Extrusion of Root Canal Filling Materials in Molars of a Turkish Subpopulation

Emre ÇULHA[1], Fatma TUNÇ[1]

Abstract

Aim This research aimed to investigate the root canal filling sealer or gutta-percha extrusion in molars in a population in Turkiye.
Material and method Cone-beam computed tomography images of 831 endodontically treated molars (284 maxillary first molars, 189 maxillary second molars, 178 mandibular first molars, and 180 mandibular second molars) were examined at three planes by two endodontists. The presence of extrusion, the number of teeth, and the type of molar were determined via the chi-square test at a p-value of 0.05 in SPSS V25 (IBM, Chicago, IL).
Results 13.71 % of the molars had extrusion of root canal filling materials. In maxillary and mandibular molars, extrusion was observed in 17.5% and 8.7% of cases, respectively. Extrusion was seen in 15.8% of maxillary first molars, 20.1% of maxillary second molars, 8.4% of mandibular first molars, and 8.9% of mandibular second molars.
Conclusion Root canal filling material extrusion was statistically detected more in maxillary molars than in mandibular molars. Extrusion was more observed in maxillary second molars than in other molar categories.

Keywords Endodontics, Molar, Root canal obturation, Root canal preparation, Root canal therapy

Introduction

One of the fundamentals of root canal therapy is obturating the root canal space to protect it from bacterial contamination. The root canal obturation material should, in principle, approach the apex without reaching the periapical tissues or other nearby structures (1). However, there is no agreement on the limit of root canal obturation in the apical region. While some authors predicate the apical limit on the apical foramen, apical constriction, or cement-dentin-canal junction, others assert that it is difficult to identify these structures clinically (2, 3, 4). Endodontic treatment shows the best success rate in obturations that ended 0-2 mm short of the length of the root while underfilling and overfilling have substantially lower success rates (5, 6). In the presence of an oval-shaped apical foramen, apical foramina, or lateral canal, extrusion of the root canal sealer is possible (2). The future of the extruded filler material is influenced by its volume and consistency, solubility, and sensitivity to phagocytosis, while biocompatibility determines the compound's influence on endodontic therapy (7).

On whether descending the canal beyond the apex prolongs the periapical healing process, the research is divided. The apical size of root canal fillings is not directly associated with treatment failure (8) unless there is an infection. In addition, the vast majority of overfilled teeth recover successfully with proper endodontic treatment (9). Extruded root canal sealer has no adverse effect on root canal treatment outcomes (7). Other studies, however, have linked root canal therapy failure to overfilling (2, 9, 10). The prognosis of teeth with apical periodontitis is negatively affected by root canals that are overfilled (11).

Gutta-percha, combined with an appropriate sealer, is the most common root canal filling material. Root canal sealers are harmful to cells and have the potential to irritate the tissues around the apex. Gutta-percha is more biocompatible than root canal sealers (12). However, these materials may cause tissue reactions when extruded by functioning as a foreign body in the periradicular tissue (13). This reaction is significantly influenced by the relationship between the material's characteristics, the location of the extrusion, and the immune response (8). Furthermore, the presence of an extraradicular filling substance may hinder the healing phase of apical periodontitis (14). Chemical factors resulting from the cytotoxic effects of root canal filling materials, mechanical factors resulting from canal filling material overflowing into anatomical structures, and thermal factors resulting from the overheating of adjacent tissues as a result of warm filling techniques can all cause tissue damage (15, 16). In addition, overfilled root canals are four times more prone to be unsuccessful than underfilled canals (17).
Cone-beam computed tomography (CBCT) is an imaging method that not only permits clinicians to diagnose and plan treatment but also to investigate extended root fillings in three dimensions (18). This research aimed to assess the presence of extruded root canal sealer or gutta-percha in molars with endodontic treatment in a Turkish subpopulation by using CBCT. The null hypothesis of this research was that there was no difference in the extrusion of root canal-filling materials between molar groups.

Material and Methods

The investigation was conducted with the authorization of the local research ethics commission. The study included a total of 831 molar teeth that had undergone root canal therapy. The

Correspondence: Emre ÇULHA, emreculha@hotmail.com

[1] Gaziantep University, Faculty of Dentistry, Department of Endodontics Gaziantep, Turkiye

Received: 09.07.2023 / Accepted: 02.08.2023 / Published: 31.08.2023

teeth of subjects younger than 18 years old were excluded from the investigation. Exclusion criteria include teeth with exposed apices, external root resorption, advanced periodontal disease, periapical pathology, and teeth that could not be evaluated reliably due to CBCT errors.

A private dental clinic's database was searched for all full-size scans (Orthophos XG 3D, Sirona Dental Systems, USA) with a field volume of 8 x 8 cm and a voxel size of 0.4 mm. This study had no relevance to the radiographic examination. DICOM images were captured and displayed in a dark environment on a 20-inch LED screen with a high resolution. Using the CBCT software (Sirona Galaxis Galileos Viewer Version 1.9.2, Sirona Dental Systems, Germany) images were evaluated concurrently by two endodontists with more than 10 years of CBCT experience. After comparing the results, a definitive consensus was reached. To analyze the periapical sections, the axial, coronal, and sagittal planes of the CBCTs were aligned to the long axis of every root. For this investigation, a root canal was considered to be overfilled and root canal filling material extruded when the root canal sealer or gutta-percha extended beyond the radiographic apex.

Maxillary first molars (n = 284), maxillary second molars (n = 189), mandibular first molars (n = 178), and mandibular second molars (n = 180) were studied. All personal information has been made anonymous. The data included the patient's age, gender, number of teeth, and types of molars. The presence of gutta-percha or canal sealer extrusion in at least one of the roots of molar teeth was also documented.

Statistical analysis

All parameters were evaluated with Windows-based statistical software (SPSS V25; IBM, USA) and presented as frequencies and percentages. Using the chi-square test and a significance level of 0.05, proportional differences were evaluated using the chi-square test.

Results

52.2% (n = 434) of the owners of the molars included in the investigation were female, and 47.8% (n = 397) were male. The average age of the owners of the teeth was 51.5 (standard deviation 12.8, minimum 21, maximum 90). There was no statistical link identified between age, gender, and the presence of root canal-filling material extrusion in molar teeth.

13.71 % of the root canal-treated molar teeth included in the study had extrusion of the canal obturation material. Regarding extrusion, there was a statistical association with the maxillary and mandibular molars. Extrusion occurred substantially more frequently in maxillary molars than in mandibular molar teeth ($p<0.05$) (Table 1).

Table 1: Distribution of molars with extrusion.

	Extrusion		χ^2	p
	Absent n(%)	Present n(%)		
Maxillary molars	390 (82.5)	83 (17.5)	13.601	0.001*
Mandibular molars	327 (91.3)	31 (8.7)		

*p<0.05; chi-square test

Table 2: Distribution of maxillary molars with extrusion.

	Extrusion		χ^2	p
	Absent n(%)	Present n(%)		
Maxillary 1st molars	239 (84.2)	45 (15.8)	1.424	0.233
Maxillary 2nd molars	151 (79.9)	38 (20.1)		

chi-square test

Although more extrusion was observed in maxillary second molars compared to first molars, no statistical difference was detected. Extrusion was most common in maxillary second molars among all molar groups in the current study (Table 2). In the aspect of extrusion, there was no statistically significant variance between mandibular molar teeth. (Table 3).

Table 3: Distribution of mandibular molars with extrusion..

	Extrusion		χ^2	p
	Absent n(%)	Present n(%)		
Mandibular 1st molars	163 (91.6)	15 (8.4)	0.024	0.877
Mandibular 2nd molars	164 (91.1)	16 (8.9)		

chi-square test

Discussion

Regarding the extent of apical root canal obturation, there is no consensus. Some authors suggest that the apical border of the obturation is terminated within the apical narrowing of the root canal (2). However, obturation up to the radiographic apex is typically extruded because the actual apical foramen of the tooth rarely overlaps the radiographic apex (19). Other researchers advocate filling canals that are shorter than the radiographic length of the root (20). There is no agreement on the degree of shortness of the root canal filling (9, 21). There is consensus, however, that root canal filling should not extend beyond the apex. The effectiveness of endodontic treatment with a root canal filling extending 1 mm beyond the apex is inadequate (22). Extruded root canal filling is defined as a material composed of gutta-percha and canal sealer that extends through the periodontal ligament (PDL). Typically, this extrusion only extends to the PDL region at the apical foramen.

Overinstrumentation is the most common cause of extruded fillings. Due to the incorrect determination of the working length, the apical foramen enlarges and the apical structure gets harmed (23). Complex root canal anatomy, apical resorption, and immature roots, which influence the formation of the apical barrier, are frequently observed in teeth with overextended root canal fillings (24, 25). Clinically, primary endodontically treated

non-vital teeth and teeth undergoing retreatment are more likely to be overextended (7, 24, 26). During root canal filling procedures, excessive condensation force, hydrostatic pressure, injectable hot gutta-percha, and the usage of a lentulo spiral contribute to overextended root canal fillings (24, 25, 27, 28). In addition, conditions associated with the filling materials, such as the excessive viscosity of some sealers, the use of excessive sealing material, and gutta-percha that do not meet the standards, lead to overextended fillings (25, 27, 28). No materials and techniques prevent extrusion beyond the apex with certainty (29).

The prognosis of the extruded material depends on its physicochemical properties, particularly its water solubility (30). Although root canal sealers are resorbed to the point where they cannot be detected radiographically, microscopic particles may persist in the periradicular tissues (31). There is no correlation between the nature of the extruded material or its resorption, periapical healing, and treatment outcome (26, 32). Furthermore, there is no consensus regarding the impact of overfilling on the efficacy of endodontic treatment in teeth with periradicular lesions. In teeth with apical periodontitis, excess filling that does not extend beyond 2 mm of the radiographic apex does not affect the result of treatment (9). On the other hand, unsuccessful treatments are intimately related to infection and are not initiated by the material's cytotoxicity (33). In addition, extrusion of obturation material can activate the host's immune system and diminish the healing outcome (7). Although gutta-percha is well tolerated by tissue (12), extruded gutta-percha can delay periapex healing (34). Gutta-percha points may exacerbate this process because zinc may dissolve from its structure (35). Also, extruded gutta-percha cones have a biofilm that allows bacteria to proliferate and makes them immune to the body's defenses (36). This structure could trigger an inflammatory response, resulting in the accumulation of macrophages (37).

The canal-filling technique is the determining factor in gutta-percha and canal sealer extrusion (38). Consequently, the combined use of lateral and vertical condensation techniques statistically considerably increases the potential for overfilling when compared to the single cone or vertical condensation techniques alone. In addition, as a result of the fluidity produced by the heat-applied compaction techniques, more canal sealer may be applied than with the lateral condensation technique, causing it to overflow (39).

Previous investigations assessed the quality of root canal fillings as adequate or inadequate based solely on their length (40, 41) or on their length and lateral adaptation (42, 43). A study focusing on endodontic procedural errors revealed that overfilling was the most prevalent error among all teeth undergoing endodontic treatment (44). Another research using CBCT to assess the condition of root canal fillings discovered that 8.1% of root canal-filled teeth included any kind of extruded material (45). Literature shows that approximately 1.09 to 31.8% of the time, root-filling material overextends (45, 46, 47, 48, 49). Although it is radiographically difficult to distinguish between gutta-percha and root canal sealers, studies investigating only paste extrusion found a prevalence of 6.9% to 8.12% in all teeth (45, 50).

The first limitation of the investigation was the possibility of root canal-filling materials that were too resorbed to be identified by CBCT but detectable histologically (51). The second limitation is that the present study did not evaluate CBCT images of teeth in terms of primary or secondary endodontic interventions. In addition, it was not documented whether the teeth were vital or non-vital before the endodontic procedure, nor was the technique used to fill the root canal recorded. In detecting the presence of extrusion, the current study considered the radiographic apex rather than the apical constriction (52), which was another limitation. Furthermore, while analyzing the extrusion of root canal filling material, it was challenging to distinguish from gutta-percha to root canal sealers using CBCT images.

When all molar groups were evaluated for extrusion, a higher result (13.71%) was determined from previous studies. Besides, our findings revealed a higher incidence of maxillary molar extrusion (17.5%) than studies in the literature (2.13-11.6%) (47, 49, 53, 54). When the numbers relating to the long canal obturations and sealer puffs in a German study, which was the only study in the literature to generate separate data for every molar type, were evaluated collectively, our findings showed higher extrusion in each molar group (45). The current study probably included CBCT images of all patients who applied for varied reasons, not simply endodontic purposes, which may have contributed to these differences in findings.

In the current investigation, the incidence of root canal filling material extrusion in maxillary molars was statistically higher than in mandibular molars, similar to many studies (45, 47, 49). However, while a Turkish study detected overfilling incidences close to each other in maxillary and mandibular molars (53), a Serbian study reported more overfilling in mandibular molars, contrary to the current study (54). These differences may be because these two studies were performed on two-dimensional periapical radiographs may have resulted in results. Although no statistical difference was observed, there was more extrusion in maxillary second molars compared to first molars. Compared to percentage, extrusion was most common in maxillary second molars among all molar groups. This situation may be because of the position of the tooth that did not allow dental operators for appropriate endodontic treatment.

Conclusion

In conclusion, maxillary molars had more root canal-filling material extrusion than mandibular molars. Extrusion was most common in maxillary second molars among all molar groups, with no statistical difference between mandibular molar teeth. Dentists should be especially careful about the extrusion of the obturation material during root canal filling of maxillary molars.

Declarations

Author Contributions: *Conception/Design of Study- E.Ç.; Data Acquisition- F.T., E.Ç.; Data Analysis/Interpretation- F.T.; Drafting Manuscript- F.T., E.Ç.; Critical Revision of Manuscript- F.T., E.Ç.; Final Approval and Accountability- F.T., E.Ç.; Material and Technical Support- F.T., E.Ç.; Supervision- F.T.*

Conflict of Interest: *Authors declared no conflict of interest.*

Financial Disclosure: *Authors declared no financial support.*

REFERENCES

1. Sabeti MA, Nekofar M, Motahhary P, Ghandi M, Simon JH. Healing of apical periodontitis after endodontic treatment with and without obturation in dogs. J Endod. 2006;32(7):628-33.
2. Ricucci D, Langeland K. Apical limit of root canal instrumentation and obturation, part 2. A histological study. Int Endod J. 1998;31(6):394-409.
3. Dummer PM, McGinn JH, Rees DG. The position and topography of the apical canal constriction and apical foramen. Int Endod J. 1984;17(4):192-8.
4. Ponce EH, Vilar Fernández JA. The cemento-dentino-canal junction, the apical foramen, and the apical constriction: evaluation by optical microscopy. J Endod. 2003;29(3):214-9.
5. Siqueira JF, Jr., Rôças IN, Alves FR, Campos LC. Periradicular status related to the quality of coronal restorations and root canal fillings in a Brazilian population. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;100(3):369-74.
6. Gomes AC, Nejaim Y, Silva AI, Haiter-Neto F, Cohenca N, Zaia AA, et al. Influence of Endodontic Treatment and Coronal Restoration on Status of Periapical Tissues: A Cone-beam Computed Tomographic Study. J Endod. 2015;41(10):1614-8.
7. Ricucci D, Rôças IN, Alves FR, Loghin S, Siqueira JF, Jr. Apically Extruded Sealers: Fate and Influence on Treatment Outcome. J Endod. 2016;42(2):243-9.
8. Sjögren U, Figdor D, Persson S, Sundqvist G. Influence of infection at the time of root filling on the outcome of endodontic treatment of teeth with apical periodontitis. Int Endod J. 1997;30(5):297-306.
9. Sjogren U, Hagglund B, Sundqvist G, Wing K. Factors affecting the long-term results of endodontic treatment. J Endod. 1990;16(10):498-504.
10. Bergenholtz G, Lekholm U, Milthon R, Heden G, Odesjö B, Engström B. Retreatment of endodontic fillings. Scand J Dent Res. 1979;87(3):217-24.
11. Siqueira JF, Jr., Rôças IN, Ricucci D, Hülsmann M. Causes and management of post-treatment apical periodontitis. Br Dent J. 2014;216(6):305-12.
12. Olsson B, Wennberg A. Early tissue reaction to endodontic filling materials. Endod Dent Traumatol. 1985;1(4):138-41.
13. Dalopoulou A, Economides N, Evangelidis V. Extrusion of root canal sealer in periapical tissues: Report of two cases with different treatment management and literature review. Balkan Journal of Dental Medicine. 2017;21(1):12-8.
14. Fristad I, Molven O, Halse A. Nonsurgically retreated root filled teeth--radiographic findings after 20-27 years. Int Endod J. 2004;37(1):12-8.
15. Santos-Junior AO, De Castro Pinto L, Mateo-Castillo JF, Pinheiro CR. Success or failure of endodontic treatments: A retrospective study. J Conserv Dent. 2019;22(2):129-32.
16. Scolozzi P, Lombardi T, Jaques B. Successful inferior alveolar nerve decompression for dysesthesia following endodontic treatment: report of 4 cases treated by mandibular sagittal osteotomy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;97(5):625-31.
17. Swartz DB, Skidmore AE, Griffin JA, Jr. Twenty years of endodontic success and failure. J Endod. 1983;9(5):198-202.
18. Pruthi PJ, Dharmani U, Roongta R, Talwar S. Management of external perforating root resorption by intentional replantation followed by Biodentine restoration. Dent Res J (Isfahan). 2015;12(5):488-93.
19. Seltzer S. Long-term radiographic and histological observations of endodontically treated teeth. J Endod. 1999;25(12):818-22.
20. Cheng L, Zhang R, Yu X, Tian Y, Wang H, Zheng G, et al. A comparative analysis of periapical radiography and cone-beam computerized tomography for the evaluation of endodontic obturation length. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;112(3):383-9.
21. Ng YL, Mann V, Gulabivala K. A prospective study of the factors affecting outcomes of non-surgical root canal treatment: part 2: tooth survival. Int Endod J. 2011;44(7):610-25.
22. Moura MS, Guedes OA, De Alencar AH, Azevedo BC, Estrela C. Influence of length of root canal obturation on apical periodontitis detected by periapical radiography and cone beam computed tomography. J Endod. 2009;35(6):805-9.
23. Bergenholtz G, Lekholm U, Milthon R, Engstrom B. Influence of apical overinstrumentation and overfilling on re-treated root canals. J Endod. 1979;5(10):310-4.
24. Vier FV, Figueiredo JA. Prevalence of different periapical lesions associated with human teeth and their correlation with the presence and extension of apical external root resorption. Int Endod J. 2002;35(8):710-9.
25. ElAyouti A, Weiger R, Löst C. Frequency of overinstrumentation with an acceptable radiographic working length. J Endod. 2001;27(1):49-52.
26. Goldberg F, Cantarini C, Alfie D, Macchi RL, Arias A. Relationship between unintentional canal overfilling and the long-term outcome of primary root canal treatments and nonsurgical retreatments: a retrospective radiographic assessment. Int Endod J. 2020;53(1):19-26.
27. Tennert C, Jungbäck IL, Wrbas KT. Comparison between two thermoplastic root canal obturation techniques regarding extrusion of root canal filling--a retrospective in vivo study. Clin Oral Investig. 2013;17(2):449-54.
28. Khabbaz MG, Papadopoulos PD. Deposition of calcified tissue around an overextended gutta-percha cone: case report. Int Endod J. 1999;32(3):232-5.
29. Brooks JK, Kleinman JW. Retrieval of extensive gutta-percha extruded into the maxillary sinus: use of 3-dimensional cone-beam computed tomography. J Endod. 2013;39(9):1189-93.
30. Faria-Júnior NB, Tanomaru-Filho M, Berbert FL, Guerreiro-Tanomaru JM. Antibiofilm activity, pH and solubility of endodontic

sealers. Int Endod J. 2013;46(8):755-62.
31. Lin LM, Pascon EA, Skribner J, Gängler P, Langeland K. Clinical, radiographic, and histologic study of endodontic treatment failures. Oral Surg Oral Med Oral Pathol. 1991;71(5):603-11.
32. Sari S, Duruturk L. Radiographic evaluation of periapical healing of permanent teeth with periapical lesions after extrusion of AH Plus sealer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;104(3):e54-9.
33. Siqueira JF, Jr. Aetiology of root canal treatment failure: why well-treated teeth can fail. Int Endod J. 2001;34(1):1-10.
34. Strindberg L. The dependence of the results of pulp therapy on certain factors. An analytic study based on radiographic and clinical follow-up examination. Actadont Scand. 1956;14.
35. Pascon EA, Spngberg LS. In vitro cytotoxicity of root canal filling materials: 1. Gutta-percha. J Endod. 1990;16(9):429-33.
36. Gutiérrez JH, Brizuela C, Villota E. Human teeth with periapical pathosis after overinstrumentation and overfilling of the root canals: a scanning electron microscopic study. Int Endod J. 1999;32(1):40-8.
37. Noiri Y, Ehara A, Kawahara T, Takemura N, Ebisu S. Participation of bacterial biofilms in refractory and chronic periapical periodontitis. J Endod. 2002;28(10):679-83.
38. Da Silva D, Endal U, Reynaud A, Portenier I, Orstavik D, Haapasalo M. A comparative study of lateral condensation, heat-softened gutta-percha, and a modified master cone heat-softened backfilling technique. Int Endod J. 2002;35(12):1005-11.
39. Gençoğlu N, Garip Y, Baş M, Samani S. Comparison of different gutta-percha root filling techniques: Thermafil, Quick-fill, System B, and lateral condensation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;93(3):333-6.
40. Saunders WP, Saunders EM, Sadiq J, Cruickshank E. Technical standard of root canal treatment in an adult Scottish sub-population. Br Dent J. 1997;182(10):382-6.
41. De Moor RJ, Hommez GM, De Boever JG, Delmé KI, Martens GE. Periapical health related to the quality of root canal treatment in a Belgian population. Int Endod J. 2000;33(2):113-20.
42. De Cleen MJ, Schuurs AH, Wesselink PR, Wu MK. Periapical status and prevalence of endodontic treatment in an adult Dutch population. Int Endod J. 1993;26(2):112-9.
43. Imfeld TN. Prevalence and quality of endodontic treatment in an elderly urban population of Switzerland. J Endod. 1991;17(12):604-7.
44. Yousuf W, Khan M, Mehdi H. Endodontic Procedural Errors: Frequency, Type of Error, and the Most Frequently Treated Tooth. Int J Dent. 2015;2015:673914.
45. Bürklein S, Schäfer E, Jöhren H-P, Donnermeyer D. Quality of root canal fillings and prevalence of apical radiolucencies in a German population: a CBCT analysis. Clinical Oral Investigations. 2020;24:1217-27.
46. Kabak Y, Abbott PV. Prevalence of apical periodontitis and the quality of endodontic treatment in an adult Belarusian population. Int Endod J. 2005;38(4):238-45.
47. Nascimento EHL, Gaêta-Araujo H, Andrade MFS, Freitas DQ. Prevalence of technical errors and periapical lesions in a sample of endodontically treated teeth: a CBCT analysis. Clin Oral Investig. 2018;22(7):2495-503.
48. Moreno JO, Alves FR, Gonçalves LS, Martinez AM, Rôças IN, Siqueira JF, Jr. Periradicular status and quality of root canal fillings and coronal restorations in an urban Colombian population. J Endod. 2013;39(5):600-4.
49. Barrieshi-Nusair KM, Al-Omari MA, Al-Hiyasat AS. Radiographic technical quality of root canal treatment performed by dental students at the Dental Teaching Center in Jordan. J Dent. 2004;32(4):301-7.
50. Koçak B, Önay EO, Koç C, Üngör M. Taşkın kök kanal dolgu patları ve bunların çeşitli risk faktörleriyle ilişkilerinin incelenmesi: Retrospektif bir araştırma. Turkiye Klinikleri J Dental Sci.2022.
51. Ricucci D, Siqueira JF. Endodontology: an integrated biological and clinical view: Quintessence Publishing London; 2013.
52. Ng YL, Mann V, Rahbaran S, Lewsey J, Gulabivala K. Outcome of primary root canal treatment: systematic review of the literature -- Part 2. Influence of clinical factors. Int Endod J. 2008;41(1):6-31.
53. Er O, Sagsen B, Maden M, Cinar S, Kahraman Y. Radiographic technical quality of root fillings performed by dental students in Turkey. Int Endod J. 2006;39(11):867-72.
54. Vukadinov T, Blažić L, Kantardžić I, Lainović T. Technical quality of root fillings performed by undergraduate students: a radiographic study Sci World J. 2014;2014:751274.