Endodontics and diabetes: association versus causation

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Abstract


Endodontic Medicine has gained more attention and is becoming a more important issue in Endodontics. As an example, more than one hundred articles on this topic have been published in the last eight years. Several of these studies have found an association between endodontic variables, that is the prevalence of apical periodontitis, the prevalence of root canal treatment (RCT) and the outcome of RCT assessed as root filled teeth (RFT) with radiolucent periapical lesions (RPL) or non-retained RFT, and several systemic diseases, such as diabetes, cardiovascular disease, smoking habits, osteoporosis, inherited coagulopaties, biological medications, low birth weight or physical fitness. However, the demonstration of association does not prove by itself the existence of a cause–effect relationship. Two variables can be related statistically to each other without either variable directly affecting the values of the other thus resulting in a non-causal relationship. Causality is assumed when one variable is shown to contribute to the development of the other, and its removal is shown to reduce the frequency of disease. Therefore, once a significant statistical association has been found between two variables, it is necessary to exclude the presence of bias, which would imply that the association is artefactual, and to analyse if the causation criteria defined by Hill (Proceedings of the Royal Society of Medicine 1965; 58: 295–300) are fulfilled to establish a causal relationship. Only if they are satisfied, can it be concluded that the association is causal. The aim of this study was to analyse the difference between association and causation, applying the criteria of causality to the specific case of the association between endodontic disease and diabetes mellitus.

Keywords: apical periodontitis, causation criteria, diabetes mellitus, endodontic medicine, root canal treatment, systematic review.

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Introduction

When pulp necrosis is established, bacteria with their toxins, immunological agents, and the products of pulp degeneration and tissue necrosis, reach the peri-radicular tissues through several pathways, mainly the apical foramen, giving rise to inflammatory and immunologic reactions causing apical periodontitis (Segura-Egea et al. 2013). Apical periodontitis is a prevalent disease with studies conducted in European countries, using periapical and panoramic radiographs or CBCT, reporting a prevalence of apical periodontitis ranging from 34 to 61% of adults and 2–14% of teeth, with a mean of five per cent (Jiménez-Pinzón et al. 2004, Segura-Egea et al. 2004, Gulsahi et al. 2008, López-López et al. 2012a,b, Dutta et al. 2014, Van der Veken et al. 2017).
On the other hand, root canal treatment is also very prevalent. In Europe, data from several epidemiological studies suggest that around 2–12% of teeth have been root filled (Jiménez-Pinzón et al. 2004, Segura-Egea et al. 2004, López-López et al. 2012a,b, Dutta et al. 2014, Van der Veken et al. 2017).

Endodontic Medicine

Taking into account that both apical periodontitis and root canal treatment are prevalent conditions, two questions could be asked: first, does the periapical inflammatory process or root canal treatment compromise general health? and second, do systemic diseases influence periapical health or the outcome of root canal treatment? Endodontic Medicine is trying to answer these questions (Segura-Egea et al. 2015). The term ‘Endodontic Medicine’ could be considered by some to be redundant because Endodontics is part of Dentistry and Dentistry is part of Medicine. So, why use the term Endodontic Medicine? It could be argued that the medical aspects of Endodontics are being eclipsed by the technical and mechanical aspects of endodontic therapy (Segura-Egea et al. 2015). The technological development of Endodontics, which occupies the main part of most endodontic congresses, should not forget that Endodontics is not only root canal treatment, rotary files, gutta-percha, operative microscope, electronic apex locator, etc. On the contrary, the principal objective of Endodontology is the study of the biological and clinical aspects of endodontic diseases. Consequently, the main contribution that Endodontic Medicine can make is to highlight the biological and medical aspects of Endodontology, studying the systemic consequences of apical periodontitis and root canal treatment, as well as the influence of systemic diseases on periapical inflammation, periapical repair and root canal treatment outcome (Kvist & van der Sluis 2015, Segura-Egea et al. 2015).

From focal infection theory to Endodontic Medicine

The possible relationship between apical periodontitis and systemic diseases is not a new topic. In the early 20th century, the theories of focal infection and elective localization described an association between systemic inflammatory complications with bacteria found in dental infections. Miller (1891) became the first to reveal the existence of bacteria in samples of dental pulp tissue, proposing that oral microorganisms or their products may have a role in the development of a variety of diseases in sites distant from the oral cavity. Consequently, Miller advised treating and filling root canals (Pallasch & Wahl 2003). On the contrary, in 1910, William Hunter, a British surgeon, lecturing in Montreal at McGill University, criticized bad dentistry and held oral infections and oral sepsis responsible for many diseases, such as kidney diseases, colitis, anaemia, gastritis and many others, igniting the fire of focal infection (Hunter 1900). Almost at the same time, Frank Billings, in Chicago, published case reports claiming that tonsillectomies and tooth extraction cured infections in distant organs. He replaced the Hunter’s term oral sepsis with focal infection (Billings 1914). In addition, Edward Rosenow, a pupil of Billings, developed the principle of elective localization, according to which microorganisms have affinities for particular organs. He published many articles over a period of fifteen years on this subject, relating periapical infection with the colonization of bacteria in different organs (Rosenow 1928).

Endodontics came under particular scrutiny: all pulpless teeth, including those in which radiographs did not reveal evidence of infection, were considered a probable focus of infection, and the extraction of healthy teeth was justified to prevent focal infection. An American dentist, Weston Price, published results supporting the local infection theory in relation to endodontically treated teeth, recommending eliminating all pulpless teeth (Price 1925). He suggested that the treatment of dental infections must always imply the extraction of the affected tooth. During that period, millions of tonsils, adenoids and teeth were removed in an ‘orgy of extractions’ as described by Grossman (Grossman 1955, 1960, Pallasch & Wahl 2000).

The reaction of many endodontists was to investigate more deeply the pathogenesis of apical periodontitis. It was shown that root canal treatment cured apical periodontitis (Grossman 1940, Easlick 1951). Of course, nowadays, the advances experienced by medicine and dentistry have discredited the focal infection theory.

It seemed that this problem had been forgotten and overcome. However, in recent decades, numerous epidemiological studies have found an association between periodontal disease and important systemic diseases, such as diabetes mellitus (Katz 2001, Sokolne & Klinger 2001), coronary heart disease (Dörfer et al. 2004, Grau et al. 2004), osteoporosis (Bullon et al. 2005) and pregnancy outcome (Jeffcoat et al.
The term Periodontal Medicine was proposed to name the field of Periodontology encompassing the study of the contribution of periodontal infections on systemic conditions, and the study of the connections of other systemic pathologies and periodontitis (Williams & Offenbacher 2000). Although the scientific evidence supporting an aetiopathological role for periodontal pathogens is substantial, the multifactorial nature of systemic chronic diseases makes it difficult to establish a definitive causal role for periodontal pathogens in systemic infections (Kumar 2017). However, the evidence of the possible association between periodontal diseases and systemic diseases has focused attention on the diagnosis and treatment of periodontal disease, improving the oral and, possibly, systemic health of patients with periodontal conditions. Subsequently, Endodontic Medicine has followed the same step as Periodontal Medicine on the basis that there is a now a substantial body of evidence to suggest the existence of an association between endodontic disease and several systemic diseases (Cotti & Mercuro 2015, Kvist & van der Sluis 2015, Segura-Egea et al. 2015).

The results of epidemiological studies on periodontal and endodontic medicine are posing a serious problem, the risk of the local infection theory re-emerging. Interestingly, the website of the American Association of Endodontists provides information and advice to patients to counteract the miss-information that is publicized by individuals and groups who still promote the concepts inherent in the local infection theory (American Association of Endodontists 2014). In fact, several recent articles have discussed whether research on the relationship between periodontal or endodontic diseases and systemic health could mean the revival of the focal infection theory (Pallasch & Wahl 2000, 2003, Tjäderhane 2015).

Why is this happening? It can be hypothesized that the results of studies on the possible relationship between oral infections and systemic conditions are being translated to people, to the media and, unfortunately, in some cases to doctors and dentists, as if it had already been proven that this association is causal (Hujoe et al. 2006, Niederman & Weyant 2012). Results that only demonstrate the association between endodontic or periodontal diseases and certain systemic diseases, such as cardiovascular disease or diabetes, are being interpreted as if the causal link is already proven.

On the other hand, the problem of the possible causal link between endodontic infection and systemic diseases does not only involve descriptive issues of science but also moral matters of society. If apical periodontitis can cause diabetes or cardiovascular disease it becomes an ethical problem and not only a scientific one (Hofmann 2011).

The aim of this study was to analyse the difference between association and causation, applying the criteria of causality to the specific case of the association between endodontic disease and systemic diseases, taking as an example the case of diabetes mellitus.

**Methodological approach**

Although the objective of this work is not to perform a systematic review, it has been necessary to review the scientific evidence on the relationship between diabetes and endodontic pathosis. Epidemiological studies carried out on the association between diabetes and apical periodontitis or root canal treatment published in English until 8 October 2018 were identified and analysed. An electronic search of PubMed, Web of Science and Scopus was conducted using appropriate keywords: (endodontic OR dental pulp OR pulpitis OR apical periodontitis OR periapical granuloma OR root canal treatment OR root filled teeth) AND (diabetes OR diabetic) AND (epidemiological OR cross-sectional OR retrospective OR case-control OR prospective OR longitudinal OR cohort OR clinical trial OR systematic review). Human cross-sectional and prevalence studies, retrospective and case–control studies, prospective and cohort studies, and systematic reviews were included. Animal and experimental studies as well as case reports or case series studies were excluded. Seventy-six articles were selected, and its results were analysed.

**Interpretation of the studies on endodontic medicine: causation or association**

Many epidemiological studies have been conducted investigating the possible association of apical periodontitis and endodontic treatment with various systemic conditions. The first three systemic conditions investigated were diabetes mellitus, cardiovascular diseases and smoking habits.

Firstly, with the studies of Bender et al. (1963), diabetes mellitus was the first systemic disease whose possible association with apical periodontitis was


In addition, the potential association of many other diseases with apical periodontitis and root canal treatment has also been investigated, such as inherited coagulation disorders (Castellanos-Cosano et al. 2013a,b), osteoporosis (López-López et al. 2015), biological medications (Cotti et al. 2014), physical fitness (Hoppe et al. 2017), cirrhosis and chronic liver disease (Castellanos-Cosano et al. 2013a,b, Grønkjær et al. 2016), low birth weight (Leal et al. 2015), end-stage renal disease (Khalighinejad et al. 2017) and inflammatory bowel disease (Piras et al. 2017).

Therefore, in the last few decades one of the topics that is being given more attention in endodontic research is Endodontic Medicine. A search in PubMed using the keywords: (endodontic OR apical periodontitis OR endodontic disease) AND (systemic disease OR systemic health), located a total of 218 items in 30 years (Fig. 1), with more than a hundred in the last eight years.

Interpretation of the statistical results of epidemiological studies

The application of statistical methods to the results of epidemiological studies determines if there is an association between two variables. But the demonstration of an association, by itself, is not proof that there is a cause–effect relationship. Two variables can be statistically related to each other without either variable directly affecting the values of the other setting up a non-causal relationship. Causality is assumed when one variable (be it diabetes or oral infections) is shown to contribute to the development of the other, and its removal is shown to reduce the frequency of disease (Hill 1965).

Therefore, once a significant association has been found between two variables, it is necessary to exclude the presence of bias, which would imply that the association is artefactual, and to analyse if the causation criteria defined by Hill (1965) are fulfilled to establish a causal relationship. If they are satisfied, it could be concluded that the association is causal (Fig. 2).

Hill’s causation criteria

The connection between cigarette smoking and lung cancer was demonstrated by Doll & Hill (1950). Sir

![Figure 1](image-url)
Austin Bradford Hill, trying to answer the question ‘What aspects of the association should especially be considered before deciding that the most likely interpretation of it is causation?’, defined a list of causation criteria to provide epidemiologic evidence of the existence of causal relationship (Hill 1965) (Table 1). Although not explicitly, the discussion of scientific papers reporting results on the possible association of endodontic pathosis with some systemic disease, should evaluate and analyse the fulfilment of these criteria. However, unfortunately, the discussions of many of the articles published on endodontic medicine do not describe these criteria.

Diabetes mellitus – endodontic disease: causation or association?

Taking as an example the possible association between endodontic disease and diabetes mellitus, the achievement of Hill’s criteria (strength of the association, temporal relationship, dose–response gradient, consistency of the association, coherence and plausibility of the association) will be analysed. Firstly, it is necessary to review briefly the scientific evidence and, secondly, consider if the Hill criteria of causation are fulfilled.

Scientific evidence on the association between endodontic disease and diabetes

The endodontic variables analysed in these epidemiological studies are as follows: a) the prevalence of apical periodontitis, b) the prevalence of root canal treatment and c) the outcome of root canal treatment, assessed as c.1) the prevalence of root filled teeth with or without periapical lesions or c.2) the prevalence of tooth extraction after root canal treatment.

(a) Prevalence of apical periodontitis in diabetic and control subjects

The first question to be answered is whether there is an association between the prevalence of apical periodontitis and diabetes. This association was proposed by Bender et al. (1963). They observed a high percentage of diabetics amongst patients with odontogenic infections, together with greater periapical inflammatory reactions and delayed periapical healing in poorly controlled diabetic patients. They proposed that the increased local inflammation as a consequence of apical periodontitis causes an intensification of diabetes with a rise in the blood glucose, placing the patient in an uncontrolled diabetic status and developing a vicious circle. Since then, six studies have found a significantly greater prevalence of periapical lesions in diabetics compared to healthy subjects (Bender et al. 1963, Falk et al. 1989, Ueta et al. 1993, Segura-Egea et al. 2005, López-López et al. 2011, Marotta et al. 2012), one study reported that the frequency of periradicular lesions was higher in long-term diabetic patients than in short-term diabetic patients (Mesgarani et al. 2014), and another study reported the size of periapical lesions in diabetic patients was larger (Falk et al. 1989).

On the contrary, other studies (Britto et al. 2003, Correia-Sousa et al. 2015, An et al. 2016, Smadi 2017) have not found a significant association. So, prospective studies must be conducted to confirm whether there is or not a relationship between apical periodontitis and diabetes.
The association is limited to specific
Analogy In some circumstances it would be fair to
Experiment Occasionally it is possible to appeal to
Consistency Different studies, carried out by different
Plausibility The suspected causation is biologically
Coherence The cause–effect interpretation of the
Experimen Occasionally it is possible to appeal to
Analog In some circumstances it would be fair to
Specificity The association is limited to specific

(b) Prevalence of root canal treatment in diabetic and controls subjects
The second question can be formulated as whether there is association between the prevalence of root canal treatment and diabetes. In addition to studying the prevalence of apical periodontitis, six studies have also investigated the frequency of root canal treatment in diabetic and control subjects. Three studies did not find a greater prevalence of RCT in diabetic patients compared to controls (Falk et al. 1989, Segura-Egea et al. 2005, Marotta et al. 2012), but three studies did (López-López et al. 2011, Correia-Sousa et al. 2015, Smadi 2017). Therefore, there is no conclusive evidence about the association of diabetes with the prevalence of RCT.

(c) Outcome of RCT in diabetic and control subjects
Finally, the third question that can be formulated is whether an association exists between DM and the outcome of RCT. This possible relationship can be investigated analysing the prevalence of RFT with persistent AP, or investigating the prevalence of tooth extraction after root canal treatment.

(c.1) Prevalence of RFT with apical periodontitis
Studies investigating the prevalence of RFT with apical periodontitis in diabetic and healthy control subjects, have demonstrated delayed periapical healing in diabetic subjects, with a lower rate of repair associated with root filled teeth (Bender et al. 1963, Arya et al. 2017), and slower reduction of periapical lesions in poorly controlled diabetic patients (Cheraskin & Ringsdorf 1968). Other studies have found a greater percentage of RFT with AP in diabetics, compared to control subjects, but without a significant difference (Falk et al. 1989, Britto et al. 2003, Fouad & Burleson 2003, Segura-Egea et al. 2005, López-López et al. 2011, Marotta et al. 2012, Marques-Ferreira et al. 2014). However, some of these studies have found significant differences only in diabetic women (Falk et al. 1989), or only in diabetic men (Britto et al. 2003) or in cases with preoperative periapical lesions (Fouad & Burleson 2003). Another study found a significantly higher prevalence of RFT with AP in all diabetics compared to control subjects (Smadi 2017).

(c.2) Retention of RFT
The possible relationship between diabetes and outcome following root canal treatment can also be investigated comparing the prevalence of tooth extraction after treatment in diabetic patients and normal healthy subjects. Six studies have analysed this topic demonstrating a greater likelihood of RFT loss in diabetic patients (Mindiola et al. 2006, Ng et al. 2011, Wang et al. 2011, Lin et al. 2014) and a marginal association between RFT loss and diabetes (Doyle et al. 2007). In summary, it can be concluded that the prognosis of root filled teeth is worse in diabetic patients, who are more likely to lose their root filled teeth.

Compliance with Hill’s criteria when analysing the association between diabetes and endodontic disease
It has been demonstrated that several endodontic variables, such as the prevalence of apical periodontitis, the prevalence of root canal treatment and the prevalence of root filled teeth with radiolucent periapical lesions, are associated with diabetic status. As a consequence, it is essential to assess whether Hill’s causation criteria are met to determine whether or not the association is causal.
(a) Strength of the association
The first criteria refer to the size of the relative risk found. Relative risk can be determined in cohort studies and clinical trials from the incidence data. However, the odds ratio calculated in cross-sectional and case–control studies is a good approximation to the relative risk, especially when the outcome is rare (Bland & Altman 2000). The greater the strength of the association the more likely that it is to be causal (Hill 1965).

Most epidemiological studies evaluating the relationship between Endodontics and diabetes are cross-sectional, nevertheless only some of them have determined the strength of the association by calculating the odds ratio values. A value of OR equal to 1 implies that the first variable (generally the exposure) does not affect the probabilities of the second variable (the outcome) (Bland & Altman 2000). When the OR is >1, it implies that the exposure is associated with higher odds of the outcome. When the OR is <1, the exposure is associated with lower odds of the outcome. The confidence interval (CI) is used to estimate the precision of the OR. A 95% CI means that when sampling the same population on several occasions, the calculated interval would comprise the right population parameter in approximately 95% of the cases, always assuming the absence of bias or confounding factors (Morris & Gardner 1988). A large CI indicates a low level of precision of the OR, whereas a small CI indicates a higher precision of the OR. However, the 95% CI does not determine the statistical significance, as it is inappropriate to interpret an OR with 95% CI that spans the null value (e.g. OR = 1) as indicating evidence for lack of association between the exposure and outcome.

In the cross-sectional studies conducted to analyse the relationship between diabetes and Endodontics, the ORs calculated are not constant and are not always significant (Table 2). Moreover, the estimated 95% CI overlap, in many cases, the null value, indicating that the OR could be 1 or less. However, there are six studies analysing the outcome of RCT in diabetics and control subjects in which the P value is significant. The OR values ranged from 1.3 to 5.3, and their lower limits of the 95% CI ranged from 1.2 to 2.0 (Table 2). At a 10% disease rate in the control group, the reference OR values reflecting a ‘weak association’, a ‘moderate association’ and a ‘strong association’ are 1.5, 2.5 and 4.1 (Chen et al. 2010).

An important point to keep in mind is the age of the patients included in studies. Since incidence of both diabetes and AP and RCT increases with age, a spurious association could be found if the age of the patients is not taken into account in the design of the study. In addition, long-term diabetics are expected to be older than short-term diabetics. Therefore, it is important to indicate which studies made adjustments for the age in the analysis of their results and in the calculation of the OR (Table 2). As it can be seen, most studies calculated ORs without adjusting for age. Therefore, the age of the patients is also an important point to take into account in the design of new studies on the association between diabetes and endodontics.

In conclusion, the OR values do not support the existence of association between Endodontics and

Table 2 Strength of the association ‘endodontics/diabetes’

<table>
<thead>
<tr>
<th>Study</th>
<th>Variable</th>
<th>Odds ratio</th>
<th>Age adjustment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segura-Egea et al. (2005)</td>
<td>Prevalence of AP</td>
<td>3.2</td>
<td>No</td>
<td>0.04*</td>
</tr>
<tr>
<td>López-López et al. (2011)</td>
<td>Prevalence of AP</td>
<td>3.9</td>
<td>No</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Segura-Egea et al. (2005)</td>
<td>Prevalence of RCT</td>
<td>0.6</td>
<td>No</td>
<td>0.25</td>
</tr>
<tr>
<td>López-López et al. (2011)</td>
<td>Prevalence of RCT</td>
<td>2.3</td>
<td>No</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Falk et al. (1989)</td>
<td>Prevalence of RFT-AP</td>
<td>1.3</td>
<td>No</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Fouad &amp; Burleson (2003)</td>
<td>Prevalence of RFT-AP</td>
<td>8.1</td>
<td>Yes</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Segura-Egea et al. (2005)</td>
<td>Prevalence of RFT-AP</td>
<td>3.3</td>
<td>No</td>
<td>0.05</td>
</tr>
<tr>
<td>López-López et al. (2011)</td>
<td>Prevalence of RFT-AP</td>
<td>2.7</td>
<td>No</td>
<td>0.05</td>
</tr>
<tr>
<td>Smadi (2017)</td>
<td>Prevalence of RFT-AP</td>
<td>4.1</td>
<td>No</td>
<td>0.02*</td>
</tr>
<tr>
<td>Arya et al. (2017)</td>
<td>Prevalence of RFT-AP</td>
<td>5.3</td>
<td>No</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Wang et al. (2011)</td>
<td>Prevalence of retained RFT</td>
<td>1.8</td>
<td>Yes</td>
<td>0.003*</td>
</tr>
<tr>
<td>Ng et al. (2011)</td>
<td>Prevalence of retained RFT</td>
<td>3.3</td>
<td>Yes</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>
| Lin et al. (2014)       | Prevalence of retained RFT | 1.3      | Yes            | 0.0001* 

AP, Apical periodontitis; RCT, Root canal treatment; RFT, Root filled teeth.

*Significant P value.
diabetes. Only the outcome of RCT could be considered moderately associated with the diabetic state.

(b) Temporal relationship of the association
This second criterion means that one of the variables (the cause) must precede the other variable (the effect). Taking into account that cross-sectional studies measure both variables, the exposure and the outcome, at the same time, they cannot establish a temporal relationship. On the contrary, follow-up studies, especially longitudinal studies, allow to establish a temporal relationship.

Regarding the temporal relationship between Endodontics and diabetes, no longitudinal study is available. The published studies are cross-sectional, focusing on the prevalence of AP, RCT and AP in teeth with RCT. But prevalence is not very useful to establish causality (Hernan 2004, Rothman & Greenland 2005). A high prevalence of periapical radiolucent lesions may reflect a high incidence of apical periodontitis, but also a delay in the healing of these lesions.

However, two cross-sectional studies (Falk et al. 1989, Mesgarani et al. 2014) provide some information about the possible temporal relationship. Both studies found worse periapical status in long-term diabetic patients compared to short-term diabetics. The longer the duration of diabetes, the greater the prevalence of AP and the extension of periapical lesions. However, prospective studies are needed, despite being more difficult to develop and more expensive, to definitively establish the temporal relationship.

(c) Dose–response gradient of the association
The third criterion refers to the change in effect provoked by differing amount, intensity or duration of the cause. If a dose–response gradient can be demonstrated, the likelihood that the association is causal increases.

Two studies have analysed the association of glycated haemoglobin (HbA1c) levels with the prevalence of endodontic variables, and found a significant association between higher HbA1c levels and the prevalence of apical periodontitis (Sánchez-Domínguez et al. 2015), the prevalence of RFT (Smadi 2017) and the prevalence of RFT with AP (Smadi 2017). However, no studies have been carried out comparing the prevalence levels of AP or RCT with the prevalence of diabetes.

(d) Consistency of the association
The fourth causation criterion implies that different studies, carried out by different investigators, and conducted on different populations, and sometimes in different countries, resulted in the same association. Therefore, the greater the number of studies finding the association, the more consistency and more likely that the association is causal.

Seven studies have found a higher prevalence of teeth with radiolucent periapical lesions in diabetic patients compared to healthy controls (Table 3). Nevertheless, only three of them (Segura-Egea et al. 2005, López-López et al. 2011, Marotta et al. 2012) were significant. Four other studies found no significant differences (Falk et al. 1989, Britto et al. 2003, Correia-Sousa et al. 2015, Smadi 2017). Therefore, the association between diabetes and apical periodontitis is not consistent. A systematic review with meta-analysis is needed to reach a definitive conclusion.

In relation to the association between the prevalence of RCT and diabetes (Table 4), again there are three studies finding significant differences between diabetics and controls (López-López et al. 2011, Correia-Sousa et al. 2015, Smadi 2017), and three others that did not (Falk et al. 1989, Segura-Egea et al. 2005, Marotta et al. 2012). The results are not consistent, and a systematic review with meta-analysis is required to reach a definitive conclusion.

Finally, the association between diabetes and the prevalence of RFT with periapical radiolucenties has been analysed in eight studies (Table 5). Only one study reported significant differences between diabetic patients and healthy controls (Smadi 2017), with seven studies not finding any differences (Falk et al. 1989, Britto et al. 2003, Fouad & Burleson 2003, Segura-Egea et al. 2005, López-López et al. 2011, Marotta et al. 2012, Marques-Ferreira et al. 2014). However, in this case, a systematic review with meta-analysis has been carried out (Segura-Egea et al. 2019).

<table>
<thead>
<tr>
<th>Study</th>
<th>Controls (%)</th>
<th>Diabetics (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falk et al. (1989)</td>
<td>1.8</td>
<td>3.6</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Britto et al. (2003)</td>
<td>87</td>
<td>97</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Segura-Egea et al. (2005)</td>
<td>58</td>
<td>81</td>
<td>0.04*</td>
</tr>
<tr>
<td>López-López et al. (2011)</td>
<td>42</td>
<td>74</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Marotta et al. (2012)</td>
<td>7</td>
<td>10</td>
<td>0.03*</td>
</tr>
<tr>
<td>Correia-Sousa et al. (2015)</td>
<td>2.4</td>
<td>2.4</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Smadi (2017)</td>
<td>12</td>
<td>13</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

*Significant P value.
This review concluded that diabetic patients have a significantly greater prevalence of radiolucent periapical lesions associated with root filled teeth, compared to control subjects (OR = 1.42; 95% CI = 1.11–1.80; \( P = 0.006 \)). Therefore, it can be concluded that the association between diabetes and the prevalence of periapical radiolucent lesions is consistent and diabetes is significantly associated with a higher prevalence of radiolucent periapical lesions in RFT.

On the other hand, it has been commented previously that the prognosis of RFT is worse in diabetic patients, who are more likely to lose their root filled teeth. A recently published systematic review with meta-analysis has concluded that diabetics have a significantly higher prevalence of extracted RFT than healthy non-diabetic subjects (OR = 2.44; 95% CI = 1.54–3.88; \( P = 0.0001 \)) (Cabanillas-Balsera et al. 2019). However, this does not allow the direct conclusion that losing teeth in diabetic patients is because of endodontic failures. Diabetics have more caries and/or worse oral hygiene, two variables that could be acting as confounding factors (Kanjirath et al. 2011, Arheiam & Omar 2014).

c) Coherence of the association and biological plausibility

The fifth and sixth criteria analyse whether the suggested association is consistent with existing biological and medical knowledge and with the natural history and biology of the disease. In this sense, what is biologically plausible depends upon the biological knowledge of the day and, in fact, it can never be ruled out that the observed association observe may be new to science or medicine. The association between endodontic diseases and diabetes does not raise conflicts with the generally known facts of the natural history and biology of both diseases. On the contrary, there are biological mechanisms by which diabetes could affect the periapical status and vice-versa (Segura-Egea et al. 2015). In diabetic patients, impaired innate immunity, hyperglycaemia and high serum levels of advanced glycation end products (AGEs), would predispose to chronic inflammation, diminishing tissue repair capacity, impairing bone turnover, and delaying periapical wound healing in RFT, increasing the prevalence of persistent apical periodontitis. Few studies have investigated these suggested mechanisms, so the fulfillment of the criteria of coherence and biological plausibility cannot be definitively established. In relation to the clinical studies, Rudranaik et al. (2016) found that type 2 diabetics had chronic and larger sized lesions when compared to control subjects, showing delayed clinical and radiographic healing. However, Rudranaik et al. (2016) used very strict criteria (Strindberg 1956) to assess periapical status, so slower healing could easily be interpreted as failure. If they had used the PAI index (Ørstavik et al. 1986), including ‘healing’ lesions, the outcome and the interpretation could be categorized as slower healing, as shown in the studies of Fouad & Burleson (2003) and Arya et al. (2017). In short, taking together the results of the clinical studies (Fouad & Burleson 2003, Rudranaik et al. 2016, Arya et al. 2017) diabetic patients are associated with successful root canal treatment but with a slower healing rate.

Regarding the possible repercussion of periapical inflammation on diabetic health, chronic periapical inflammation involves activation of the broad axis of innate immunity through the lipopolysaccharide from anaerobic gram-negative bacteria, and could

### Table 4 Consistency of the association between the prevalence of Root canal treatment (RCT) and diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Controls (%)</th>
<th>Diabetics (%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falk et al. (1989)</td>
<td>13</td>
<td>16</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Segura-Egea et al.(2005)</td>
<td>42</td>
<td>31</td>
<td>0.25</td>
</tr>
<tr>
<td>López-López et al.(2011)</td>
<td>50</td>
<td>70</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Marotta et al. (2012)</td>
<td>15</td>
<td>13</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Correia-Sousa et al. (2015)</td>
<td>4.3</td>
<td>6</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Smadi (2017)</td>
<td>1.8</td>
<td>4.2</td>
<td>&lt;0.05*</td>
</tr>
</tbody>
</table>

*Significant \( P \) value.

### Table 5 Consistency of the association between the prevalence of root filled teeth (RFT) with AP and diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Controls (%)</th>
<th>Diabetics (%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falk et al. (1989)</td>
<td>21</td>
<td>26</td>
<td>0.20</td>
</tr>
<tr>
<td>Fouad &amp; Burleson (2003)</td>
<td>31</td>
<td>36</td>
<td>0.42</td>
</tr>
<tr>
<td>Britto et al. (2003)</td>
<td>44</td>
<td>46</td>
<td>0.82</td>
</tr>
<tr>
<td>Segura-Egea et al. (2005)</td>
<td>60</td>
<td>83</td>
<td>0.17</td>
</tr>
<tr>
<td>López-López et al. (2011)</td>
<td>24</td>
<td>46</td>
<td>0.09</td>
</tr>
<tr>
<td>Marotta et al. (2012)</td>
<td>38</td>
<td>46</td>
<td>0.21</td>
</tr>
<tr>
<td>Marques-Ferreira et al. (2014)</td>
<td>20</td>
<td>43</td>
<td>0.06</td>
</tr>
<tr>
<td>Smadi (2017)</td>
<td>19</td>
<td>28</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

*Significant \( P \) value.
promote an increase in the overall insulin resistance, altering the metabolic control in diabetic patients (Segura-Egea et al. 2015).

In summary, an attempt has been made to analyse each of the Hill criteria to the association between Endodontics-diabetes. The association between diabetes and the prevalence of apical periodontitis and RCT has only a tentative link with causation. On the contrary, the scientific evidence demonstrates a larger percentage of RFT with apical periodontitis and lower retention of root filled teeth in diabetic patients compared to control subjects. The significant ORs calculated in two systematic reviews with meta-analysis (Segura-Egea et al. 2016, Cabanillas-Balsera et al. 2019) give strength to the association between diabetes and RCT outcome.

However, although the association between the outcome of RCT and diabetes seems to fulfill most of Hill’s causation criteria, the design of the studies on which this conclusion is based does not rule out the presence of confounding variables. In particular, the higher percentage of RFT with apical periodontitis and lower retention of RFT teeth in diabetics could reflect not only the success rate of RCT and the healing of AP, but also the incidence of caries and periodontal disease in diabetic subjects. Unfortunately, studies relating these variables (diabetes, caries, periodontal disease, AP, RFT and extractions, including the primary cause of extraction) are lacking.

These conclusions should be translated to the clinical practice. Dentists should be aware of the relationship between DM and the outcome of RCT, considering diabetes as a preoperative factor that could influence the outcome of the root canal treatment.

Conclusions

The results of the studies on Endodontic Medicine cannot be interpreted without taking account of the causation criteria. The OR values evaluated separately, although being high and significant, do not indicate by themselves causal associations. The two variables analysed are associated by having common risk factors, but without the existence of a cause–effect relationship between them. The analysis of the temporal relationship, the dose–response gradient, the consistency of the association, the coherence and biological plausibility of the association should be analysed and discussed to be able to conclude that the association is causal.

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Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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