

RISK FACTORS IN DIABETIC PROSTHODONTIC PATIENTS FOR PRECANCEROUS CONDITIONS

РИЗИК ФАКТОРИ ЗА ПРЕКАНЦЕРОЗНИ СОСТОЈБИ КАЈ ПРОТЕТИЧКИ ПАЦИЕНТИ СО ДИЈАБЕТ

Berisha V.¹, Kovacevska G.², Trpevska V.³

¹University of Dentistry, Department of prosthodontics, Clinical center of Pristine, Kosovo. ²Faculty of Dentistry, Department of prosthodontics, UKIM, PHO Dental clinical center „Sv. Pantelejmon“, Clinic for prosthodontics, Skopje, ³PHO Dental clinical center „Sv. Pantelejmon“, Clinic for orthodontics, Skopje, R.S. Macedonia.

Abstract

Diabetes Mellitus has become a global epidemic and presents many complications, usually proportional to the degree and duration of hyperglycemia. Many chronic macrovascular and microvascular complications of diabetes have been reported in the literature with few reports about oral complications. At the same time, the incidence of oral cancer has not decreased over the years despite exhaustive research. Recent research has shown that diabetes is one of the contributing factors in the initiation and progression of certain cancers. In addition, certain drugs used for the treatment of diabetic patients may also have a role in cancer initiation, progression and mortality. Epidemiological studies have shown that diabetic patients are at a higher risk in case of common cancers such as pancreatic, liver, breast, colorectal, urinary tract, etc. This article will explore the relationship between diabetes and oral cancer, with its possible mechanisms of carcinogenesis. **Keywords:** Diabetes, insulin, oral manifestations, oral cancer, precancerous lesions.

Апстракт

ДМ стана глобална епидемија, чии компликации се пропорционални со степенот и времетраењето на хипергликемијата. Многу хронични макроваскуларни и микроваскуларни компликации на дијабетес се сретнуваат во литературата, посочувајќи ја појавата на орални компликации. Во исто време, инциденцата на орален карцином не се намалува во текот на годините и покрај исцрпните истражувања. Неодамнешните истражувања покажаа дека дијабетесот е еден од придонесувачките фактори за започнување и напредување на одредени карциноми. Покрај тоа, одредени лекови што се користат за третман на дијабетични пациенти, исто така, можат да имаат улога во иницирање на карцином, негова прогресија и морталитет. Епидемиолошките студии покажале дека дијабетичните пациенти се изложени на поголем ризик во случај на вообичаени карциноми, како што се карциноми на: панкреас, црн дроб, гради, колон, ректум, уринарен тракт итн. Овој труд ќе ги презентира досегашните истражувања за односот помеѓу дијабетес мелитус и оралниот карцином. **Клучни зборови:** Дијабетес, инсулин, орални манифестации, орален карцином, преканцерозни лезии.

Introduction

Diabetes mellitus is a group of metabolic diseases that leads to high levels of blood glucose and is caused when the body does not make any or enough insulin, or does not use insulin well¹. Although there are various causes for less common types of diabetes, including drug- or chemical-induced diabetes, exocrine pancreatic disease, or infections (e.g., cytomegalovirus), the two most common subtypes of diabetes are known as Type 1 or Type 2 diabetes². Type 1 diabetes, formerly known as juvenile diabetes, is a chronic autoimmune disease in which the beta cells in the pancreas create little to no insulin^{2,3}, and accounts for 5% to 10% of all diabetes cases². Type 1 diabetes is generally diagnosed in younger

individuals (usually younger than 25 years of age) and has a strong genetic predisposition. Exogenous insulin is needed to regulate blood glucose levels in people with Type 1 diabetes².

In contrast, Type 2 diabetes accounts for 85% to 90% or more of diabetes cases and is one of the most common chronic diseases, as well as one of the leading causes of death and disability in the U.S.⁴. Type 2 diabetes is characterized by decreased response of target tissues to insulin, requiring increasing levels of insulin for an adequate response, dysregulation of insulin production, and insulin resistance². Type 2 diabetes is associated with excess weight, physical inactivity, family history of diabetes, and certain ethnicities³. Although some people with Type 2 diabetes can help improve their glycemic

control with diet, exercise, and weight loss, patients may require insulin sensitizers that help peripheral tissues take up glucose (i.e., biguanides [metformin] or thiazolidinediones) or oral hypoglycemic agents that either stimulate release of insulin (i.e., insulin secretagogues such as sulfonylureas)². Initial symptoms of diabetes include increased thirst and urination. Other symptoms can include unexplained weight loss, fatigue, blurred vision, increased hunger, and sores that do not heal².

One of the most common causes of death is cancer⁵. Oral cancer, also known as mouth cancer, is cancer of the lining of the lips, mouth, or upper throat⁶. Oral cavity cancer accounts for approximately 3% of all malignancies and is a significant worldwide health problem^{7,8}. Most oral malignancies occur as squamous cell carcinomas (SCCs); despite remarkable advances in treatment modalities, the 5-year survival rate has not significantly improved over the past several decades and still hovers at about 50-60%. In the mouth, it most commonly starts as a painless white patch that thickens, develops red patches, an ulcer, and continues to grow. When on the lips, it commonly looks like a persistent crusting ulcer that does not heal, and slowly grows¹⁰. Other symptoms may include difficult or painful swallowing, new lumps or bumps in the neck, a swelling in the mouth, or a feeling of numbness in the mouth or lips¹¹. Adult males are most commonly affected, with an increased incidence among alcoholics and smokers of sixth and eighth decades of life. The commonly affected sites are buccal mucosa, hard palate, gingiva, floor of the mouth, lips, oropharynx and tongue. The most common risk factor for oral cancer is tobacco. The other risk factors include alcohol, immune defects, genetic factors and viruses such as human papilloma virus, Epstein-Barr virus, hepatitis virus, etc¹². Many oral SCCs develop from premalignant conditions of the oral cavity^{13,14}. A wide array of conditions have been implicated in the development of oral cancer, including leukoplakia, erythroplakia, palatal lesion of reverse cigar smoking, oral lichen planus, oral submucous fibrosis, discoid lupus erythematosus, and hereditary disorders such as dyskeratosis congenital and epidermolysis bullosa¹⁵.

Recent epidemiological studies have shown a strong link between diabetes and cancer. These studies report that cancer patients with diabetes have a worse prognosis than patients without diabetes after treatment. Though diabetes and cancer has many common risk factors such as obesity, male sex and ageing, both Type I and Type II diabetes are associated with more incidence of cancer¹⁶. There are differences in carcinogenesis between diabetes I and diabetes II. Studies have shown that the risk of cancers in breast, colorectum, pancreas, etc. in diabetes II is more compared to diabetes I patients¹⁷.

Diabetes mellitus causes many immunologic and metabolic changes in the oral mucosa. Many studies have shown the relationship of diabetes with periodontal disease and inflammatory diseases of the oral mucosa. Emerging evidences suggests that diabetic patients show more precancerous lesions like erythroplakia and leukoplakia that leads to oral cancer. The association between diabetes and oral cancer is unclear till date. Recent discoveries like anti-tumor effect of metformin can help the diabetologists and oncologists in discovering newer drugs for preventing diabetic complications.

Aim

This review discusses the possible association between diabetes and oral cancer with the available data.

Material and method

The material consists of reviewed articles that search the possible association between diabetes and oral cancer. Studies were selected applying the following inclusion criteria: articles published in English, between January 1998 and January 2020, in scientific journals, original research, studies conducted on a human population.

Discussion

Oral complications and manifestations of diabetes mellitus

Several soft tissue abnormalities have been reported to be associated with diabetes mellitus in the oral cavity. These complications include periodontal diseases (periodontitis and gingivitis); salivary dysfunction leading to a reduction in salivary flow and changes in saliva composition, and taste dysfunction. Oral fungal and bacterial infections have also been reported in patients with diabetes. There are also reports of oral mucosa lesions in the form of stomatitis, geographic tongue, benign migratory glossitis, fissured tongue, traumatic ulcer, lichen planus, lichenoid reaction and angular cheilitis^{18,19,20,21,22}. In addition, delayed mucosal wound healing, mucosal neurosensory disorders, dental carries and tooth loss has been reported in patients with diabetes²³. The prevalence and the chance of developing oral mucosal lesions were found to be higher in patients with diabetes compared to healthy controls²⁴. The discovery of insulin treatment justified a close correlation between the disorder of the carbohydrate metabolism and oral inflammatory complications²⁵. The adequate treatment of diabetes results in marked improvement of the gingival and periodontal lesions. Diabetes patients have further inflammatory complications of the oral mucosa. The decreased rate of

saliva secretion and the low pH value result in chronic cheilitis and glossitis with progressive atrophy of the covering epithelial layer²⁶.

Histological changes of gingiva

The coronal part of the gingival connective tissue underneath the junctional epithelium shows decreased collagen density. Reduction in collagen synthesis and replication of DNA in dermal fibroblasts are seen more in diabetic patients as compared with non-diabetic patients. It is observed that there is an increase in the collagenase activity and abnormalities in neutrophil degranulation due to gingival crevicular fluid collagenase or other metabolic abnormalities in periodontal ligament fibroblasts. The histological sections in diabetic patients showed thickened basement membrane, swollen and proliferated endothelial cells and obliteration of capillaries with narrow capillary lumen²⁷.

Diabetes and cancer

The first association between cancer and diabetes was studied in 1885¹⁰. According to few meta-analysis studies diabetic patients have an increased risk of cancers in endometrium, pancreas, colorectum, etc.^{28,29,30,31,32,33,34}.

Hyperglycemia

Hyperglycemia plays a major role in carcinogenesis. Hyperglycemia generates oxidative stress that damages the DNA and induces carcinogenesis³⁵.

Anticancer drugs and cancer risk

Insulin analogues used in the treatment of cancer have a role in cancer. Insulin is a mitogen that stimulates mitogen-activated protein kinase (AMPK) pathway, which in turn causes cancer. Many in vitro studies have revealed that, increased insulin levels affect angiogenesis and promote tumor progression by stimulating the mitogen pathway through insulin and insulin-like growth factor receptors. Studies have reported that there is less cancer risk in case of metformin as compared to other antidiabetic drugs. This is because of certain anti-tumor characteristics of metformin like cell proliferation inhibition. It could also be due to decreased cancer proliferation with the activation of activated protein kinase (AMP), AMP kinase, which is a mediator of tumor suppressor LKB1³⁶.

Precancerous changes in diabetes

Mihaela et al. reported a case having an eleven-year history of Type II diabetic mellitus with a hyperplastic lesion in the inferior vestibule. The biopsy showed moderate elongation of the rete ridges, epithelial hyperplasia

due to a moderate acanthosis, mild orthokeratosis with focal parakeratosis and basal cell hyperplasia of basal cell layer³⁷.

In the study done by Thomas et al. analyzing the risk factors of leukoplakia, they found that diabetic patients are three times more associated with leukoplakia than non-diabetic patients. This increased incidence might be due to the metabolic and immunologic changes in the oral mucosa³⁸.

Certain studies have reported a possible association between DM and potentially malignant disorders such as erythroplakia^{39,40} leukoplakia^{39,41} and lichen planus^{41,42,43,44}. However, other studies neither demonstrated this association nor found any influence of DM on the duration, distribution, or type of lesion^{45,46}.

The studies conducted in India³⁹ and Hungary⁴⁰ show an increased prevalence of premalignant lesions among diabetic patients.

A study done by Ujpál et al. revealed 25.6% of Type I and 31.3% of Type II diabetic patients had glossitis and chronic cheilitis that are considered to be precursors of malignant transformations. 10.9% of Type I and 16.9% of Type II had benign tumors. 3.2% of Type I and 11% of Type II had leukoplakia or erythroplakia. There were more incidences of gingival cancer (29%) and lip cancer (24%) as compared to the non-diabetic group⁴⁰.

In normal populations, oral cancer mainly involves the tongue, oropharynx and floor of the mouth. The lips, gingiva, dorsum of the tongue and palate are usually not affected⁴⁷. But in people with diabetes, tumors most commonly involve the gums and labial mucosa. Also in contrast to the normal population, in which males are more commonly affected by oral cancer than females, among those with diabetes, tumors are more frequent in females^{39,40}.

Dikshit Rp et al. analyzed data from randomized oral cancer screening trial in Kerala, India, to study the association between chronic diseases in general, diabetes mellitus in particular, and pre-malignant oral lesions and conditions. They found that the incidence of leukoplakia and lichen planus in diabetic patients was more in comparison with non-diabetic patients³⁹.

Bastos et al.⁴⁸ reported a significantly higher prevalence of lichen planus in dm² patients (6.1%) than in control subjects. Van Dis and Parks²⁵ observed lichen planus in 4% of patients with diabetes.

A study by Mohsin et al. revealed more oral mucosal lesions such as geographic tongue, fissured tongue, coated tongue in diabetic than non-diabetic patients. An association between premalignant lesions and diabetic patients was not significant according to their study⁴⁹. Muralidara et al. also did not find any association between precancerous lesions and diabetes. They have

found only lichen planus in diabetes patients⁵⁰. However, according to the study done by Yadiyal et al. there is no correlation between lichen planus and diabetes⁵¹. The occurrence of lichen planus in diabetes patients might also be due to the lichenoid reaction of the drugs⁵².

There are studies on other site-specific cancers which strongly support an increase in cancer risk and mortality in diabetic patients. The molecular mechanisms associated with diabetes and cancer development are still not clear. However, only few research studies have been done on diabetes and oral cancer. The association between diabetes and oral cancers may be due to shared risk factors between the two diseases, such as diet, aging, obesity and physical inactivity. However, the etiologic factors of oral cancer such as tobacco, alcohol can also contribute to oral cancer in diabetic patients. A few studies on oral cancer and diabetes have shown an association between them, while a few studies have indicated the opposite.

Conclusion

More advanced studies are necessary to show a definitive relationship between diabetes and oral cancer. Proper blood glucose control is mandatory to avoid diabetes related complications. For this reason, clinicians and patients should be aware of possible cancer risks in diabetic patients. This awareness will go a long way in reducing the incidence of oncological complications among diabetic patients.

Reference

1. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Diabetes statistics. June 2016. Accessed October 13, 2016.
2. Kidambi S, Patel SB. Diabetes mellitus: considerations for dentistry. *J Am Dent Assoc* 2008; 139 Suppl:8s-18s.
3. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Diagnoses of diabetes and prediabetes. May 2015. Accessed October 14, 2016.
4. CDC Chronic Diseases: The Leading Causes of Death and Disability in the United States. 2015.
5. Petersen PE. Oral cancer prevention and control – the approach of the World Health Organization. *Oral Oncol* 2009;45:454-60.
6. Edge, Stephen B. *AJCC cancer staging manual*. American Joint Committee on Cancer (7th ed.). New York: Springer, 2010.
7. Kademani D. Oral cancer. *Mayo Clin Proc.* 2007; 82(7):878-87.
8. Silverman S Jr. Demographics and occurrence of oral and pharyngeal cancers. The outcomes, the trends, the challenge. *J Am Dent Assoc.* 2001; 132 Suppl:7S- 11S.
9. Ries LAG, Melbert D, Krapcho M, Stinchcomb DG, Howlander N, Horner MJ, Mariotto A, Miller BA, Feuer EJ, Altekruse SF, Lewis DR, Clegg L, Eisner MP, Reichman M, Edwards BK (eds). *SEER Cancer Statistics Review, 1975-2005*, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site, 2008.

10. E., Marx, Robert. *Oral and maxillofacial pathology: a rationale for diagnosis and treatment*. Stern, Diane. Chicago: Quintessence Pub. Co, 2003.
11. CDC. 2019-01-17. Retrieved 2019-03-10.
12. Markopoulos AK. Current aspects on oral squamous cell carcinoma. *Open Dent J* 2012; 6:126-30.
13. Silverman S Jr, Gorsky M, Lozada F. Oral leukoplakia and malignant transformation. A follow-up study of 257 patients. *Cancer.* 1984; 53(3):563-8.
14. Silverman S Jr. Observations on the clinical characteristics and natural history of oral leukoplakia. *J Am Dent Assoc.* 1968; 76(4):772-7.
15. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. *J Oral Pathol Med.* 2007; 36(10):575-80.
16. Sen S, He Y, Koya D, Kanasaki K. Cancer biology in diabetes. *J Diabetes Investig* 2014;5:251-64.
17. Lin Y, Sun Z. Current views on type 2 diabetes. *J Endocrinol* 2010;204:1-11.
18. Sandberg GE, Sundberg HE, Fjellstrom CA, Wikblad KF. Type 2 diabetes and oral health: A comparison between diabetic and non-diabetic subjects. *Diabetes Res Clin Pract.* 2000;50:27-34.
19. Chomkhakhai U, Thanakun S, Khovidhunkit S-P, Khovidhunkit W, Thaweboon S. Oral health in Thai patients with metabolic syndrome. *Diabetes Metab Syndr.* 2009;3:192-7.
20. Collin HL, Niskanen L, Uusitupa M, Töyry J, Collin P, Koivisto A-M, et al. Oral symptoms and signs in elderly patients with type 2 diabetes mellitus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2000;90:299-305.
21. Guggenheimer J, Moore PA, Rossie K, Myers D, Mongelluzzo MB, Block HM, et al. Insulin-dependent diabetes mellitus and oral soft tissue pathologies: I. Prevalence and characteristics of non-candidal lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2000;89:563-9.
22. Guggenheimer J, Moore PA, Rossie K, Myers D, Mongelluzzo MB, Block HM, et al. Insulin-dependent diabetes mellitus and oral soft tissue pathologies. II. Prevalence and characteristics of Candida and candidal lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2000; 89:570-6.
23. Lamster IB, Lalla E, Borgnakke WS, Taylor GW. The relationship between oral health and diabetes mellitus. *J Am Dent Assoc.* 2008; 139:19-24.
24. Saini R, Al-Maweri SA, Saini D, Ismail NM, Ismail AR. Oral mucosal lesions in non oral habit diabetic patients and association of diabetes mellitus with oral precancerous lesions. *Diabetes Res Clin Pract.* 2010; 89:320-6.
25. Kleinman DV, Swango PA, Niessen JC: Epidemiologic studies of oral mucosal conditions: methodologic issues. *Community Dent Oral Epidemiol* 19:129-140, 1991
26. Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, Pettitt DJ: Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. *J Periodont* 1996; 67:1085-1093.
27. Seppälä B, Sorsa T, Ainamo J. Morphometric analysis of cellular and vascular changes in gingival connective tissue in long-term insulin-dependent diabetes. *J Periodontol* 1997; 68:1237-45.
28. Yoon JM, Son KY, Eom CS, Durrance D, Park SM. Pre-existing diabetes mellitus increases the risk of gastric cancer: A metaanalysis. *World J Gastroenterol* 2013; 19:936-45.
29. Parazzini F, La Vecchia C, Negri E, Riboldi GL, Surace M, Benzi G, et al. Diabetes and endometrial cancer: An Italian case-control study. *Int J Cancer* 1999;81:539-42.
30. Li J, Cao G, Ma Q, Liu H, Li W, Han L. The bidirectional interaction between pancreatic cancer and diabetes. *World J Surg Oncol* 2012; 10:171.
31. Huang CW, Sun LC, Shih YL, Tsai HL, Chen CW, Yeh YS, et al.

-
- The impact on clinical outcome of high prevalence of diabetes mellitus in Taiwanese patients with colorectal cancer. *World J Surg Oncol* 2012; 10:76.
32. Zhu Z, Zhang X, Shen Z, Zhong S, Wang X, Lu Y, et al. Diabetes mellitus and risk of bladder cancer: A meta-analysis of cohort studies. *PLoS One* 2013;8:e56662.
 33. Bordeleau L, Lipscombe L, Lubinski J, Ghadirian P, Foulkes WD, Neuhausen S, et al. Diabetes and breast cancer among women with BRCA1 and BRCA2 mutations. *Cancer* 2011; 117:1812-8.
 34. Yang X, Zhao H, Sui Y, Ma RC, So WY, Ko GT, et al. Additive interaction between the renin-angiotensin system and lipid metabolism for cancer in type 2 diabetes. *Diabetes* 2009; 58:1518-25.
 35. Noto H, Goto A, Tsujimoto T, Osame K, Noda M. Latest insights into the risk of cancer in diabetes. *J Diabetes Investig* 2013; 4:225-32.
 36. Sun G, Kashyap SR. Cancer risk in type 2 diabetes mellitus: Metabolic links and therapeutic considerations. *J Nutr Metab* 2011;708183.
 37. Girtan M, Zurac S, Staniceanu F, Bastian A, Popp C, Nichita L, et al. Oral epithelial hyperplasia in diabetes mellitus. *Rom J Intern Med* 2009; 47:201-3.
 38. Dietrich T, Reichart PA, Scheifele C. Clinical risk factors of oral leukoplakia in a representative sample of the US population. *Oral Oncol* 2004;40:158-63.
 39. Dikshit RP, Ramdas K, Hashibe M, Thomas G, Somanathan T, Sankaranarayanan R. Association between diabetes mellitus and premalignant oral diseases: a cross sectional study in Kerala, India. *Int J Cancer* 2006; 118(2):453-7.
 40. Ujjal M, Matos O, Bibok G, Somogyi A, Szabo G, Suba Z. Diabetes and oral tumors in Hungary: epidemiological correlations. *Diabetes Care* 2004; 27(3):770-4.
 41. Albrecht M, Banoczy J, Dinya E, Tamas G Jr. Occurrence of oral leukoplakia and lichen planus in diabetes mellitus. *J Oral Pathol Med* 1992; 21(8):364-6.
 42. Guggenheimer JI, Moore PA, Rossie K, Myers D, Mongelluzzo MB, Block HM, Weyant R, Orchard T. Insulin-dependent diabetes mellitus and oral soft tissue pathologies. I. Prevalence and characteristics of non-candidal lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2000;89(5):563-9
 43. Seyhan M1, Ozcan H, Sahin I, Bayram N, Karıncaoğlu Y. High prevalence of glucose metabolism disturbance in patients with lichen planus. *Diabetes Res Clin Pract.* 2007 Aug; 77(2):198-202.
 44. Skamagas M, Breen TL, Leroith D. Update on diabetes mellitus: prevention, treatment, and association with oral diseases. *Oral Dis.* 2008; 14(2):105-114.
 45. Christensen E, Holmstrup P, Jørgensen FW, Jensen BN, Pindborg JJ. Glucose tolerance in patients with oral lichen planus. *J Oral Pathol.* 1977; 6 (3):143-151.
 46. Van Dis ML, Parks ET. Prevalence of oral lichen planus in patients with diabetes mellitus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1995;79(6):696-700.
 47. Landis SH, Murray T, Bolden S, Wingo PA. *CA Cancer J Clin* 1999; 49(1):8-31.
 48. Bastos AS, Leite AR, Spin-Neto R, Nassar PO, Massucato EM, Orrico SR. Diabetes mellitus and oral mucosa alterations: Prevalence and risk factors. *Diabetes Res Clin Pract.* 2011; 92 (1):100-105.
 49. Mohsin SF, Ahmed SA, Fawwad A, Basit A. Prevalence of oral mucosal alterations in Type 2 diabetes mellitus patients attending a diabetic center. *Pak J Med Sci* 2014; 30:716-9.
 50. Yadiyal M, Shenoy N, Shenoy A, Ahmed J. Are diabetics victims of oral cancer? *Int J Bioassays* 2013; 2:904-6.
 51. Borghelli RF, Pettinari IL, Chuchurru JA, Stirparo MA. Oral lichen planus in patients with diabetes. An epidemiologic study. *Oral Surg Oral Med Oral Pathol* 1993;75:498-500.
 52. Al-Hashimi I, Schifter M, Lockhart PB, Wray D, Brennan M, Migliorati CA, et al. Oral lichen planus and oral lichenoid lesions: Diagnostic and therapeutic considerations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007;103 Suppl: S25.e1-12.