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ORIGINAL ARTICLE

High prevalence of radiolucent periapical lesions amongst patients with inherited coagulation disorders

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Summary. Apical periodontitis (AP) is an inflammatory lesion around the apex of a tooth caused by bacterial infection of the pulp canal system. AP appears radiographically as a radiolucent periapical lesion (RPL). The elective treatment for teeth with AP is root canal treatment (RCT). No study is available about the frequency of RPL and RCT in patients with inherited coagulation disorders (ICD). The aim of this study was to investigate the prevalence of RPL and RCT in patients with ICD and control subjects. In a cross-sectional study, the radiographic records of 58 patients with haemophilia A, haemophilia B or von Willebrand's disease (study group) and 58 control subjects were examined. The frequency of RPL and RCT was assessed using digital panoramic radiographs and the Periapical Index. RPL in one or more teeth was found in 67.2% of patients with ICD and in 48.3% of control subjects (odds ratio = 2.20; $P = 0.038$). At least one RCT was found in 34.5% and 65.5% of subjects in the study and control groups respectively (odds ratio = 0.28; $P = 0.001$). Multivariate logistic regression analysis indicated that subjects with ICD had RPL with higher likelihood than control subjects (odds ratio = 7.4; $P = 0.0005$). Patients with ICD disorders showed a significantly higher prevalence of RPL and lower frequency of RCT than control patients.

Keywords: apical periodontitis, coagulation disorders, endodontics, haemophilia, oral epidemiology, radiolucent periapical lesions, von Willebrand's disease

Introduction

A tight mutual network between inflammation, coagulation and fibrinolysis has been suggested [1]. Increasing evidence points to extensive cross-talk between these three systems, whereby inflammation leads not only to activation of coagulation, but coagulation also considerably affects inflammatory activity [2]. Furthermore, wound healing involves a number of physiological mechanisms including coagulation, inflammation, formation of granulation tissue and tissue remodelling [3]. It has been shown that wounds on haemophilic animals healed more slowly than wounds on wild-type animals, establishing that the coagulation defect in haemophilia is associated with delayed wound healing [4].

Apical periodontitis (AP) is inflammation of the periodontium at the root apex of a tooth consecutive to an infection of the dental pulp, generally provoked by caries. AP occurs as a sequel of tooth decay, once caries lesion reaches the pulp causing irreversible pulpitis and pulp necrosis. Then, polymicrobial and antigenic content of the root canal passes through the apical foramen, or lateral canals, and invades the periradicular or periapical connective tissue triggering an inflammatory and immune response [5]. Chronic AP develops as a chronic inflammatory process characterized radiographically by the presence of periapical radiolucency, i.e. a radiolucent image surrounding the apex of the affected tooth [6]. Thus, AP appears radiographically as a radiolucent periapical lesion (RPL). AP is a remarkably prevalent problem both in USA [7] and Europe [5,8]. The elective treatment for teeth with AP to achieve satisfactory periapical wound healing is root canal treatment (RCT) [5,7].

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The periapical radiolucency that characterized chronic AP results from the bone loss consecutive to the interaction between a microbial challenge and immune response, involving recruitment of inflammatory cells, generation of cytokines, elaboration of lytic enzymes and activation of osteoclasts, which lead to alveolar bone resorption [9]. Taking into account that chronic inflammation and tissue repair are both processes deeply involved in periapical health, periapical wound healing could be altered in patients with inherited coagulation disorders (ICD). Nevertheless, no study is available about the frequency of RPL in patients with ICD.

The purpose of this study was to determine the prevalence of RPL and RCT in a sample of patients with VWD and haemophilia comparing it with that of control healthy subjects.

Materials and methods

The protocol was approved by the Ethical Committees of the University of Sevilla (Sevilla, Spain) and the 'Virgen del Rocío' University Hospital (Sevilla, Spain). Each subject signed a consent form after being advised of the nature of the study.

Patients selection

Participants were recruited amongst patients presenting consecutively seeking routine dental care (not emergency care) at the 'Virgen del Rocío' University Hospital (Sevilla, Spain) between the years 2008 and 2011. Subjects reporting a history of haemophilia A, haemophilia B or VWD, diagnosed according to the criteria of the World Federation of Haemophilia [10], were asked to voluntarily participate. Inclusion criteria were as follows: patients older than 18 years, having at least eight remaining teeth and who agreed a radiological examination. Exclusion criteria encompassed patients younger than 18 years old, having less than eight remaining teeth or who did not agree to a radiological examination. A total of 58 patients, 41 men and 17 women (36.0 ± 11.0 years), who agreed and met the inclusion/exclusion criteria constituted the 'study group'. Type of bleeding disorder (haemophilia A, haemophilia B and von Willebrand's disease) and degree of severity of disease in patients with hereditary coagulation disorders (assessed using the criteria of the World Federation of Haemophilia) are shown in Table 1.

An additional 58 subjects, 41 men and 17 women (34.4 ± 10.2 years), reporting no history of ICD and who agreed and met the same inclusion/exclusion criteria, constituted the 'control group'. Controls were recruited from patients of the same health district, seeking for the first time routine dental care (not emergency care) at the Dental Clinic of the School of Dentistry of the University of Sevilla between the years 2008 and 2011.

Table 1. Type of bleeding disorder (haemophilia A, haemophilia B and von Willebrand's disease) and degree of severity of disease in patients with hereditary coagulation disorders (n = 58).

	Haemophilia A	Haemophilia B	von Willebrand's disease
Number (%)	33 (56.9)	5 (8.6)	20 (34.5)
Severity			
Mild	18 (54.5)	1 (20.0)	16 (80.0)
Moderate	5 (15.2)	2 (40.0)	2 (10.0)
Severe	10 (30.3)	2 (40.0)	2 (10.0)

Radiographic examination

Radiographic periapical status was diagnosed on the basis of examination of digital panoramic radiographs of the jaws. Two trained radiographic technicians, with over 10 years of experience, took the panoramic radiographs using a digital orthopantomograph machine (Promax®, Planmeca, class 1, type B, 80 KHz; Planmeca, Helsinki, Finland).

Radiographic evaluation

The periapical status was assessed using the 'Periapical Index' (PAI) score [11], as described previously [12,13]. A score greater than 2 (PAI $\geq$ 3) was considered to be a sign of periapical pathology. The worst score of all roots was taken to represent the PAI score for multirooted teeth. Teeth were categorized as root-filled teeth (RFT) if they had been filled with a radiopaque material in the root canal(s).

The following information was recorded on a structured form for each subject: (i) number of teeth present; (ii) number and location of teeth having identifiable RPLs, (iii) number and location of RFT and (iv) number and location of RFT having identifiable RPLs.

Observers' calibration

Three observers with extensive clinical experience in endodontics examined the radiographs. Before evaluation, the observers participated in a calibration course for PAI system, which consisted of 100 radiographic images of teeth, some root-filled and some not, kindly provided by Dr. Ørstavik. Each tooth was assigned to one of the PAI scores by using visual references (also provided by Dr. Ørstavik) for the five categories within the scale. After scoring the teeth, the results were compared with a 'gold standard atlas', and a Cohen kappa was calculated (0.78–0.83).

Intraobserver reproducibility was evaluated for each examiner. Every observer scored the panoramic radiographs of 20 patients (10 of each group, randomly

selected). Then, 1 month after this first examination, the observer was recalibrated in the PAI system and repeated the scoring of the radiographs of the same 20 patients. The intraobserver agreement–test on PAI scores on the 20 patients produced a Cohen's kappa ranging 0.84–0.91.

Finally, intraobservers reproducibility was also determined comparing the PAI scores on the 20 radiographs provided by each observer. The agreement–test produced a Cohen's kappa ranging 0.84–0.91. The Cohen's kappa for interobservers variability ranged 0.79–0.87. The consensus radiographic standard was the simultaneous interpretation by the three examiners of the panoramic radiograph of each patient [14,15].

Statistical analysis

The minimal sample size ($n = 58$) was calculated for the comparison of proportions in two independent samples, taking into account a two-sided significance level of 5% ($\alpha = 0.05$, $Z\alpha = 1.960$), a 80% power ($\beta = 0.20$, $Z\beta = 0.842$) to detect a significant difference, a hypothesized difference between the proportion of the two groups of 25 points (prevalence of AP reported previously in Spain ~50% [8], hypothesized prevalence of AP in the study group = 75%).

Raw data were entered into Excel (Microsoft Corporation, Redmond, WA, USA). All analyses were done in an SPSS environment (Version 11; SPSS, Inc, Chicago, IL, USA). The Student *t*-test, chi-squared test and logistic regression analysis were used to determine the significance of differences between groups. Data are reported as mean ± standard deviation.

Results

The distribution of analysed variables in the two groups is shown in Table 2. The average number of teeth per patient was 25.4 ± 3.6 and 26.8 ± 4.2 teeth in study and control groups, respectively ($P > 0.05$). In the study group, the average number of teeth with RPL was 1.4 ± 1.6, whereas in the control group it was 0.6 ± 0.8 ($P < 0.01$). The number of RFT was significantly lower in the study group (0.5 ± 0.9) compared with control (1.8 ± 2.0) ($P < 0.01$).

Table 3 shows the odds ratio (OR) values and their 95% confidence interval. In the study group 11 patients (19.0%) were smokers, whereas in the control group there were 31 smokers (53.4%). RPL in one or more teeth was found in 39 coagulopathy patients (67.2%) and in 28 control subjects (48.3%) ($P = 0.038$; OR = 2.20; CI 95% = 1.04–4.67). One or more RFT were found in 20 (34.5%) and 38 (65.5%) subjects of the study and control groups respectively ($P = 0.001$; OR = 0.28; 95% CI = 0.13–0.60). Amongst patients with coagulation disorders with RFT, 14 (70%) had RPL affecting at least one treated tooth. In control subjects with RFT, 14

Table 2. Distribution of analysed variables amongst patients with hereditary coagulation disorders (study group) and normal subjects (control group).

	Study group $n = 58$ (50%)	Control group $n = 58$ (50%)	Total $n = 116$ (100%)	*P* value
Age/years				
Mean ± SD	36.0 ± 11.0	34.4 ± 10.2	35.2 ± 10.6	*t*-test > 0.05
Gender				
Male (%)	41 (70.7)	41 (70.7)	82 (70.7)	χ^2 test > 0.05
Female (%)	17 (29.3)	17 (29.3)	34 (29.3)	
No. teeth				
Mean ± SD	25.4 ± 3.6	26.8 ± 4.2	26.1 ± 4.0	*t*-test > 0.05
Median	23.5	27.5	27	
Smoking				
Yes (%)	11 (19.0)	31 (53.4)	42 (36.2)	χ^2 test < 0.001
No (%)	47 (81.0)	27 (46.6)	74 (63.8)	
Teeth with AP				
Any (%)	39 (67.2)	28 (48.3)	67 (57.8)	χ^2 test < 0.05
None (%)	19 (32.8)	30 (51.7)	49 (42.2)	
No. of teeth with AP				
Mean ± SD	1.4 ± 1.6	0.6 ± 0.8	1.0 ± 1.3	*t*-test < 0.01
Median	0.5	0	1.0	
RFT				
Any (%)	20 (34.5)	38 (65.5)	58 (24.1)	χ^2 test < 0.01
None (%)	38 (65.5)	20 (34.5)	58 (75.9)	
No. of RFT				
Mean ± SD	0.5 ± 0.9	1.8 ± 2.0	1.2 ± 1.7	*t*-test < 0.01
Median	0	1	0.5	
RFT-AP				
Any (%)	14 (70.0)	14 (36.8)	28 (48.3)	χ^2 test < 0.02
None (%)	6 (30.0)	24 (63.2)	30 (51.8)	
No. of RFT-AP				
Mean ± SD	0.3 ± 0.6	0.3 ± 0.6	0.3 ± 0.6	*t*-test > 0.05
Median	0	0	0	

RFT, root-filled teeth; AP, apical periodontitis; RFT-AP, root-filled teeth with apical periodontitis.

Table 3. Estimation of odds ratio (OR) values, and their 95% confidence interval (CI), using chi-squared test, for the association between the prevalence of smoking habits, apical periodontitis, root-filled teeth (RFT) and root-filled teeth with apical periodontitis (RFT-AP) in patients with hereditary coagulation disorders (study group, SG; $n = 58$) and normal subjects (control group; $n = 58$).

	Smoking (%)	Apical periodontitis (%)	RFT (%)	RFT-AP (%)
Study group	11 (19.0)	39 (67.2)	20 (34.5)	14 (70.0)
Control group	31 (53.4)	28 (48.3)	38 (65.5)	14 (36.8)
Total	42 (36.2)	67 (57.8)	58 (50.0)	28 (48.3)
OR SG	0.20	2.20	0.28	4.00
95% CI OR	0.09–0.47	1.04–4.67	0.13–0.60	1.25–12.79
P value	0.0001	0.038	0.0008	0.016

(36.8%) had RPL affecting at least one treated tooth ($P = 0.02$; OR = 4.0; 95% CI = 1.3–12.8).

Multivariate logistic regressions were run with age, gender, number of teeth, smoking (no/yes), endodontic status (at least one root-filled tooth, no/yes) and coagulation status (control/inherited coagulation disorder) as independent variables, and periapical status (at least one tooth with RPL, no/yes) as the dependent variable and outcome (Table 4). In the multivariate analysis including all the above factors as covariates, coagulation status (OR = 7.4; 95% CI = 2.4–22.6; $P = 0.0005$) remained highly significant, indicating that subjects with ICD have RPL with higher likelihood than control subjects. Smoking (OR = 6.0; 95% CI = 2.0–18.5; $P = 0.0016$) and endodontic status (OR = 3.5; 95% CI = 1.3–9.3; $P = 0.0126$) were also significantly associated with the presence of RPL.

Discussion

This cross-sectional study aimed to investigate the prevalence of RPLs in patients with ICD and control healthy subjects. Results reveal a significant association between ICD and the presence of radiographically diagnosed periapical lesions.

In the evaluation of the apical periodontium, bone density changes present in radiographs are the most consistent feature of the presence, progression or resolution of periapical inflammation. Although there seemed to be no standard criteria for the registration of AP in epidemiological surveys, either for periapical radiographs or panoramic radiographs, the 'PAI' scoring system has been modified and applied to epidemiological [8,16–18] and clinical comparative studies of treatment outcome [19,20]. Panoramic digital images were used to diagnose periapical radiolucencies. The fact that all teeth can be seen on one panoramic radiograph, the relatively low exposure to ionizing radiation, the convenience of panoramic radiographs and the speed with which they can be obtained are advantageous when compared with full-mouth periapical radiographs [21]. Thus, panoramic radiograph is a highly viable tool to implement studies in a rapid fashion [22], and a lot of epidemiological studies have been carried out using panoramic radiographs [13,16,18,23–26].

Table 4. Multivariate logistic regression analyse of the influence of the independent variables age, gender (0 = woman, 1 = man), number of teeth, smoking (0 = non-smoker, 1 = smoker), endodontic status (0 = no root-filled teeth, 1 = at least one root-filled tooth) and 'coagulation status' (0 = healthy control, 1 = hereditary coagulation disorder) on the dependent variable 'periapical status' (0 = no tooth with apical periodontitis, 1 = one or more tooth with apical periodontitis).

Dependent variable	*B*	*P*	Odds ratio	CI 95% Inf. limit	CI 95% Sup. limit
Age	0.0204	0.3795	1.0206	0.9753	1.0680
Gender	0.4308	0.3743	1.5386	0.5947	3.9803
No. teeth	−0.0460	0.4648	0.9551	0.8443	1.0804
Smoking	1.7995	0.0016	6.0463	1.9811	18.4536
Endodontic status	1.2519	0.0126	3.4968	1.3080	9.3488
Coagulation status	1.9991	0.0005	7.3823	2.4105	22.6086

Overall model fit: $\chi^2 = 32.4826$; d.f. = 6; $P = 0.0000$.

Results show that RPLs are found in a significantly higher percentage of patients with coagulopathies (67.2%), whereas they are only found in 48.3% of control subjects (OR = 2.2; 95% CI = 1.0–4.7; $P = 0.034$). Multivariate logistic regression analysis carried out with periapical status as outcome has shown that this association remained significant after adjusting for age, gender, number of teeth, smoking status and endodontic status (OR = 7.4; 95% CI = 2.4–22.6; $P = 0.0005$). These results agree with a previous report which found a worse oral health status in haemophilic patients compared with healthy control subjects [27]. However, it has been reported that children with severe haemophilia have a significantly lower prevalence of dental caries compared with matched, healthy controls [28].

The fact that in this study ICD came out as a risk factor for periapical disease indeed is striking, particularly from the aspect that coagulopathies hardly can be regarded as a primary cause of root canal infection and AP while caries, restorative procedure and dental trauma are. Therefore, it may be that the study design had not properly considered all relevant confounding factors. The wide odds ratio confidence interval, especially in the multivariate analysis (95% CI = 2.4–22.6), could be explained by this reason. Moreover, this study is cross-sectional, and it is difficult to control for confounding factors in cross-sectional studies, particularly when any influence on AP is likely to be multifactorial [24]. Additional studies must been developed matching the cases with well-known risk factors for AP such as caries, quality of coronal restorations and history of trauma.

Root-filled teeth [8,29] and smoking habits [5,13,30,31] have been shown to be significantly associated with radiographically diagnosed periapical lesions. However, in this study the number of RFT was significantly lower in the study group (0.5 ± 0.9)

compared with control (1.8 ± 2.0) ($P < 0.01$). Moreover, the patients with ICD showed a lower proportion of RFT (34.5%) than controls (65.5%) (OR = 0.28: 95% CI = 0.13–0.60; $P = 0.0008$).

Amongst patients with coagulation disorders with RFT, 70% had RPL affecting at least one treated tooth, whereas in control subjects this percentage was only 36.8% ($P = 0.02$). Periapical radiolucent lesions associated with RFT may represent persistent chronic AP or incompletely healed lesions after RCT. So, in this study, it must be kept in mind that some root-filled teeth with periapical radiolucencies may have represented healing lesions, particularly if the time elapsed since treatment was less than 2 years [32]. This is a recognized limitation of cross-sectional studies. However, the high percentage of root-filled teeth in connection with periapical lesions amongst patients with coagulation disorders could indicate a delayed healing of the periapical wound.

In addition, in this study the number of smoker patients was significantly higher in the control group (53.4%) compared with the study group (19.0%) ($P < 0.01$). Therefore, in this study, neither endodontic status nor smoking habits can be claimed as causing the higher prevalence of AP in the study group.

Although it is not the purpose of this investigation, some considerations can be made with respect to the mechanism by which periapical status could be affected by coagulation disorders. Histologically, AP is represented by a periapical inflammatory response that arises after resorption of adjacent supporting bone and local infiltration of inflammatory cells. Wound healing after successful endodontic therapy involves coagulation, inflammation, formation of granulation tissue and tissue remodelling [3]. Normal healing requires adequate haemostatic function for the appropriate time frame [33]. Thus, coagulation function is required in the immediate response to wounding. Moreover, coagulation defect in haemophilia has been associated with delayed wound healing [4]. Normal healing requires adequate haemostatic function for an extended period of time, probably because angiogenesis during healing predisposes to bleeding, especially in the setting where haemostasis is impaired [34]. A robust thrombin generation leading to fibrin formation is a necessary component for healthy wound healing. Thus, dentists not only must take in consideration preoperative systemic precautions and intraoperative haemostatic measures but also that wound healing can be delayed in patients with haemophilia or VWD. The higher proportion of patients with at least one RFT with RPL (70.0%) found in the study group, compared to only 36.8% in the control group ($P = 0.016$), could potentially be explained by delayed wound healing of periapical tissues.

On the other hand, another possible explanation of this difference could be that the control subjects have higher access to dental care and treatment provided than patients with ICD. Indeed, in this study the patients with ICD showed significantly higher number of teeth with AP (1.4 ± 1.6) than controls (0.6 ± 0.8) ($P < 0.01$) and the proportion of RFT in the study group (0.5 ± 0.9) was lower compared with control (1.8 ± 2.0) ($P < 0.01$). In accordance with this supposition, previous studies have found a worse oral health state, less frequency of brushing and less perception of needed treatment between the haemophilic patients [27,35]. On the contrary, a recent study has found no difference in the oral health status between a group of haemophilic A and VWD patients and control subjects [36].

In this study there are several factors that have not been recorded, so it has several limitations. Firstly, the level of education and the socioeconomic status of the study and control populations have not been recorded and they may influence the periapical status and the prevalence of RCT [8]. Secondly, the quality of root canal filling and coronal restoration, which have not been considered when evaluating the presence of periapical radiolucencies, has been shown to be associated with the prevalence of chronic AP, and could act as confounding factor [12].

Conclusions

Within the limits of this study, the following conclusion can be drawn: ICD are associated with the presence of RPLs. Patients with ICD show a significantly higher prevalence of RPLs, lower frequency of RFT and higher percentage of RFT with RPLs than controls healthy patients.

Author contributions

L. Castellanos-Cosano, B. Sánchez-Domínguez and D. Torres-Lagares performed the research. J.J. Segura-Egea and G. Machuca-Portillo designed the research study, analysed the data and wrote the manuscript. J. López-López analysed the data and revised the manuscript critically.

Disclosures

The authors stated that they have no interests which might be perceived as posing a conflict or bias.

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During the copy-editing of your paper, the following queries arose. Please respond to these by marking up your proofs with the necessary changes/additions. Please write your answers on the query sheet if there is insufficient space on the page proofs. Please write clearly and follow the conventions shown on the attached corrections sheet. If returning the proof by fax do not write too close to the paper's edge. Please remember that illegible mark-ups may delay publication.
Many thanks for your assistance.

Query reference	Query	Remarks
1	AUTHOR: Please restrict the running head to 40 characters.	
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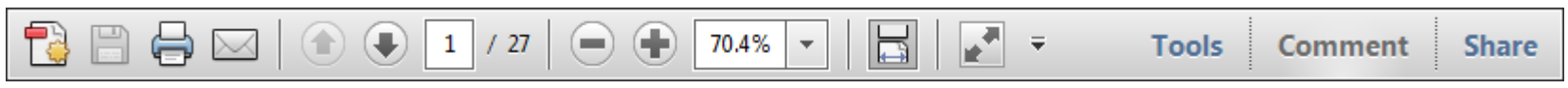
WILEY-BLACKWELL

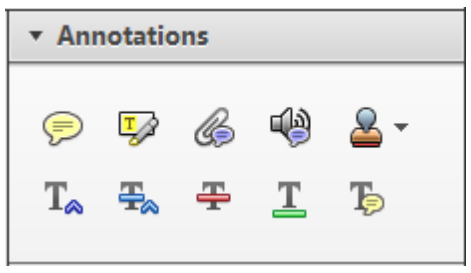
USING e-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

Required software to e-Annotate PDFs: Adobe Acrobat Professional or Adobe Reader (version 7.0 or above). (Note that this document uses screenshots from Adobe Reader X)
The latest version of Acrobat Reader can be downloaded for free at: http://get.adobe.com/uk/reader/

Once you have Acrobat Reader open on your computer, click on the Comment tab at the right of the toolbar:



This will open up a panel down the right side of the document. The majority of tools you will use for annotating your proof will be in the Annotations section, pictured opposite. We've picked out some of these tools below:

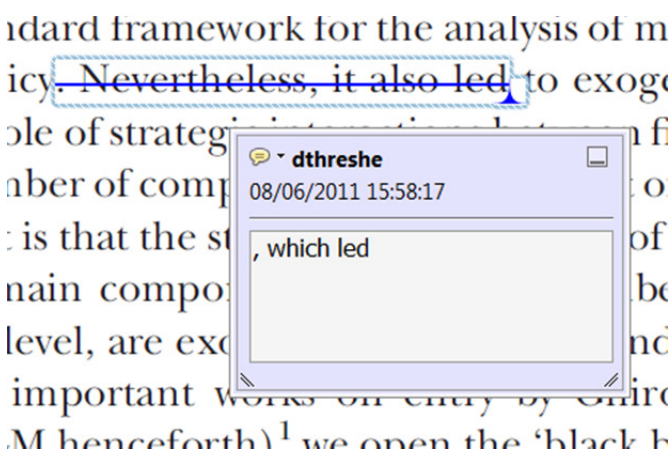


1. Replace (Ins) Tool – for replacing text.

Strikes a line through text and opens up a text box where replacement text can be entered.

How to use it

- Highlight a word or sentence.
- Click on the Replace (Ins) icon in the Annotations section.
- Type the replacement text into the blue box that appears.

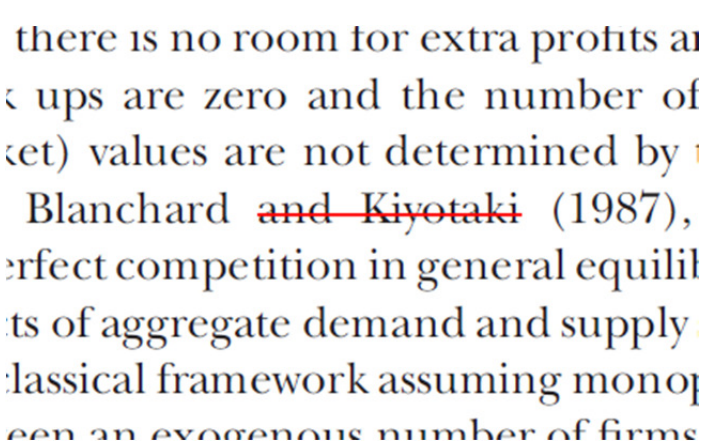


2. Strikethrough (Del) Tool – for deleting text.

Strikes a red line through text that is to be deleted.

How to use it

- Highlight a word or sentence.
- Click on the Strikethrough (Del) icon in the Annotations section.

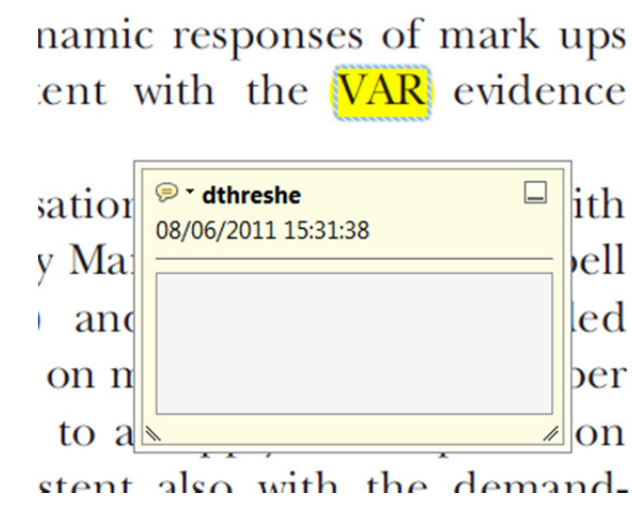


3. Add note to text Tool – for highlighting a section to be changed to bold or italic.

Highlights text in yellow and opens up a text box where comments can be entered.

How to use it

- Highlight the relevant section of text.
- Click on the Add note to text icon in the Annotations section.
- Type instruction on what should be changed regarding the text into the yellow box that appears.

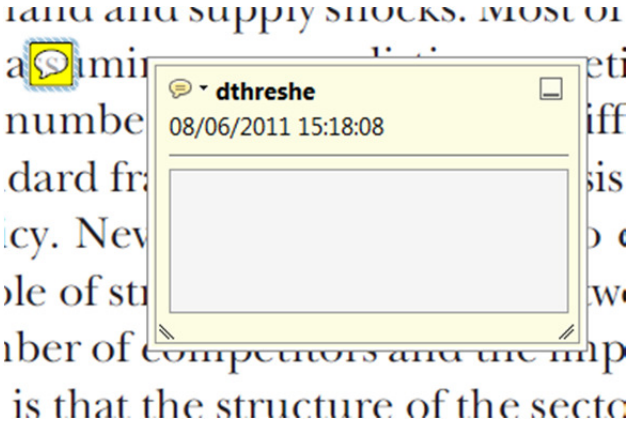


4. Add sticky note Tool – for making notes at specific points in the text.

Marks a point in the proof where a comment needs to be highlighted.

How to use it

- Click on the Add sticky note icon in the Annotations section.
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the yellow box that appears.



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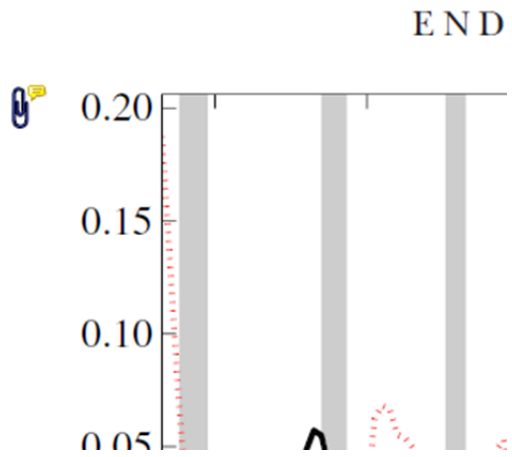
USING e-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

5. Attach File Tool – for inserting large amounts of text or replacement figures.

Inserts an icon linking to the attached file in the appropriate pace in the text.

How to use it

- Click on the Attach File icon in the Annotations section.
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
- Select the colour and type of icon that will appear in the proof. Click OK.

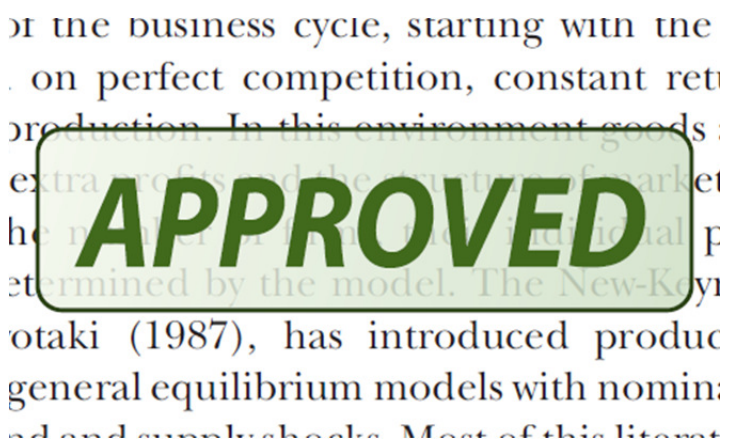


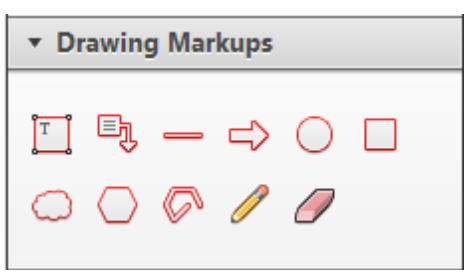
6. Add stamp Tool – for approving a proof if no corrections are required.

Inserts a selected stamp onto an appropriate place in the proof.

How to use it

- Click on the Add stamp icon in the Annotations section.
- Select the stamp you want to use. (The Approved stamp is usually available directly in the menu that appears).
- Click on the proof where you'd like the stamp to appear. (Where a proof is to be approved as it is, this would normally be on the first page).



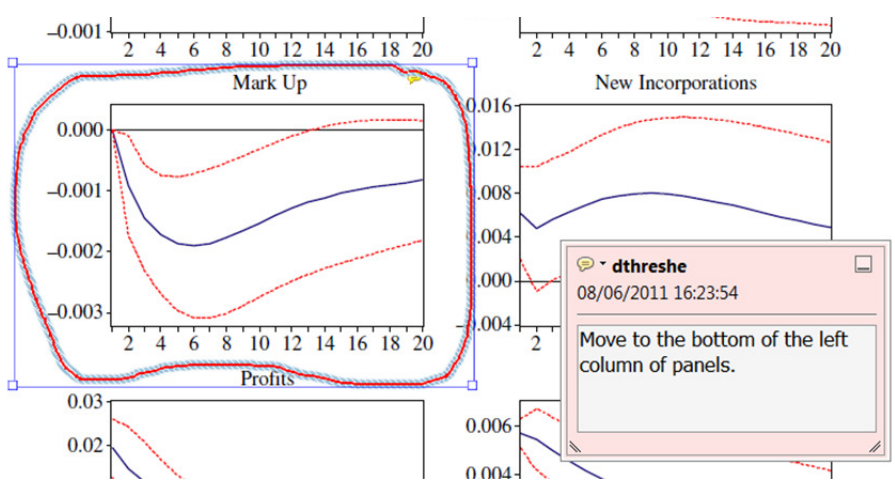


7. Drawing Markups Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks..

How to use it

- Click on one of the shapes in the Drawing Markups section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.



For further information on how to annotate proofs, click on the Help menu to reveal a list of further options: