duration of placement of gutka in the mouth was recorded using a questionnaire. Participants were categorized into two groups as follows: 1) healthy controls, FBGL <100 mg/dL; RBS (<140mg/dL); (5.6 mmol/L); and 2) individuals with prediabetes, FBGL ≥100 and <126 mg/dL ; RBS(140-199mg/dL) (7.0 mmol/L).

Exclusion criteria

The exclusion criteria were: 1) habitual tobacco smoking or alcohol consumption; 2) completely edentulous status;3) presence of other disorders including acquired immune deficiency syndrome, cardiovascular disorders, renal disease, and hepatitis B or C infection;4) malocclusion (overlapping teeth); and 5) current or recent use of corticosteroid, antibiotic, or non-steroidal anti-inflammatory medications.

Periodontal Examination

Periodontal parameters, which included plaque index (PI), bleeding on probing (BOP), probing depth (PD), and clinical attachment level (CAL) were recorded. PI was recorded on four sites; BOP, PD, and CAL were recorded at six sites on each tooth.

Measurement of FBGLs

Patients were referred to pathology department, GDCH for FBGL estimation. Participants were categorized into two groups as follows: 1) healthy controls, FBGL <100 mg/dL (5.6 mmol/L); and 2) individuals with prediabetes, FBGL≥100 and <126 mg/dL (7.0 mmol/L).

Statistical Analyses

All statistical analyses were two-tailed, with significance level at 0.05, and were calculated using statistical software.

RESULTS

In total, 50 individuals (28 males and 22 females)with prediabetes and 50 (27 males and 23 females)without prediabetes were included. The association of gutka use with periodontal inflammation was first evaluated in the total group and then within individuals with and without prediabetes. Also assessed was the independent association of gutka use with prediabetes irrespective of periodontal inflammation. The mean ages of gutka chewers and nonchewers with prediabetes were 38 years and 38 years, respectively, and without prediabetes, 36 and 39 years, respectively. The mean durations of gutka-chewing habits in individuals with and without prediabetes were 14 and 10 years, respectively. There was no significant difference in the duration of placement of gutka in the oral cavity in either group (Table 1).

Table 1. Study Design

	Individuals without pre-diabetes		Individuals with pre- diabetes	
Characteristic	Non- chewers (Group 1)	gutka chewers (group 2)	Non chewers (Group 3)	gutka chewers (group 4)
n	15	35	20	30
Age (year)	39	36	38	38
Sex (male/ female)	5/10	22/13	10/10	18/12
RBS (mg/dL)	99	98.57	165.35	169.23
Duration of gutka chewing habit (years)	10		14	
Duration of gutka placement in mouth (minutes)	10		8	

Table 2. Differences in key periodontal inflammatory parameters

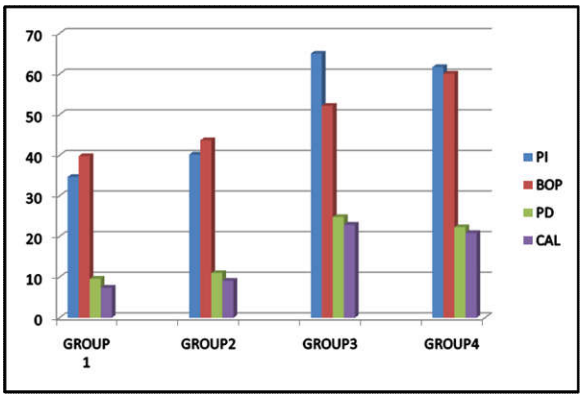
Group comparison for periodontal variables	Group mean difference (%)	95% CI of group mean difference	P value
PI(Percentage of sites)			
Grp 4/grp 3			
Grp4/grp2	61.73-65.05= -3.32	-4.75 to -1.88	NS
Grp4/grp1	61.73-40.2= 21.53	20.18 to 22.87	<0.05
Grp3/grp2	61.73-34.73=27	25.22 to 28.77	<0.05
Grp3/grp1	65.05-40.2=24.85	23.44 to 26.25	<0.05
Grp2/grp1	65.05-34.73=30.32	28.57 to 32.06	<0.05
	40.2-34.73=5.47	3.74 to 7.19	<0.05
BOP (Percentage of sites)			
Grp4/grp 3			
Grp4/grp2	60.13-52.2= 7.93	6.28 to 9.57	<0.05
Grp4/grp1	60.13-43.74= 16.39	15.11 to 17.66	<0.05
Grp3/grp2	60.13-39.8= 20.33	18.37 to 22.28	<0.05
Grp3/grp1	52.2-43.74= 8.46	7.23 to 9.68	<0.05
Grp2/grp1	52.2-39.8= 12.4	10.52 to 14.27	<0.05
	43.74-39.8= 3.94	2.46 to 5.41	<0.05
PD (Percentage of sites)			
Grp 4/grp 3			
Grp4/grp2	22.33-24.8= -2.47	-3.74 to -1.19	NS
Grp4/grp1	22.33-11= 11.33	10.35 to 12.30	<0.05
Grp3/grp2	22.33-9.6 = 12.73	11.47 to 13.98	<0.05
Grp3/grp1	24.8-11= 13.8	12.42 to 15.17	<0.05
Grp2/grp1	24.8-9.6 = 15.2	13.31 to 17.08	<0.05
	11-9.6 = 1.4	-0.01 to 2.81	<0.05
CAL (Percentage of sites)			
Grp 4/grp 3			
Grp4/grp2			
Grp4/grp1	20.9-22.9= -2	-3.90 to -1.71	NS
Grp3/grp2	20.9-9.11= 11.79	10.97 to 12.69	<0.05
Grp3/grp1	20.9-7.4= 13.5	12.60 to 14.39	<0.05
Grp2/grp1	22.9-9.11= 13.79	12.52 to 15.05	<0.05
	22.9-7.4= 15.5	13.86 to 17.13	<0.05
	9.11-7.4= 1.71	0.50 to 2.91	<0.05

Grp 1- Non chewers, non prediabetic; Grp 2- Chewers, non prediabetic; Grp 3- Non chewers, prediabetic; Grp 4- Chewers, prediabetic

The mean RBS among gutka chewers with prediabetes (169.23 mg/dL) was significantly higher than that in gutka chewers without prediabetes (98.57 mg/dL) (P <0.05) (Table 1). The non-chewers with prediabetes had significantly higher RBS (165.35 mg/dL) than gutka chewers without prediabetes (98.57 mg/dL) (P <0.05). In individuals with prediabetes, there was no significant difference in RBS among gutka chewers and non-chewers (Table 1). Periodontal inflammatory conditions (PI, BOP, PD and CAL) were higher in chewers and non-chewers with prediabetes than chewers or non-chewers without prediabetes (P <0.05) [Table 2 and Graph 1].

Table 3. Group comparisons

Group	P Value
Gutka chewers Non-chewers	NS
Prediabetic patients Individuals without prediabetes	<0.0001
Gutka chewers with prediabetes Non chewers with prediabetes	NS
Gutka chewers without prediabetes Non chewers without prediabetes	NS



Graph 1. Periodontal inflammatory conditions in different groups

Table 4. Multivariable analysis of predictors of periodontal inflammatory conditions

Variable	P Value
Female/male	NS
Gutka chewers/ non chewers	NS
With/ without prediabetes	<0.05

Gutka chewing alone, chewing among individuals with and without prediabetes did not statistically increase periodontal inflammation (Table 3). Irrespective of chewing, individuals with prediabetes were more likely to have periodontal inflammation than individuals without prediabetes (Table 4). There was no significant interaction between gutka chewing and prediabetes in relation to periodontal inflammation.

DISCUSSION

Prediabetes has been associated with periodontal disease measures, such as alveolar bone loss (Saito, 2009) A higher percentage of bleeding on probing (BOP) was found among individuals with type 2 diabetes as compared with non‐diabetic individuals (Sandberg, 2000), Other recent studies have reported positive or non‐significant associations mostly between BOP and established type 2 diabetes (Farina, 2010). Different mechanism pathways have been postulated to explain the potential association between established diabetes and periodontal diseases (Manouchehr, 1981). Patients with diabetic mellitus have an increased risk for periodontitis development, probably due to vascular changes, neutrophil dysfunction, altered systemic inflammatory responses, altered collagen synthesis, microbiotic factors or genetic predisposition (Oliver, 1994). Impaired glycemic status has been associated with an increased production and accumulation of reactive oxygen species (ROS) in the body tissues, including the periodontium. This augments periodontal inflammation and alveolar bone loss by decreasing endothelial nitric oxide synthase expression and producing pro-inflammatory cytokines that jeopardize periodontal tissues. ROS production has also been associated with habitual gutka usage. However, the intensity of oxidative stress induced as a result of hyperglycemia exceeds that of gutka chewing (Ohnishi, 2009 and Shevalye, 2012). In this study population, all individuals with prediabetes had raised RBS levels compared with those without prediabetes. It seems that the hyperglycemic state in individuals with prediabetes boosts oxidative stress and pro inflammatory proteins, which in turn masks the contribution of gutka consumption toward jeopardizing periodontal tissues. Multivariate analysis of the predictors of periodontal inflammation also showed pre-diabetic status to be a stronger predictor of periodontal inflammation than gutka chewing habit. In the control group, periodontal inflammatory conditions were worse in gutka chewers compared with nonchewers. The reason may be due to the fact that slaked lime (aqueous calciumhydroxide), an essential ingredient in gutka, has been associated with the oral mucosal inflammation. In parallel, areca nuts contain alkaloids (arecoline) that harms periodontal tissues. Regardless of the form of usage, all tobacco products contain hazardous chemicals with over 4000 known constituents, including carbon monoxide, hydrogencyanide, reactive oxidizing radicals, carcinogens and nicotine. Nicotine is possibly a major contributing factor for almost all the deleterious effects associated with tobacco. Its vasoconstrictive properties are hypothesized to impair gingival blood flow; it binds to root surface (Ryder, 1998), and *in vitro* studies show it alters fibroblast attachment (Persson, 2001 and Boström, 1999) and integrin expression (Giannopoulou, 2003), and decreases collagen production while increasing collagenase production (Rawlinson, 2003), Cultured gingival keratinocytes (Ryder, 2002) and fibroblasts (Evans, 2000), exposed to nicotine produce higher amounts of the proinflammatory cytokines IL-1 and IL-6, respectively.

Furthermore, there is evidence of a synergistic effect on inflammatory mediator production when bacterial lipopolysaccharide is combined with nicotine (Quinn, 1996 and Tangada, 1997), Animal studies have shown that local nicotine delivery negatively impacts bone healing (Barbour, 1997), which may be related to inhibited expression of various growth factors (Benowitz, 1984) and delayed revascularization(Baab, 1987). These findings might help explain the poor outcome of treatment to surgical periodontal procedures, especially those involving tissue regeneration. The fact that the non-chewers with prediabetes had more intense periodontal inflammation than gutka chewers without prediabetes may once again be associated with the hyperglycemic state of the individuals with prediabetes in this study. In this context, the only predictor of periodontal inflammatory conditions in this study population is prediabetes. It has been reported that the severity of periodontal inflammation increases with advancing age. In the study by Javed *et al*. individuals >60 years of age were more prone to periodontal inflammation than younger individuals. In the present study, all participants were approximately 38 years old. It is hypothesized that elderly individuals who habitually chew gutka may display a worse periodontal status than young gutka chewers. However, further studies on a larger sample size are warranted in this regard.

Conclusion

Within the limits of the present study, it is concluded that:

- In patients with chronic periodontitis, gutka chewers have worse periodontal inflammatory conditions compared to non-chewers.
- In patients with both chronic periodontitis and prediabetes, hyperglycemia governs the severity of periodontal inflammation compared to habitual gutka usage.

REFERENCES

Baab, D.A., Oberg, P.A. 1987. The effect of cigarette smoking on gingivalblood flow in humans. *J ClinPeriodontol.,* 14:418-24.

Balkau, B., Charles, M.A. 1999. European Group for the Study of Insulin Resistance (EGIR). Comment on the provisional report from the WHO consultation. DiabetMed 16:442-443.

Barbour, S.E., Nakashima, K., Zhang, J.B., Tangada, S., Hahn, C.L., Schenkein, H.A., *et al*. 1997. Tobacco and smoking: Environmental factorsthat modify the host response (immune system) and have an impacton periodontal health. *Crit Rev Oral Biol Med*., 8:437-60.

Bathi, R.J., Parveen, S., Burde, K. 2009. The role of gutkachewing in oral submucous fibrosis: A case-controlstudy. *Quintessence Int.,* 40:e19-e25.

Benowitz, N.L., Jacob, P. 3rd. 1984. Daily intake of nicotine during cigarette smoking. *ClinPharmacolTher.*, 35:499-504.

Boström, L., Linder, L.E., Bergström, J. 1999. Smoking and crevicularfluid levels of IL-6 and TNF-alpha in periodontal disease. *J ClinPeriodontol.,* 26:352-7.

Chang, M.C., Kuo, M.Y., Hahn, L.J., Hsieh, C.C., Lin, S.K., Jeng, J.H. 1998. Areca nut extract inhibits the growth,

attachment, and matrix protein synthesis of culturedhuman gingival fibroblasts. *J Periodontol.,* 69:1092-1097.

Evans, P., Der, G., Ford, G., Hucklebridge, F., Hunt, K., Lambert, S. 2000. Social class, sex, and age differences in mucosal immunity in alarge community sample. Brain BehavImmun, 14:418.

Farina, R., Scapoli, C., Carrieri, A., *et al*. 2010. Prevalence of bleeding on probing: a cohort study in a specialist periodontal clinic. Quintessence Int., 42: 57–68 [PubMed]

Gacka, M., Dobosz, T., Szymaniec, S., *et al*. 2010. Proinflammatory and atherogenic activity of monocytes in type 2 diabetes. *J Diabetes Complications,* 24: 1–8 [PubMed]

Giannopoulou, C., Kamma, J.J., Mombelli, A. 2003. Effect of inflammation,smoking and stress on gingival crevicular fluid cytokine level. *JClinPeriodontol.,* 30:145-53.

Greer, R.O. Jr, Poulson, T.C. 1983. Oral tissue alterations associatedwith the use of smokeless tobacco by teen-agers, Part I. Clinicalfindings. *Oral Surg Oral Med Oral Pathol* 56:275-84.

Javed, F., Al-Askar, M., Al-Hezaimi, K. 2012. Cytokine profile inthe gingival crevicular fluid of periodontitis patientswith and without type 2 diabetes: A literature review. *J Periodontol.,* 83:156-161.

Javed, F., Altamash, M., Klinge, B., Engstro¨m, P.E. 2008. Periodontalconditions and oral symptoms in gutkachewers with and without type 2 diabetes. *Acta Odontol Scand.,* 66:268-273.

Javed, F., Bello, Correra, F.O., Chotai, M., Tappuni, A.R., Almas, K. 2010. Systemic conditions associated with arecanut usage: A literature review. *Scand J Public Health.,* 38:838-844.

Javed, F., Chotai, M., Mehmood, A., Almas, K. 2010. Oralmucosal disorders associated with habitual gutkausage: A review. Oral Surg Oral Med Oral Pathol *Oral Radiol Endod.,* 109:857-864.

Javed, F., Tenenbaum, Nogueira-Filho, 2013. Periodontal inflammatory conditions among gutka chewers and non-chewers with and without prediabetes. *J Periodontal.,* 84:1158-1164.

Jeng, J.H., Hahn, L.J., Lin, B.R., Hsieh, C.C., Chan, C.P., Chang, M.C. 1999. Effects of areca nut, inflorescence piper betleextracts and arecoline on cytotoxicity, total and unscheduled DNA synthesis in cultured gingival keratinocytes. *J Oral Pathol Med*., 28:64-71.

Manouchehr Pour, M., Spagnuolo, P.J., Rodman, H.M, *et al*. 1981. Impaired neutrophil chemotaxis in diabetic patients with severe periodontitis. *J Dent Res*., 60: 729–730 [PubMed]

Ohnishi, T., Bandow, K., Kakimoto, K., Machigashira, M, Matsuyama, T., Matsuguchi, T. 2009. Oxidative stress causesalveolar bone loss in metabolic syndrome model mice with type 2 diabetes. *J Periodontal Res.,* 44:43-51.

Oliver, R.C., Tervonen, T. 1994. Diabetes–a risk factor for periodontitis in adults? *J Periodontol*., 65(5 Suppl): 530–538 [PubMed]

Olson, D.E., Rhee, M.K., Herrick, K., Ziemer, D.C., Twombly, J.G., Phillips, L.S. 2010. Screening for diabetes and pre-diabeteswith proposed A1C-based diagnostic criteria. Diabetes Care., 33:21842189.

Persson, L., Bergström, J., Ito, H., Gustafsson, A. 2001. Tobacco smokingand neutrophil activity in patients with periodontal disease. *JPeriodontol.,* 72:90-5.

Poulson, T.C., Lindenmuth, J.E., Greer, R.O. Jr. 1984. A comparison of theuse of smokeless tobacco in rural and urban teenagers. *CA CancerJ Clin.,* 34:248-61.

Pucher, J., Stewart, J. 2004. Periodontal disease and diabetes mellitus. *Curr Diab Rep.,* 4:46-50.2.Albander JM, Brunelle JA, Kingman A. Destructive periodontaldisease in adults 30years of age and older in United States. *J Periodontol* 70:13-29.

Quinn, S.M., Zhang, J.B., Gunsolley, J.C., Schenkein, J.G., Schenkein, H.A., Tew, J.G. 1996. Influence of smoking and race on immunoglobulinG subclass concentrations in early onset periodontitis patients. *Infect Immun* 64:2500-5.

Rawlinson, A., Grummitt, J.M., Walsh, T.F., Ian Douglas, C.W. 2003. Interleukin-1 and receptor antagonist levels in gingival crevicularfluid in heavy smokers versus non-smokers. *J ClinPeriodontol.,* 30:42-8.

Robertson, P.B., Walsh, M., Greene, J., Ernster, V., Grady, D., Hauck, W. 1990. Periodontal effects associated with the use of smokeless tobacco. *J Periodontol.,* 61:438-43.

Ryder, M.I., Fujitaki, R., Lebus, S., Mahboub, M., Faia, B., Muhaimin, D., *et al*. 1998. Alterations of neutrophil L-selection and CD18 expressionby tobacco smoke: Implications for periodontal diseases. JPeriodontal Res 33:359-68.

Ryder, M.I., Saghizadeh, M., Ding, Y., Nguyen, N., Soskolne, A. 2002. Effectsof tobacco smoke on secretion of interleukin1□, tumor necrosisfactor-□□and transforming growth factor-□□from peripheral bloodmononuclear cells. *Oral MicrobiolImmunol.,* 17:331-3.

Saito, T., Shimazaki, Y., Kiyohara, Y., *et al.* 2004. The severity of periodontal disease is associated with the development of glucose intolerance in non□diabetics: the Hisayama study. *J Dent Res*., 83: 485–490[PubMed]

Sandberg, G.E., Sundberg, H.E., Fjellstrom, C.A., *et al* 2000. Type 2 diabetes and oral health: a comparison between diabetic and non□diabetic subjects. *Diabetes Res ClinPract.,* 50: 27–34 [PubMed]

Shevalye, H., Lupachyk, S., Watcho, P., *et al*. 2012. Prediabeticnephropathy as an early consequence of the highcalorie/high-fat diet: Relation to oxidative stress. *Endocrinology.,* 153:1152-1161.

Tangada, S.D., Califano, J.V., Nakashima, K., Quinn, S.M., Zhang, J.B., Gunsolley, J.C., *et al*. 1997. The effect of smoking on serum IgG2 reactive with Actinobacillus actinomycetemcomitans in early-onsetperiodontitis patients. *J Periodontol*., 68:842-50.

Vernillo, A.T. 2003. Dental considerations for the treatment of patientswith diabetes mellitus. *J Am Dent Assoc* 134(supplement I):245□335.

Warnakulasuriya, S., Trivedy, C., Peters, T.J. 2002. Areca nutuse: An independent risk factor for oral cancer. *BMJ.,* 324:799-800.

Wild, S., Roglic, G., Green, A., Sicree, R., King, H. 2004. Estimates for theyear 2000 and projections for 2030. Diabetes Care., 27:1047-53.

Wray, A., McGuirt, W.F. 1993. Smokeless tobacco usage associated withoral carcinoma. Incidence, treatment, outcome. *Arch OtolaryngolHead Neck Surg.,* 119:929-33.

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