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內文：

一. Abstract

✓ Periodontal disease (PD) is one of the most commonly known human chronic disorders.The relationship between PD and several systemic diseases such as diabetes mellitus (DM) has been increasingly recognized over the past decades.

✓ Objective:

Data interpretation is often confounded by varying definitions of DM, PD and different clinical criteria were applied to determine the prevalence, extent and severity of PD, levels of glycemic control and diabetes-related complications.

✓ Methods:

Primary research reports on investigations of relationships between DM/DM control, PD/periodontal treatment and PD/DM diabetes-related complications identified relevant papers and meta-analyses published in this period.

✓ Results:

1) The effect of DM on PD
2) The effects of glycemic control on PD
3) The effects of PD on glycemic control and on diabetes-related complications

✓ Conclusions:

The scientific evidence reviewed supports diabetes having an adverse effect on periodontal health and PD having an adverse effect on glycemic control and on diabetes-related complications.

二. Introduction

✓ PD is a chronic infectious disease, caused by Gram-negative microorganisms. An imbalancebetween a localized infection and an exaggerated host inflammatory response plays a pivotal role in determining gingival tissue damage.

✓ Recent evidence suggests that the effect of PD might not be limited just to the oral cavity but it might have systemic consequences. Indeed, PD has also been associated with a moderate systemic inflammatory response.

✓ Although, the mechanisms behind this association remain unclear, PD might represent one distant source of low-grade systemic inflammation

✓ There is strong evidence that the prevalence, severity and progression of PD are significantly higher in people with DM

三. Periodontal disease

✓ PD is a chronic bacterial infection that affects both the gingiva and the bone that supports the teeth and is caused by anaerobic Gram-negative microorganisms that are present in the bacterial plaque that adheres to the teeth.

✓ PD has even higher prevalence in minorities, in poor and developing countries and a considerable global variation

✓ The presence of anaerobic Gram-negative bacteria causes a local inflammatory response that becomes chronic and progressive; this inflammationof the gingiva causes alveolar bone destruction and loss of the tissue attachment to the teeth,

caused by components of microbial plaque that have the capacity to induce an initial infiltrate of inflammatory cells, such as lymphocytes, macrophages, and polymorphonuclear leukocytes (PMNs)

- ✓ Some microbial components, especially lipopolysaccharide (LPS), activate macrophages that synthesize and secrete a great variety and amount of pro-inflammatory molecules, such as the cytokines interleukin-1 (IL-1) and tumor necrosis factor-α(TNF-α): prostangladins, especially prostaglandin E2 (PGE2); and some other enzymes
- ✓ Bacterial toxins can also activate T lymphocytes to produce IL-1 and lymphotoxin (LT), a molecule with properties that are similar to those of TNF-α
- ✓ These cytokines show potent pro-inflammatory and catabolic activities, and have important roles in periodontal tissue destruction caused by collagenolytic enzymes such as metalloproteinases (MMPs)
- ✓ The attachment loss deepens the sulcus, creating a periodontal pocket that contains thousands of millions of bacterial cells. This stage is the transition between gingivitis and periodontitis, the most common PDs
- ✓ Many conditions can predispose and/or facilitate the occurrence of PD such as smoking, genetic influences, estrogen deficiency, estrogen excess, dyslipidemia and obesity. The prevalence of obesity is increasing worldwide. This epidemic is also associated with an increased occurrence of obesity-related diseases like hypertension, cardiovascular disease, metabolic syndrome and DM that are also linked to PD

四. Diabetes mellitus

- ✓ DM is classified according to its etiology as type 1 (T1D), type 2 (T2D), gestational diabetes (GDM) and other specific types.
- ✓ T1D results from the destruction of beta-cells within the islets of Langerhans of the pancreas, which results in a complete insulin deficiency; it can be immune-mediated or have an idiopathic etiology
- ✓ T2D ranges from an insulin resistance which progresses into an insulin deficiency due to a secondary failure in the pancreatic beta-cells
- ✓ GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy.
- ✓ Developed countries have a higher prevalence of DM than developing countries and more women than men are affected with DM
- ✓ In developed countries, the majority of people with DM are older than 65 years. DM will be increasingly occurring in urban areas

五. Effects of diabetes mellitus on periodontal disease

Figure 1- Effects of diabetes mellitus on periodontal disease

Effects of diabetes mellitus on periodontal disease								
Reference	Year	Study design	Diabetes type	Number of subjects (DM/control)	Age (years)	Periodontal evaluation	Other diabetes related variables considered	Conclusions
Cianciola, et al.[13]	1982	Cross-sectional	1	263/208	4 to 33	Prevalence and severity of PD	Diabetes duration	Prevalence and severity of PD in T1D is more strongly related to chronological age than diabetes duration
Emrich, et al.[19]	1991	Cross-sectional	2	1,342/1,877	15 to >55	Probing attachment level, alveolar bone loss, age, sex, calculus index, plaque index, gingival index, fluorosis	Diabetes control	T2D increases the risk of PD independently of age, sex, and hygiene or other dental measures
Thorstensson, et al.[103]	1993	Cross-sectional	1	83/99	40 to 69	Gingival conditions, probing pocket depth and alveolar bone level	Diabetes duration	Age of onset appears to be an important risk factor for PD
Shlossman, et al.[85]	1990	Cross-sectional	1 and 2	736/2,483	5 to ≥45	Probing attachment loss and radiographic bone loss	Biennial oral glucose tolerance test	Subjects with DM had a higher prevalence of PD; DM may be a risk factor for PD
Nelson, et al.[70]	1990	Longitudinal	2	1,363/910	≥15	Tooth loss and interproximal crestal alveolar bone loss	-	PD in subjects with DM is 2.6 times more prevalente than in non-diabetic controls
Taylor, et al.[100]	1998	Longitudinal	2	24/362	15 to 57	Severity of bone loss	-	DM2 is associated with the incidence of alveolar bone loss and increased rate of alveolar bone loss progression
Tervonen, et al.[102]	2000	Cross-sectional	1	35/10	29	Bone loss	Glycemic control; duration of diabetes; diabetes severity	Increased bone loss in subjects with complicated T1D already at an early age.
Sandberg, et al.[80]	2000	Cross-sectional	2	102/102	64	Gingivitis and bone loss	Glycemic control; duration of diabetes; diabetes severity	Subjects with T2D in some oral conditions exhibited poorer oral health
Taylor GW[97]	2001	Review	1,2 and GDM	-	Mixed ages	Evaluation of a bidirectional relationship between DM and PD	-	The majority of the studies provided consistent evidence of a greater prevalence, severity, extent or progression of PD in subjects with DM
Orbak, et al.[74]	2002	Cross-sectional	2	40/20	41	Gingivitis	Glycemic control; diabetes complications	T2D and smoking are high-risk factors for PD
Tsai, et al.[106]	2002	Cross-sectional	2	502/3,841	>45	Loss of periodontal attachment	Glycemic control	Positive association between poorly controlled T2D and severe PD
Zielinski, et al.[113]	2002	Cross-sectional	2	32/40	>60	Pocket depth	Glycemic control; duration of diabetes	No differences in oral health were found between subjects with T2D and those in the control group
Arrieta-Blanco, et al.[5]	2003	Cross-sectional	1 and 2	70/74	11 to 81	Pocket depth; loss of periodontal attachment; bone loss	Glycemic control; duration of diabetes; diabetes severity	The gingivitis index was higher and the treatment was more complex in subjects with DM
Endean, et al.[20]	2004	Cross-sectional	2	289/1,706	15 to ≥45	Pocket depth; tooth loss	None	The severity of PD and tooth loss was greater in subjects with DM than in controls
Lu and Yang[59]	2004	Cross-sectional	2	72/92	54	Gingivitis and loss of periodontal attachment	Glycemic control; duration of diabetes; diabetes severity	In subjects with T2D, PD is more severe than in healthy individuals
Campus, et al.[10]	2005	Cross-sectional	2	71/141	35 to75	Gingivitis and pocket depth	Glycemic control	Subjects with T2D have a susceptibility for more severe PD
Chuang, et al.[12]	2005	Cross-sectional	2	43/85	28 to 85	Pocket depth	Glycemic control; end-stage renal disease	Diabetic uremic patients undergoing hemodialysis exhibited a higher risk for dental decay and xerostomia
Ogunbodede, et al.[73]	2005	Cross-sectional	1 and 2	65/54	25 to 82	Pocket depth	Duration of diabetes	Oral health of a subject with DM with adequate metabolic control, may not be different from that of a non-diabetic
Mattout, et al.[90]	2006	Cross-sectional	2	71/2,073	35 to 75	Gingivitis; pocket depth; loss of periodontal attachment	Fasting blood glucose	PD is more severe in subjects with T2D
Borges-Yánez, et al.[8]	2006	Cross-sectional	2	247/78	>60	Loss of periodontal attachment	Fasting blood glucose	Poorly significant greater prevalence of PD in T2D
Xiong, et al.[112]	2006	Cross-sectional	1, 2 and GDM	256/4,234	15 to 44	Pocket depth or loss of periodontal attachment	Diabetes type	Positive association between PD, GDM and pregestational diabetes (T1D and T2D)
Novak, et al.[71]	2006	Cross-sectional	2 and GDM	113/4,131	20 to 59	Gingivitis and pocket depth and loss of periodontal attachment	Glycemic control; duration of diabetes	Women with GDM may be at greater risk for developing more severe PD than women without GDM
Mittas, et al.[65]	2006	Cross-sectional	GDM	64/88	28	Gingivitis	None	Gingival inflammation seems to be more prevalent in women with GDM
Mealey, et al.[61]	2006	Review	1, 2 and GDM	-	Mixed ages	Relationship between PD and DM	-	All types of DM increase the risk of PD
Jansson, et al.[43]	2006	Transversal	2	191/0	Mixed ages	PD	Glycemic contrrol	Subjects with T2D are at increased risk for PD
Khader, et al.[46]	2006	Meta- analysis (1970 to 2003)	1 and 2	23 studies (total of 19,245)	5 to 78	PD	Severity of PD	Subjects with DM had a significantly higher severity but the same extent of PD than nondiabetics
Lalla, et al.[54]	2006	Case-control	1	182 /160	6 to 18	Gingivitis	Evolution of PD severity	Periodontal destruction can start very early in life in subjects with T1D
Lalla, et al.[53]	2007	Cross-sectional	1 and 2	350/350	6 to 18	Gingivitis and pocket depth and loss of periodontal attachment	Glycemic control; duration of diabetes	Positive association between T1D and an increased risk for PD even very early in life
Demmer, et al.[17]	2008	Longitudinal	1 and 2	652/9,296	25 to 74	Presence of PD and its severity	-	PD is an independent predictor of incident DM2

六. Effects of glycemic control on periodontal disease

- ✓ Current evidence also supports poorer glycemic control contributing to poorer periodontal health
- ✓ Glycemic control worsens in parallel with the worsening of PD

Figure 2- Effects of glycemic control on periodontal disease (GDM= gestational diabetes mellitus)

Effects of glycemic control on periodontal disease						
Reference	Year	Study design	Diabetes type	Age group	Control group	Effect
Sastrowijoto, et al.[82]	1990	Prospective	1	Adults	No	No
Tervonen, et al.[102]	2000	Cross-sectional	1	Adults	Yes	Yes
Sandberg, et al.[80]	2000	Cross-sectional	2	Adults	Yes	No
Tsai, et al.[106]	2002	Cross-sectional	2	Adults	Yes	Yes
Arrieta-Blanco, et al.[5]	2003	Cross-sectional	1 and 2	Mixed ages	Yes	No
Guzman, et al.[37]	2003	Cross-sectional	1 and 2	Adults	No	Yes
Karikoski and Murtomaa[45]	2003	Prospective	1, 2 and others	Adults	No	No
Lu and Yang[59]	2004	Cross-sectional	2	Adults	Yes	Yes
Negishi, et al.[68]	2004	Cross-sectional	1 and 2	Adults	No	Yes
Campus, et al.[10]	2005	Cross-sectional	2	Adults	Yes	Yes
Chuang, et al.[12]	2005	Cross-sectional	2	Adults	No	No
Peck, et al.[75]	2006	Cross-sectional	2	Adults	No	Yes
Jansson, et al.[43]	2006	Cross-sectional	2	Adults	No	Yes
Mealey, et al.[61]	2006	Review	1,2 and GDM	Mixed ages	Yes/No	Yes

七. Effects of periodontal disease on glycemic control and on diabetics-related complications

Figure 3- Effects of periodontal disease on glycemic control and diabetes-related complications

Effects of diabetes mellitus on periodontal disease										
Reference	Year	Study design	Diabetes type	Subjects DM/Control	Age (years)	Study duration	Periodontal treatment	Control group	Metabolic control	Effects on metabolic control and on diabetes-related complications
Williams and Mahan.[109]	1960	Clinical cases	-	9/0	20 - 32	3 - 7 m	Extractions; scaling and probing; gingivectomy; systemic antibiotics	No control group	Insulin requirement; diabetes control	7 in 9 subjects had significant reduction in insulin requirements
Wolf J[110]	1977	Non-RCT	1 and 2	117/0	16 - 60	8 - 12 m	Scaling; home care instructions on oral hygiene; periodontal surgery; extractions; endodontic treatment; restaurations; denture replacement or repair	No control group	Blood glucose levels; 24 hour glycosuria; insulin dose	The treatment of periodontal inflammation and periapical lesions does little to improve diabetes control
Miller, et al.[64]	1992	Non-RCT	1	10/0	Unknown	8 wk	Scaling; systemic doxycycline	No control group	HbA1c; glycated albumin	Decrease in HbA1c and glycated albumin in patients with improved gingival inflammation; patients with no improvement in gingival inflammation had either no change or increase in HbA1c after treatment
Seppala, et al.[84]	1994	Non-RCT	1	38 (1 year); 22 (2 years) **	35 - 56	1 - 2 y	Scaling; surgery and extraction	No control group	HbA1c; blood glucose levels	Improvement of HbA1c levels in poorly controlled and in well controlled T1D
Aldrige, et al.[1]	1995 (Study 1)	RCT	1	16/15	16 - 40	2 m	Oral hygiene instructions; scaling	No treatment	HbA1c; fructosamine	Periodontal treatment showed no effect on improving HbA1c
Aldrige, et al.[1]	1995 (Study 2)	RCT	1	12/10	20 - 60	2 m	Oral hygiene instructions; scaling; extractions and root canal therapy	No treatment	HbA1c	Periodontal treatment showed no effect on improving HbA1c
Grossi, et al.[34]	1996	RCT	2	89/24	25 - 65	12 m	Ultrasonic bactericidal curettage with irrigation using either water, chlorhexidine or polvidone-iodine with or without systemic doxycycline	Ultrasonic curettage with irrigation using water and placebo	HbA1c	The three groups receiving doxycycline and ultrasonic bacterial curettage showed significant reductions in mean HbA1c after three months
Smith, et al.[91]	1996	Non-RCT	1	18/0	26 - 57	2 m	Scaling; oral hygiene instructions	No control group	HbA1c	Periodontal treatment showed no statistically significant effect on improving HbA1c
Westfelt, et al.[108]	1996	Non-RCT	1 and 2	20/20	45 - 65	5 y	Oral hygiene instructions; scaling; periodic prophylaxy; surgery at sites with bleeding on probing; periodontal pocket depth > 5 mm	Same treatment as subjects with T1D	HbA1c	The mean value of glycated HbA1c between baseline untill 24 months was not significantly different from that between 24-60 months
Taylor, et al.[99]	1996	Prospective cohort	2	49 and 56 subjects with severe and lees severe periodontitis and no treatment	18 - 67	2 - 4 y	Not applicable	No control group	HbA1c	Subjects with severe periodontitis were about 6 times more likely to have poor glycemic control at follow-up
Grossi, et al.[33]	1997	RCT	2	89/24	25 - 65	6 m	Periodontal treatment included ultrasonic scaling and curettage combined with one of four different antimicrobial regimens	No treatment	Serum glucose levels; HbA1c	Effective treatment of periodontal infection and reduction of periodontal inflammation is associated with a reduction in levels of HbA1c
Christgau, et al.[11]	1998	Non-RCT	1 and 2	20/20	30 - 66	2 m	Scaling; subgingival irrigations with chlorhexidine; oral hygiene instructions; extractions	Same treatment as subjects with DM	HbA1c	No effect on HbA1c
Collin, et al.[14]	1998	Retrospective cohort	2	25/40 - no subjects received treatment	58 - 77	2 - 3 y	Not applicable	No treatment	HbA1c	In subjects with T2D the HbA1c levels are significantly increased in those with advanced periodontitis
Iwamoto, et al.[41]	2001	Non-RCT	2	13/ 0	19 - 65	1 m	Local minocycline in every periodontal pocket and mechanical debridment once a week for a month	No control group	HbA1c	Anti-infectious treatment is effective in improving metabolic control
Stewart, et al.[94]	2001	Non-RCT	2	36/36	62 - 67	18 m	Scaling; subgingival curettage and root planing; oral hygiene instructions	No treatment	HbA1c; changes in medications doses	Periodontal theraphy was associated with improved glycemic control

Continuation

Rodrigues, et al.[79]	2003	RCT	2	15/15	Unknown	3 m	Scaling; systemic amoxicillin/ clavulanic acid; oral hygiene instructions at baseline and every two w	Same as treatment group, except no medication	HbA1c and fasting plasma glucose	Periodontal therapy was associated with improved glycemic control in treatment group
Skaleric, et al.[80]	2004	RCT	1	10/10	26 - 58	24 wk	Scaling and minocycline microspheres in pockets ≥5 mm at baseline and at 12 w	Scaling	HbA1c	Decreased HbA1c in test and control groups; treatment with minocycline is significantly more effective than scaling alone
Kiran, et al.[44]	2005	RCT	2	22/22	31 - 79	3 m	Scaling; oral hygiene instructions	No treatment	HbA1c; fasting and 2-h post-prandial glucose levels	Decreased HbA1c and 2-h post-prandial glucose levels in treatment group
Promsudthi, et al.[74]	2005	Non-RCT	2	27/25	55 - 80	3 m	Mechanical periodontal treatment and systemic doxycycline for 15 d	No treatment	HbA1c and fasting plasma glucose	No association between periodontal treatment with adjunctive antimicrobial treatment and changes in HbA1c levels
Janket, et al.[4]	2005	Meta- analysis	1 and 2	4/16	Mixed ages	25 y	Scaling; antibiotic	No treatment	HbA1c	Decrease in HbA1c of 0.68% in those patients with type 2 diabetes without antibiotic use, and of 0.71% in those that used antibiotics
Talbert, et al.[75]	2006	Non-RCT	2	25/0	16 - 64	3 m	Scaling	No control group	HbA1c; fasting glucose levels and fasting plasma insulin	Treatment did not decrease the levels of HbA1c
Schara, et al.[43]	2006	Non-RCT	1	10/0	38	12 m	Scaling and local chlorhexidine	No treatment	HbA1c	Decrease in HbA1c after three months of treatment, but no decrease 6 months after the end of the study
Faria-Almeida, et al.[39]	2006	Non-RCT	2	10/10	35-70	6 m	Scaling	Scaling	HbA1c	Significant decrease in HbA1c levels
Jansson, et al.[45]	2006	Transversal	2	38/153	55	2y	No treatment	No control group	HbA1c	The best predictor for severe PD in subjects with T2D is smoking followed by HbA1c levels; T2D subjects are at increased risk for PD
Jones, et al.[44]	2007	RCT	2	82/83	59	4 m	Scaling; doxycycline 100 mg daily for 14 days; chlorhexidine 30 ml during 4 m	Usual care	HbA1c; insulin use	Periodontal and systemic therapies improved glycemic control
Demmer, et al.[7]	2008	Longitudinal	2	9,296	25 - 74	20 y	No treatment	No control group	-	Subjects with PD showed a two-fold increase in the chance of having DM; patients with advanced PD show greater risk for T2D
Darré, et al.[16]	2008	Meta- analysis	1 and 2	9 studies (485)	Mixed ages	-	Periodontal treatment	No treatment	HbA1c	Significant decrease in HbA1c levels
Lamster, et al.[38]	2008	Review	1 and 2	-	Mixed ages	6 y	-	No treatment	-	37/44 cross-sectional studies and 7/7 prospective studies showed a realtionship between DM and PD
Teeuw, et al.[50]	2010	Meta- analysis	2	5 studies (199/183)	Mixed ages	3 - 9 m	Periodontal treatment	No treatment	HbA1c	A significant average decrease of 0.40% in the HbA1c levels, the most important reductions in HbA1c levels were observed in two studies that did not use antibiotics
Simpson, et al.[47]	2011	Meta- analysis	1 and 2	-	18-80	-	Periodontal treatment with and without antibiotics; oral hygiene instructions	No treatment	HbA1c	Improvement in glycemic control after periodontal treatment
Koromantzos, et al.[51]	2011	RCT	2	30/30	40 - 75	6 m	Oral hygiene instructions; non-surgical periodontal treatment every 7 d	Ultrasound prophylaxy	HbA1c	Significant decrease in HbA1c levels in the treatment group
Koromantzos, et al.[52]	2012	RCT	2	30/30	40 - 75	6 m	Oral hygiene instructions; non-surgical periodontal treatment every 7 d	Ultrasound prophylaxy	HbA1c	Effective non-surgical periodontal treatment of subjects with T2D and moderate to severe PD improved significantly HbA1c levels but did not result in a statistically significant improvement in serum levels of inflammatory markers

Abbreviations: RCT, randomized controlled trial; Non-RCT, non-randomized controlled trial-treatment study; D, days; Wk, weeks; M, months; Y, years; HbA1c, glycated hemoglobin - PD= periodontal disease - DM=diabetes mellitus - T1D=diabetes mellitus type 1 - T2D=diabetes mellitus type 2 - GDM=gestational diabetes mellitus

Periodontal disease and diabetes mellitus

八. Summary and conclusions

- ✓ The clinical and epidemiological evidence found in the literature we reviewed provides support for the concept that DM can have adverse effects on PD, that PD worsens in parallel with glycemic control and finally that PD is associated with an increase in the risk for diabetes-related complications.
- ✓ However, further prospective, rigorous, controlled trials with a larger number of patients, in ethnically diverse populations are warranted to establish these relationships and that treating PD can positively influence glycemic control and possibly reduce the burden of diabetes-related complications.

題號	題目
1	下列有系統性疾病與牙周炎關係的敘述，何者錯誤 (A) 隨著牙周炎的嚴重度增加，心臟冠狀動脈疾病的發生率也有增高的趨勢 (B) 未經控制或控制不好的糖尿病患者，會有增高的牙周炎感染率 (C) 若患者曾患有慢性阻塞性肺病（chronic obstructive pulmonary disease）可能會有較多的牙周附連組織喪失情形 (D) 牙周炎不是造成早產、體重過輕嬰兒（preterm、low-birth-weight infants）的危險因數之一
答案(D)	出處：Lindhe Clinical Periodontology and Implant Dentistry, 2008
題號	題目
2	55 歲女性病患有糖尿病，HbAlc 值為 6.5%，接受牙周基本治療後，再評估時發現左下顎第二大白齒遠心側囊袋從 9 mm 改善至 7 mm，X 光片顯示為 3 壁骨缺損，有探測流血，最適合之治療方式為何? (A) 牙周翻瓣手術，但不適合放置骨粉等材料，會容易造成感染 (B) 給予抗生素 HbAlc 降至 6 %以下才能手術 (C) 牙周再生手術 (D) 傷口癒合差，不適合進行牙周手術，直接安排定期維護治療
答案(C)	出處：Clinical Periodontology, Carranza and Newman, Saunders W.B. Co, 2006