ASSOCIATION BETWEEN TYPE II DIABETES AND APICAL PERIODONTITIS: A CRITICAL REVIEW AND BEFORE/AFTER STUDY ON THE OUTCOME OF ENDODONTIC TREATMENT IN AN EMIRATI ADULT POPULATION

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ABSTRACT

Association between type II diabetes and apical periodontitis: A critical review and before/after study on the outcome of endodontic treatment in an adult population in an Emirati adult population.

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The work presented here consists of two distinct parts.

Part 1: A Critical Review of the literature

Background: Diabetes has been found to be associated with increased risk of infections, impaired immune response and delayed wound healing. Studies have found that these complications contribute to an increased prevalence of periapical lesions and decreased endodontic success.

Aim: To critically review the literature with regards to the association between apical periodontitis and diabetes.

Materials and Methods: An extensive search was carried out using MEDLINE (ovid), Embase, Pubmed, The Cochrane Central Register Search of controlled trials, and Cochrane Reviews to identify suitable human-based studies. These studies included adult participants, a diabatic and a control group, and used a radiographic assessment of periapical radiolucency.

Results: The critical review included 11 studies conducted between 1989 to April 2019. From these studies, 4 studies found a significantly higher prevalence of apical periodontitis in diabatic patients compared to non-diabatic patients before endodontic treatment while 7 studies found

significantly higher prevalence of apical periodontitis after endodontic treatment in diabatic than non-diabatic cases.

Conclusion: An association was found between diabetes and apical periodontitis before and after Endodontic treatment.

Part 2: Association between Type II Diabetes and Apical Periodontitis before and after Endodontic Treatment in an Adult Population in the United Arab Emirates

Background: Diabetes Mellitus is one of the most common systemic disorders. Diabetes Mellitus results in hyperglycemia which can affect the healing of the dental pulp. Clinical studies have shown a higher prevalence of periapical lesions in uncontrolled diabetes although the exact relationship is not clearly understood.

Aim: To determine the association between Type II diabetes and apical periodontitis (AP) before and after Endodontic treatment in an adult population in the United Arab Emirates. The null hypothesis that Type II diabetes has no effect on the size of AP lesions was tested.

Materials and methods: A sample of 50 patients with Type II diabetes were selected from a database in a specialist Endodontic unit who had received endodontic treatment on one tooth. These were matched in terms of age and gender with a non-diabetic control group who received Endodontic treatment on the same tooth. For each group, the size of the AP lesion was recorded using the Periapical Index (PAI) scoring system preoperatively and 1 to 4 years post endodontic treatment. The 50 diabetic patients were made up of 27 controlled and 23 uncontrolled (HbA1c value of 8% or higher) diabetics.

Results: The mean PAI score for the uncontrolled diabetic group (n=23) prior to endodontic treatment was 3.3 compared to 2.3 for the matched non-diabetic control group. The Wilcoxon sign

rank test revealed that this was statistically significant (p=0.002) indicating that uncontrolled Type II diabetes influences the size of the AP lesion. These figures were reduced to a mean PAI score of 1.9 in the uncontrolled diabetic group and 1.5 in the healthy control group in the post endodontic treatment periapical radiographs. The corresponding mean PAI value prior to endodontic treatment were 2.4 and 2.7 in the controlled diabetic patients and their matching control group respectively. The differences were not statistically significant (p=0.13). For the sample as a whole (n=50), the mean PAI value for both diabetic and non-diabetic groups reduced to 1.7 and 1.6 respectively post Endodontic periapical radiographs. The Wilcoxon sign rank test revealed a statistically significant improvement in healing in both these groups (p<0.001).

Conclusions: PAI scores, prior to Endodontic treatment, were significantly higher in the uncontrolled diabetic group compared to the controlled diabetic group. In all cases the Endodontic treatment significantly reduced the size of the AP lesions

DEDICATION

To my country, that provided me with the best educational institutes and all the needed resources to reach to this educational level. To my family whom I get all the support and motivation from. To every teacher, instructor, and professor I have honorably encountered in my educational journey in which they have enriched my knowledge and developed my skills.

DECLARATION

I declare that all the content of this thesis is my own work. There is no conflict of interest with any other entity or organization

Name: Alaa Tariq AlMutawa

Signature: _____

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LIST OF ABBREVIATION

1. AP	Apical Periodontitis
2. CBCT	Cone Beam Computed Tomography
3. DHA	Dubai Health Authority
4. DNA	Deoxyribonucleic Acid
5. GAD	Glutamic Acid Decarboxylase
6. HBA1C	Hemoglobin A1C
7. HNF	Hepatocyte Nuclear Factor
8. HLA	Human Leukocyte Antigen
9. IL-1B	Interleukin 1 Beta
10. IPF	Insulin Promotor Factor
11. MBRU	Mohammed Bin Rashed University of Medical and Health Sciences
12. PAI	Periapical Index
13. PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
14. SOP	Standard Operation Procedures
15. TNFB	Tumor Necrosis Factor Beta

1. INTRODUCTION

Diabetes Mellitus is a chronic metabolic disease characterized by increased cell starvation and high blood glucose levels (American Diabetes Association 2010; Siddiqui et al. 2013). Diabetes found to be associated with various serious complications which include increased risk of infection, impaired immune response and delayed wound healing (Casqueiro et al. 2012; Muller et al. 2005). Studies have found that these complications contribute to an increased prevalence of periapical lesions (Lima 2013, Segura-Egea et al 2005; Marotta et al. 2012) and decreased endodontic success (Cheraskin et al. 1968; Britto et al. 2003).

Diabetes is considered a common systemic disease encountered in dental settings. Thus, investigating its association with endodontic treatment is essential. This study would first introduce the relevant topics; then critically review the literature related to the association between diabetes and apical periodontitis before and after endodontic treatment. Moreover, it would determine this association between type II diabetes and apical periodontitis in an adult population in the United Arab Emirates.

2. REVIEW OF THE LITERATURE

2.1 Diabetes:

2.1.1 Overview

Diabetes is defined as a series of metabolic conditions with different etiological factors characterized by hyperglycemia resulting from inability of the human body to regulate the amount of glucose accumulated in the blood. This occurs either due to deficient insulin secretions, insulin action, or both (American Diabetes Association 2010; Siddiqui et al. 2013, Alberti 1998). Insulin is a hormone secreted by Beta Cells in the pancreas which has an important role in ensuring sufficient glucose intake by body cells. This role is considered an important mechanism for various body activities (Siddiqui et al. 2013) including protein, fat, and carbohydrate metabolism. This pathology occurs either due to autoimmune destruction of pancreatic cells which results in inadequate insulin secretion or abnormal resistance to insulin action expressed by diminished tissue response within any point of the hormonal pathway. The two abnormalities may sometimes coexist in the same patient (American Diabetes Association 2010).

Diabetes is divided into several types depending on the etiology of the disease. Type I Diabetes is further divided by the American Diabetes Association in 1997 into Immune-Mediated Diabetes (Type 1A Diabetes) and Idiopathic Diabetes (Type 1B Diabetes) (Echeverri and Tobón 2013). The Immune-Mediated Diabetes, previously known as insulin-dependent diabetes or juvenile-onset diabetes, is characterized by cellular mediated autoimmune destruction of Beta cells located in the pancreas. This pathology is associated with immune destruction markers which includes islet cell autoantibodies, insulin autoantibodies, glutamic acid decarboxylase (GAD) autoantibodies and tyrosin phosphatase autoantibodies and linked to several genes which includes Human Leukocyte Antigen complex. However, the rate of cell destruction varies, and its first symptoms ranges from

modest fasting hyperglycemia to ketoacidosis. The cell destruction is found to be more severe and rapid in children than in adults. Beside genetic factors, environmental factors were also found to contribute to the etiology of the disease, nevertheless the relationship is not clear yet. This type of diabetes accounts for about 5 to 10% of the diabetic population and is commonly associated with childhood or adolescence onset, however it may also start in any age (American Diabetes Association 2010, Echeverri and Tobón 2013).

On the other hand, idiopathic diabetes, has no clear etiology. In this type, no immunological evidence for Beta cell autoimmunity is detected nor an association with Human Leukocyte Antigen (HLA) genes. Patients with this type of diabetes exhibit episodes of ketoacidosis accompanied with different levels of insulin deficiency between the episodes. This type of diabetes is considered rare. (American Diabetes Association 2010)

While in Type II diabetes, previously known as non-insulin dependent diabetes or adult-onset diabetes, insulin resistance is detected in patients which might be accompanied with relative insulin resistance (American Diabetes Association 2010). Hormonal imbalance, increase in cytokines concentration, and decreased cytokines signaling lead to insulin intolerance which with time would affect Beta cells secretion (Siddiqui et al. 2013). This type of diabetes is associated with obesity or a high percentage of body fat concentrated in the abdominal region rather than with autoimmune etiology. This type develops gradually and requires several years to be detected as no symptoms may reveal in the first years (American Diabetes Association 2010). Type II is considered the most prevalent contributing to more than 85% of the total diabetic population (American Diabetes Association 2010, Forouhi and Wareham 2014). Patients with this form of diabetes may have normal or elevated insulin secretions to compensate for the insulin resistance. Insulin resistance may be improved through weight loss or pharmacological methods but rarely

returned into normal. This form of diabetes is associated with increased risk of macrovascular or microvascular complications (American Diabetes Association 2010).

Forms of diabetes is not constricted to the above-mentioned types. Maturity onset diabetes of the young is characterized by evolving of the hyperglycemia symptoms in an early age; before 25 years old. In this type of diabetes, secretion of insulin is impaired with normal or minimal impairment in insulin action. This form is associated with monogenetic defects in Beta cell function. It is found to be associated with mutations on different chromosomes; commonly in the hepatic transcription factor on chromosome 12, and to lesser extents in glucokinase gene on chromosome 7p. It may rarely also affect other transcription factors; HNF-4, HNF-1, and IPF-1. Moreover, point mutations in DNA mitochondria was also found to lead to diabetes. These mutations cause A to G transition. This mutation would lead to inability to convert proinsulin into insulin or production of mutant insulin molecules with impaired receptors. However, these mutations lead to mild glucose intolerance or glucose metabolism respectively. (American Diabetes Association 2010)

Another form of diabetes is genetic mutations which alters insulin action; previously termed as type A insulin resistance. Although this form is considered rare, the resulting hyperglycemia ranges from mild to severe. These mutations may be associated with other abnormalities such as acanthosis nigricans, women virilization, Leperechaunism and Rabson-Mendenhall syndrome. Moreover, diseases of the pancreases which results in extensive damage to this exocrine organ would also contribute to diabetes. Theses disease include pancreatitis, trauma to the pancreas, infection, pancreatectomy, and pancreatic carcinoma. Similarly, hormonal disorders may also contribute to diabetes. In other words, excessive amount of growth hormones, cortisol, glucagon, and epinephrine would antagonize insulin action leading to diabetes. These pathologies are present

in several diseases such as Cushing's syndrome, pheochromocytoma, acromegaly, and glucoganoma. (American Diabetes Association 2010)

Diabetes may also be induced through the use of drugs. These drugs may either impair insulin secretions leading to diabetes in susceptible individuals, affect insulin action such as glucocorticoids and nicotinic acid, or permanently destroy the pancreatic cells through toxins such as Vacor and pentamidine. On the other hand, viruses may also contribute to infections that would lead to pancreatic cell destruction. These viruses include cytomegalovirus, adenoviruses, mumps and congenital rubella. Furthermore, several immune mediated diseases and genetic syndromes may contribute to diabetes. These diseases include stiff-man syndrome and anti-insulin receptor antibodies diseases, Down syndrome, Klinefelter syndrome, Turner syndrome, and Wolfram syndrome (American Diabetes Association 2010).

Furthermore, Gestational diabetes is another form of diabetes in which the onset of the disease begins during pregnancy. Most of these cases resolve after pregnancy, however some may persist. According to the International Association of Diabetes and Pregnancy Study Groups, those cases detected with high risk of diabetes in the prenatal visits are not considered within the Gestational form. This form of diabetes appears in about 7% of all pregnancies. (American Diabetes Association 2010)

Despite the different forms of diabetes, patients with hyperglycemia would exhibit characteristic symptoms which includes polyuria, polydipsia, weight loss, polyphagia, weight loss, and blurred vision. Nevertheless, the symptoms may appear in a more severe form which is represented as ketoacidosis or a non-ketotic hyperosmolar syndrome (Alberti 1998; American Diabetes Association 2010).

2.1.2 Standard Diagnostic Indicator

Diabetes is a chronic disease; in which monitoring its progress is essential. Glycated hemoglobin (HBA1C) is recommended as a standard of care diagnostic indicator of long-term glycemic control (World Health Organization 2011). This indicator would provide a reliable biomarker of cumulative glycemic control within two or three months. This would also reflect the risk of developing long-term complications (Sherwani et al. 2016). The recent recommendation according to the American College of physician for type II Diabetes is to have an HBA1C between 7 and 8 percent. This recommendation was based upon evidences that no difference was observed in terms of complications between patients with HBA1C of 7 and those with HBA1C of 8. Thus, cases with HBA1c above 8 would be considered as cases of uncontrolled diabetes (Qassem et al. 2018).

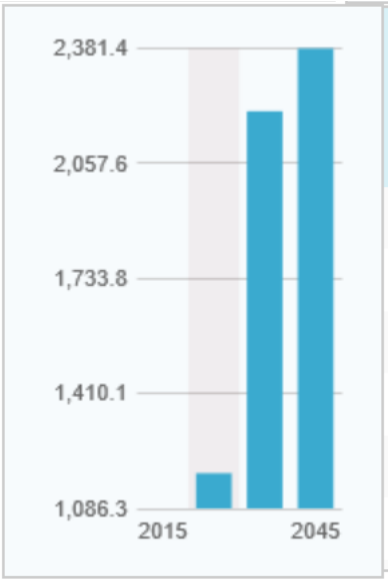
2.1.3 Epidemiology

According to the International Diabetes Federation, the latest global statistics conducted in 2017 revealed that diabetes is now affecting more than 425 million people worldwide (International Diabetes Federation 2017). The prevalence of diabetes has been increasing with time; as it raised from 108 million in 1980, 4.7% of adult population, to 422 million in 2014, 8.5% of adult population (World health Organization 2018). The prevalence is estimated to reach to 629 million cases by 2045 if the situation proceeded on the same track (International Diabetes Federation 2017).

In UAE specifically, the prevalence of diabetes is high; it was found to be 17.3% among all adult population in the country in 2017 which accounts for 1,185 million case in the country. It is estimated that the prevalence would increase to reach to 2,381 million case by 2045 (International Diabetes Federation 2018) as shown in Figure 1. While concentrating on the city of Dubai in the

same year; 19% of all Emirati adults in the city are diagnosed with diabetes (Dubai Health Authority 2017). These high numbers infer the need to consider this medical condition in dental clinical settings.

Figure 1. The estimated increase in prevalence of diabetes in UAE (International Diabetes Federation, 2018)



2.1.4 Complications

Both starvation of cells and accumulation of high glucose level in blood may lead to serious complications and long-term damages (Alberti 1998; Fowler 2008; American Diabetes Association 2010). These complications can be broadly classified as macrovascular which includes arterial diseases and stroke besides to microvascular which includes diabetic retinopathy impairing the vision, nephropathy disturbing the kidney function, autonomic neuropathy affecting the gastrointestinal, genitourinary, and cardiovascular systems and peripheral neuropathy leading to feet ulcers and the joints diseases (Fowler 2008; American Diabetes Association 2010). The macrovascular and microvascular complications mainly occur due to increase in oxygen free

radicles and the formation of superoxide (West 2000, Leite 2010). These complications may further contribute to various organs failure (Alberti 1998). Moreover, this would also contribute to increased risk of atherosclerotic cardiovascular, cerebrovascular, and peripheral arterial diseases (American Diabetes Association 2010). Impairment of growth is also found to be associated with diabetes (American Diabetes Association 2010).

It is also associated with an increased risk of infection; as studies have found increased lower respiratory tract infection (Muller et al. 2005), urinary tract infections (Patterson and Andriole 1997; Muller et al. 2005), skin infections, and mucus membrane infections in diabetic patients (Muller et al. 2005, Shah and Hux 2003, Yosipovitch et al.1998). This increased risk is explained by a rise in pathogen virulence in the hyperglycemic environment, reduction in T cells response, alteration in leukocyte function, and impaired humoral immunity (Casqueiro et al. 2012). The casual relationship between each of these impaired physiology and increased infection is still unclear (Muller et al. 2005); however, a combination of these defects presented in non-controlled diabetic patients would together increase the susceptibility to infections (Rayfield et al. 1982).

Impaired leukocyte function is considered one of the most highlighted reasons (Delmaire 1997). This impairment is explained by the downregulation of adhesion molecules available in vascular walls leading to decreased presence of leukocytes in inflammatory sites due to impaired leukocyte-endothelial cell interactions (De Oliveira 2006). Moreover, the interaction between glucose with proteins and lipids in the body result in advanced glycation end products (Brownlee 2001). Accumulation of these products in the body would as well alter leukocyte functions (Alba-Loureiro et al. 2007). Another explanation that contribute to leukocyte function impairment is the conversion of excess glucose to sorbitol which affects the polyol pathway which is essential for normal leukocyte function (Cruz et al. 2000).

These complications contribute to several oral manifestations that are associated with this condition which includes periodontal disease, fungal infections, xerostomia, altered taste sensation, oral mucosal lesions, and caries (Al-Maskari et al. 2011). Diabetic patients are three times more prone to periodontal disease than non-diabetic (Ryan et al. 2003). Impaired immune response correlated with changes in collagen metabolism contribute to increased accumulation of glycation products and bacterial persistence in the periodontium resulting in periodontal destruction and compromised tissue healing. Delayed wound healing in the oral cavity is associated with decreased blood flow, declined innate immune system, and reduced production of growth factors. This process is more elaborated in patients with uncontrolled diabetes (Al-Maskari et al. 2011).

2.2 Apical Periodontitis:

2.2.1 Overview

Persistent polymicrobial irritants in the root canal system may cause acute or chronic periapical lesions around the root apex (Segura-Egea 2012, Fernandes and De Ataide 2010). These inflammatory lesions are referred to as apical periodontitis (Segura-Egea 2012). It develops in response to a defensive mechanism to confine the spread of bacteria resulting from necrotic pulp or secondary to either reinfected or unsuccessful root canal treated teeth. These lesions may present as either symptomatic associated with tenderness, pain, and swelling or asymptotic revealed during radiographic investigations (Metzger et al. 2009, Fernandes and De Ataide 2010). The development of the lesion would depend upon the concentration of the irritant and host response as it might be more exaggerated in patients with systemic diseases (Bender et al. 1963).

The bone loss accompanied with this defensive mechanism is activated by the release of Interleukin 1 Beta (IL-1β) and Tumor Necrosis Factor Beta (TNFβ) from macrophages and T Lymphocytes respectively which results in increased osteoclastic activity. Bone less can be detected on radiographs by the presence of radiolucent lesions (Segura-Egea et al. 2016). However, early bone resorption is not radiographically detected unless it reaches to the cortical bone level. Eliminating the infection through successful conventional or surgical root canal treatment would help in resolving the lesion and deposition of new bone in the area (Metzger 2009).

Periapical lesions can be classified as dental granulomas, radicular cysts or abscesses. According to Nair (2002); Granuloma account for the largest percentage of all periapical lesions (73%) followed by abscesses (12%), true cysts (9%), and pocket cyst (6%). Confirming the type of the periapical lesion is essential for choosing the suitable treatment option; as true cysts require endodontic surgery to be removed while others would resolve with adequate non-surgical endodontic treatment (Nair 2002). This is possible only through histological means. Nevertheless, preliminary diagnosis could be based upon the size, vitality of the involved teeth, radiographic interpretation, and the content of the lesion. For instance, periapical cysts tend to have a size greater than 200 mm^2, associated with non-vital teeth, seen on the radiograph as well-defined circumscribed radiolucency, and has a straw-colored fluid content (Fernandes and De Ataide, 2010).

2.2.2 Evaluation

Radiography is considered a reliable mean to evaluate periapical lesions (Orstavik et al. 1986; Segura-Egea et al. 2016); as clinical signs and symptoms may vary with different cases. Despite the limitations of a periapical radiograph, as it produces a single sagittal plane image of three-

dimensional structure (Filho 2018), it exhibits characteristic features which are essential for diagnosis and treatment assessment (Orstavik et al. 1986).

Nevertheless, to compare the different periapical lesions a reliable and reproduceable criteria is required. Several attempts to construct a reliable tool based on periodontal ligament width and lamina dura integrity, whereas these tools were not adequate (Orstavik et al. 1986). Brunolf (1967) proposed a standardized evaluation method of periapical lesions using a series of periapical radiographs to be used as a reference to evaluate the existing periapical pathology. This tool was then enhanced by Orstavik et al. (1986) through an ordinal scale of 1 to 5; where 1 is considered a state of health and 5 is a state of severe periodontitis associated with exacerbating factors. The combination of the two systems is shown in Figure 2. The PAI score system is considered to be reasonably accurate and reproducible. It is appropriate to be used in retrospective analysis of endodontic treatment outcomes, in clinical trials, and in epidemiological studies (Orstavik et al. 1986). The PAI scoring system in shown in Table 1.

Figure 2. A combination of Brunolf (1967) radiographic reference and PAI score (Orstavik et al. 1986).

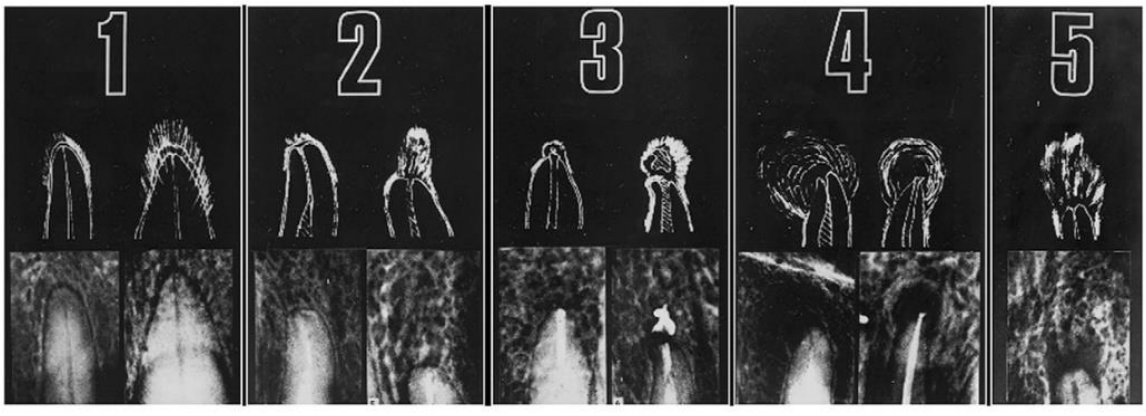


Table 1. PAI scoring system (Orstavik et al. 1986)

Score	Interpretation
1	Normal periapical structure
2	Small changes in bone structure
3	Changes in bone structure with some material loss
4	Periodontitis with well-developed radiolucent area
5	Severe periodontitis with exacerbating factors

2.3 Association between Diabetes and Apical Periodontitis:

Considering the inflammatory nature of apical periodontitis with increased susceptibility to infection and impaired healing in diabetic patients, studies have found an association between the two variables. The prevalence of periapical lesions is considered higher in patients with uncontrolled diabetes (Lima 2013). For instance, a study by Segura-Egea et al. (2005) found that 81.3% of diabetic patients had apical periodontitis compared to 58% of non-diabetic patients. Similarly, Morroto et al. (2012) found a higher prevalence of apical periodontists among diabetic patients (15%) than non-diabetic (12%) in a Brazilian population. The higher prevalence was also detected in a study performed by Lopez-Lopez et al. (2011) in Spanish population; where the percentages were 46% for diabetic and 24% for non-diabetic. Moreover, the longer the duration of diabetes onset the higher the prevalence of apical periodontitis. This was detected in a study by Falk et al. (1989) performed on a Swedish population.

This higher prevalence is associated with increased number of root canal microbiota. Eubacterium infirmum is found to be significantly more in root canals of diabetic patients than non-diabetic (Fouad et al. 2003). While Porphyromonas endodotalis and Prophyromonas gingivalis were found

to be present in higher number in diabetic patients; yet the difference is not significant (Fouad et al. 2002).

Concentrating on the endodontic aspect, successful root canal treatment is expected to eliminate and prevent further infection of the periapical tissue. However, the alterations that occur in the body normal functions may also affect the healing process. Several studies investigated the healing of periapical lesions after endodontic treatment in diabetic patients. Britto et al. (2003) found that residual lesions remaining after endodontic treatments tend to be higher in diabetic patients. Cheraskin et al. (1968) concluded that reduction in periapical lesions was higher in patients with low glucose level than those with high glucose; the percentages were 74% and 48% respectively. Fouad and Burlesson (2003) stated that endodontic treatment success is reduced in diabetic patient with preoperative periapical lesions. On the other hand, Bender et al. (1963) suggested that periapical lesions would resolve if the blood glucose level is well controlled. However, a study by Fouad et al. (2003) have found that endodontic treatment outcomes is not affected by the blood glucose level of the patient.

Moreover, it is found that hyperglycemia affects the blood circulation in dental pulp resulting in increased risk of pulpal infections that could spread to the periapical region. Studies have found that apical periodontitis being similar to periodontal disease can lead to increase insulin resistance and poor glycemic control. (Chakravarthy 2013). Similarity between apical periodontitis and periodontal diseases lies within the presence of gram-negative anaerobic pathogens and accumulation of inflammatory mediators with systemic effects tendency (Segura-Egea 2012).

3. AIM

This work consists of two distinct parts:

i. A critical review highlights the association between apical periodontitis and diabetes.

ii. A retrospective study to investigate the association between type II diabetes specifically and apical periodontitis before and after endodontic treatment in an Emirati adult population.

iii. The null hypothesis that there is no association between type II diabetes and apical periodontitis before and after endodontic treatment was tested.

4. MATERIALS AND METHODS

4.1 Part I: A Critical Review of the literature

4.1.1 Eligibility criteria:

Only English articles could be selected those which met our search terms before and after the "AND" string was eligible. The search looked for guidelines published from 1946 with the final search being 2019. During our search we could not have access to some full-length articles. These studies were excluded. The data from the included studies were extracted independently after thorough assessment. The studies were limited to those employing human participants. The following studies were excluded from our search:

1) Animal studies
2) Laboratory studies
3) Studies with only a diabetic group
4) Studies of outcomes of denovo root canal
5) Studies without radiographic assessment of periapical radiolucency
6) Studies of subjects below the age of 18 years old.

4.1.2 Search Strategies:

In order to identify the articles, search was conducted in the following scientific databases; MEDLINE (ovid), Embase, Pubmed, The Cochrane Central Register Search of controlled trials, and Cochrane Reviews. The search looked for publications from 1946 with the final search being 2019. The terms used for MEDLINE (Ovid), Embase, and Pubmed searches are shown in Table 2.

Table 2. List of MeSH and keywords combinations used for the search strategy

((“diabetes” [MeSH Terms]) OR (“diabetes”[All Fields]) OR (“diabetes mellitus”[MeSH Terms]) OR (“diabetes mellitus” [All Fields]) OR (“diabetes” [All Fields] AND “mellitus” [All Fields]) OR (“hyperglycemia”[MeSH Terms]) OR (“hyperglycemia” [All Fields]) AND (“Periapical lesion” [MeSH Terms]) OR (“Periapical lesion” [All Fields]) OR (“Periapical” [All Fields] AND “lesion” [All Fields]) OR (“Apical Periodontitis” [MeSH Terms]) OR (“Apical Periodontitis” [All Fields]) OR (“Apical” [All Fields] AND “Periodontitis” [All Fields]) OR (“PAI score” [MeSH Terms]) OR (“PAI score” [All Fields]) OR (“PAI” [All Fields] AND score” [All Fields]) OR (“Apical radiolucency” [MeSH Terms]) OR (“Apical radiolucency” [All Fields]) (“Apical” [All Fields] AND “radiolucency” [All Fields]) OR (“Endodontics” [MeSH Terms]) OR (“Endodontics” [All Terms]) OR (“Root Canal Treatment” [MeSH Terms]) OR (“Root Canal Treatment” [All Fields]) OR (“Root” [All Fields] AND “Canal” [All Fields] AND “Treatment” [All Fields]) OR (“Root Canal Therapy” [MeSH Terms]) OR (“Root Canal Therapy”[All Fields]) OR (“Root” [All Fields] AND “Canal” [All Fields] AND “Therapy” [All Fields]))

After that, manual hand searching was performed using google scholar searches.

4.1.3 Study Selection:

A single assessor scanned the result to remove any irrelevant publications. A second screening was undertaken with a second assessor against the eligibility criteria. Any case of disagreement between assessors were discussed until a consensus was obtained. The details of the search process were filled in a distinct flowchart (Fig 1.) which is recommended by PRISMA (Moher et al. 2009).

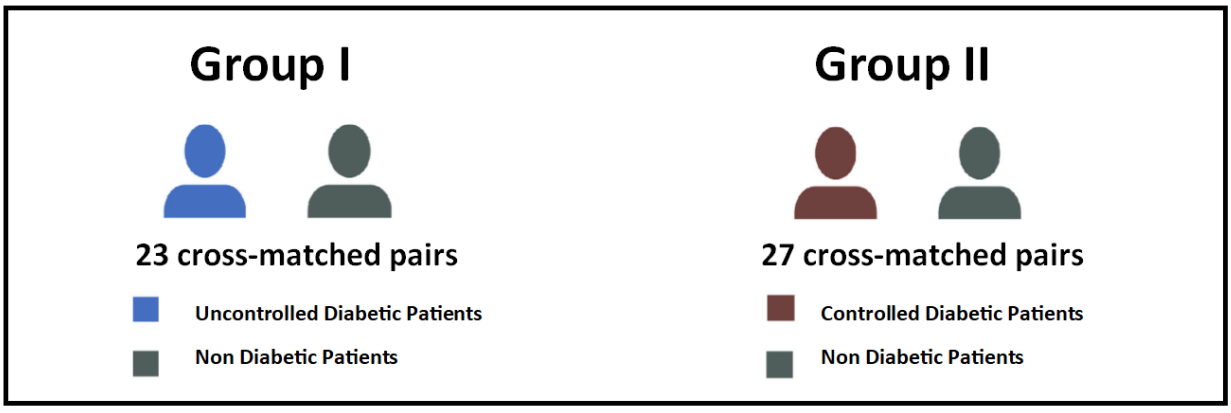
4.2 Part II: Association between Type II Diabetes and Apical Periodontitis before and after Endodontic Treatment in an Emirati Adult Population.

This study aimed at using a pair-matched cross-sectional design with data collected through patient record review and examination of dental intra-oral radiographs as detailed below.

4.2.1 Patient Selection:

All patients in Dubai Health Authority (DHA) treated in endodontic clinics for root canal treatment between 2012 and 2018 were taken from DHA database. The target population was divided into two groups; diabetic patients as cases and the same number of non-diabetic patients as a control. A sample of 50 patients with type II diabetes were selected from the database then pair-matched with non-diabetic patients by age, gender, medical condition. A similar root canal treatment completion time and follow-up duration was also considered. The sample was then further divided into controlled and non-controlled diabetic patients as shown in Figure 3.

Figure 3. Study groups (pair-matched)



- Inclusion criteria:

The inclusion criteria were all adult diabetic UAE national male and female patients with root filled teeth.

- Exclusion criteria:

The exclusion criteria were patients under the age of 18 and patients with non-diagnostic radiographs. Additionally, any patient with inadequate root canal treatment was excluded.

All patients' data were pseudonymized. Patient images were accessed at DHA by the author. The author assigned a number to each set of patient notes selected for the study. The key linking the patient name to the collected data was stored electronically on a password protected computer at MBRU. Digital images were stored on DHA computers and only accessed by the author following standard operations procedures (SOPs).

4.2.2 Radiographic examination:

All periapical radiographs selected for this study were confined to those taken 1-4 years after completion of root canal treatment. Teeth were categorized as root-filled teeth if they had been filled with a radiopaque material in the pulp chamber and/or in the root canals.

The periapical status was examined using the periapical index (PAI) scoring system (Orstavik et al. 1986) and recorded by assigning scores from 1 to 5 as below:

1- Normal periapical structure

2- Small changes in bone structure

3- Changes in bone structure with some material loss

4- Periodontitis with well-developed radiolucent area

5- Severe periodontitis with exacerbating factors

The PAI scoring system represents an ordinal scale of registration of periapical infection. The highest score of all roots were taken to represent the PAI score for multirooted teeth. The PAI scores were dichotomized in accordance of either absence (PAI <3) or presence (PAI ≥ 3) of a

periapical lesion. A score of equal to or greater than 3 (PAI ≥ 3, i.e. score of 3,4,5) was considered a sign of periapical pathology (Orstavik, Kerekes, and Eriksen, 1986).ie. a score of 3,4,5.

The results were dichotomized by assigning 0 (absence of pathology) and 1 (presence of pathology) which is based on the Toronto study (Farzaneh, Abitbol, and Friedman, 2004).

Other variables considered in the study included type of teeth involved, gender, age, and medical conditions. The data collection tables are presented in Appendix1.

Figure 4. Radiographic reference of PAI scores (Orstavik et al. 1986).

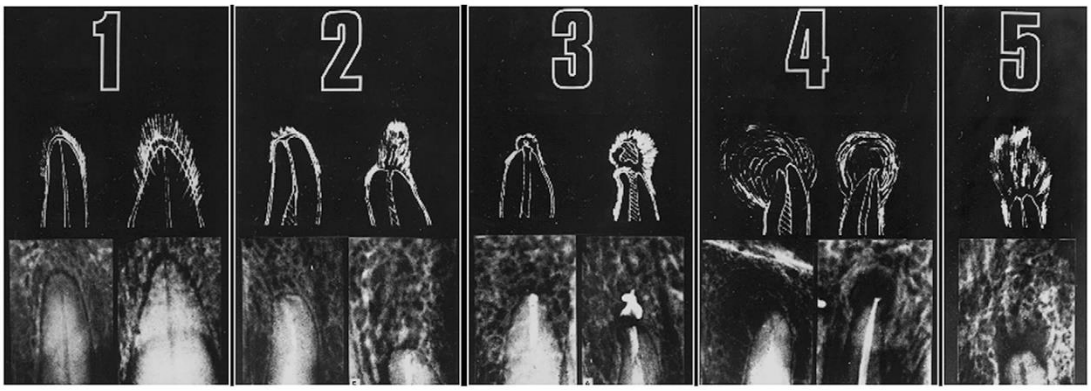
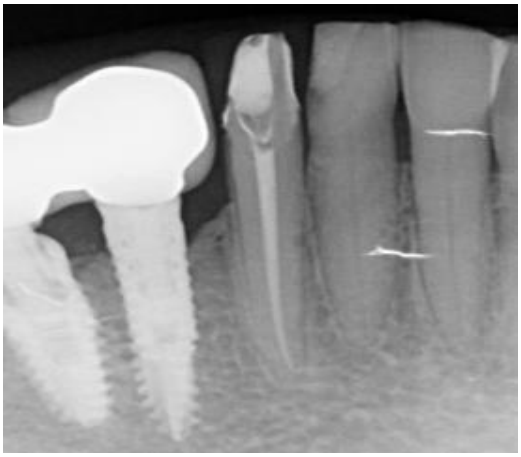
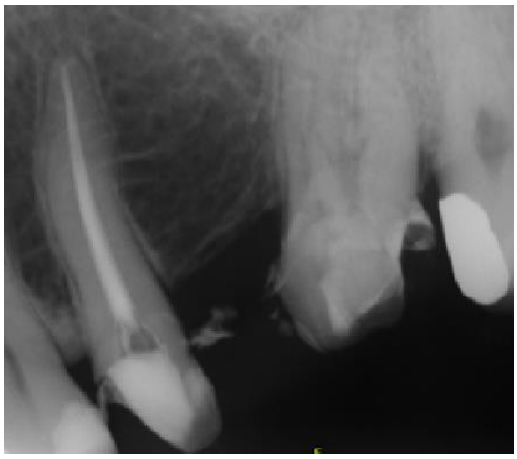


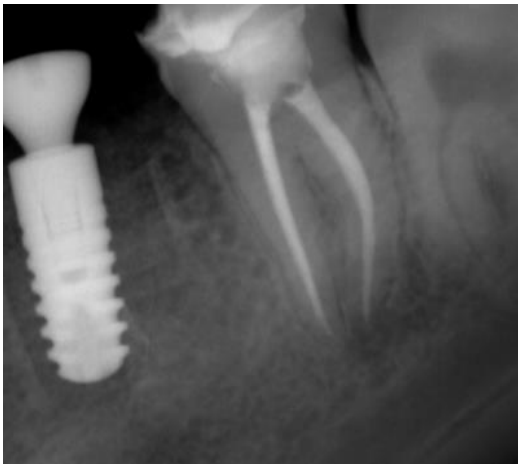
Figure 5. Example of periapical radiographs with PAI scores



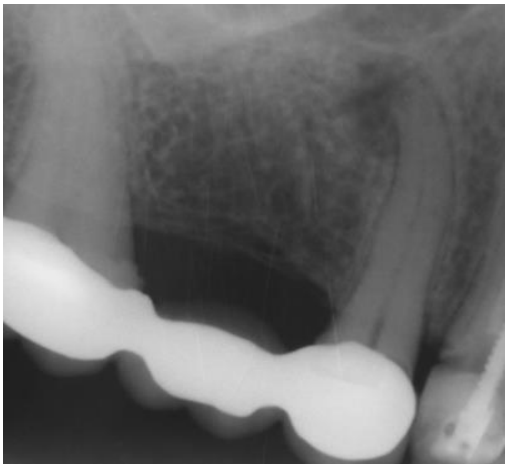
Tooth LL3 has a PAI score of 1



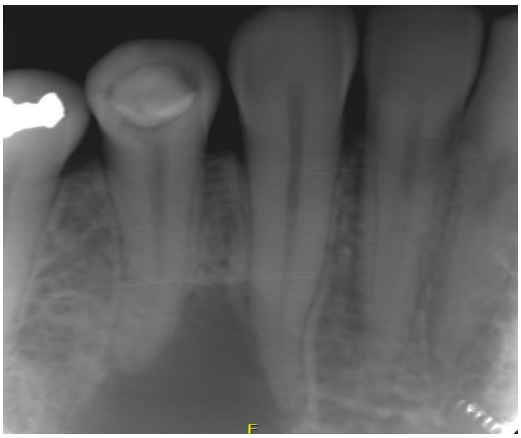
Tooth UL5 has a PAI score of 2



Tooth LL7 has a PAI score of 3



Tooth UR5 has a PAI score of 4



Tooth LL3 has a PAI of 5

4.2.3 Observer

The author examined the radiograph. Intra-observer reproducibility was evaluated by repeating all the scores 3 months after the first examination. The purpose of the time separation between the two assessments aimed to minimize any risk of the observer giving an opinion contaminated by the memory of the previous viewing. The radiographs were then also evaluated by a second assessor. The intra-observer and inter-observer agreement were assessed via Cohen's Kappa test.

4.2.4 Ethical Considerations

Ethical approval of this study was obtained from the Ethics Committee in Hamdan Bin Mohammed College of Dental Medicine – MBRU on 6/5/2018 (Appendix 1) as well as the Ethics Committee at Dubai Health Authority on 28/10/2018 (Appendix 2).

4.2.5 Statistical Analysis

SPSS for windows version 20.0 (SPSS Inc., Chicago, IL) was used to analyze the data. Intra and inter observer agreement for PAI scores were assessed using kappa statistics. The data for PAI scores in diabatic and non-diabatic groups did not follow a normal distribution as was verified using the Shapiro-Wilk statistical test. The data were, therefore, analyzed using the Wilcoxon Sign Rank test at $p<0.05$.

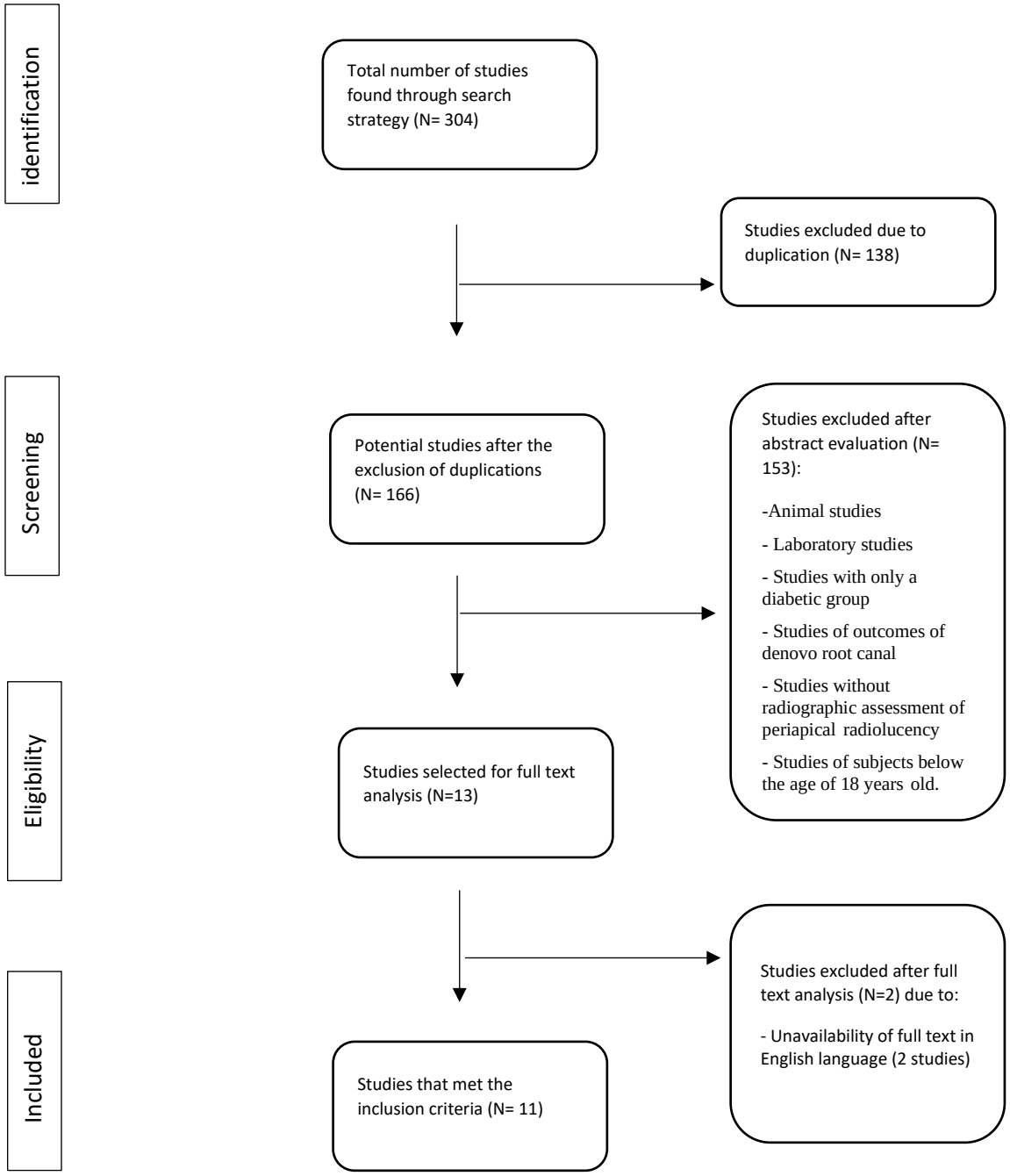
5. RESULTS

5.1 Part I: A Critical Review of the literature

5.1.1 Studies Selection Process

The selection process of the studies included in this critical review is displayed in Figure 6. The MeSH terms and keywords combination presented in Table 2 resulted in 304 articles. From these articles, 138 were excluded due to duplications. The abstracts of the remaining 166 articles were then investigated; resulting in 13 potential studies. Full text analysis of the potential articles resulted in 11 studies that meets the inclusion and exclusion criteria of this critical review. From the 13 potential studies, 2 studies were excluded due to unavailability of the full text in English Language.

Figure 6. The selection process of the studies included in this critical review



5.1.2 Studies Characteristics

After analyzing the potential studies, 11 studies were included in this critical review. These studies are Segura-Egea et al. (2005), Marrota et al. (2012), Smadi L. (2017), Ferreira et al. (2014), Britto et al. (2003), Fouad and Burlesson (2003), Lopez-Lopez et al. (2011), Falk et al. (1989), Laukkanen et al. (2018), Sisli S. (2019), Arya et al.(2017). Table 3 summarizes these articles by presenting the aim, type of study, sample size, statistics used, and the outcomes of each study.

The time frame in which the selected studies were conducted ranged from 1989 to April 2019. In details, 1 study was conducted in 1989, 3 studies were conducted between 2003 and 2005, 3 studies were conducted between 2011 and 2014, and 4 studies were conducted between 2017 and 2019. In terms of study design, the selected studies included 7 cross-sectional, 2 prospective cohort, and 2 retrospective cohort designs.

Table 3. Summary of the included studies

No	Authors	Year of Publication	Aim & Objective	Type of study	Sample size	Statistics	Outcomes
1	Segura-Egea et al.	2005	Comparing the prevalence of Apical Periodontitis between patients with type II Diabetes and non-diabetic patients.	Retrospective cohort study	32 patients with well-controlled type II diabetes and 38 non-diabetic patients	Cohen's J test, analysis of variance and logistic regression	- 83% of diabetic patients had root filled teeth with apical periodontitis, in comparison to 60% in the control group. (P=0.17) - Among untreated teeth, 6% had AP in diabetic patient compared to 3% in the control group. (P=0.004)

No	Authors	Year of Publication	Aim & Objective	Type of study	Sample size	Statistics	Outcomes
2	Marrota et al.	2012	Comparing the prevalence of apical periodontist among patients with type II diabetes and non-diabetic patients in an adult Brazilian population.	Cross-sectional	30 patients with type II diabetes pair-matched with 60 non-diabetics	Wilcoxon signed rank, McNemar tests, and chi-square test	- the prevalence of apical periodontist was significantly more in diabetic patients (15%) than in nondiabetic (12%) (P = 0.05). - the prevalence of AP in untreated teeth in diabetic patients (10%) was significantly more than in nondiabetics (7%) (P = .03). While the difference in endodontically treated teeth is not significant (46% and 38% respectively, P= 0.25).
3	Smadi L.	2017	Comparing the prevalence of apical periodontitis in diabetic patients compared with nondiabetic patients and to examine the effect of glycemic control on the prevalence of AP	Cross-sectional	82 controlled diabetic patients, 63 uncontrolled diabetic patients, and 146 non diabetic controls.	Mann–Whitney U-test, chi squared test, and Fisher's exact test	- the prevalence of apical periodontitis was found to be higher in diabetic group than in the nondiabetic (13.5 *vs* 11.9% respectively) with higher AP to endodontic treatment ratio (27.7 *vs* 19.3 respectively). - Poorly controlled diabetes had significantly higher prevalence of AP lesions compared with the well-controlled (18.29 *vs* 9.21 respectively) with higher AP to endodontic treatment ratio (32.0 *vs* 21.8% respectively).
4	Ferreira et al.	2014	To evaluate the effect of diabetes on the periapical tissues and the success of root canal treatment in diabetic patients	Cross-sectional	37 diabetic case (Type I and II) and 25 non-diabetic.	Mann-Whitney, Fischer exact test.	- inconclusive results regarding the increased prevalence of apical periodontitis in diabetic patients. -the success rate in diabetic patients was found to be lower, though not statistically significant; 62% in the diabetic group and 80% in the control group ($p > 0.05$).
5	Britto et al.	2003	To compare the prevalence of radiographic peri radicular radiolucency in teeth with root canal treatments and those without root canal treatment in diabetic and non-diabetic patients.	Retrospective cohort study	30 cases with diabetes (Type I and II) and 23 control cases.	Analysis of variance	- Men with Type II diabetes who had endodontic treatments were more likely to have residual lesions after treatment.

No	Authors	Year of Publication	Aim & Objective	Type of study	Sample size	Statistics	Outcomes
6	Fouad and Burlesson	2003	to compare the endodontic diagnostic and treatment outcome data in diabetic and non-diabetic patients.	Prospective Cohort Study	58 patients with Type I diabetes, 184 patients with Type II diabetes, and 5,002 non-diabetic patients.	Chi square analysis, Anova, and multivaraite regression	- Diabetic patients had increased periodontal disease associated with endodontically treated teeth compared to non-diabetic. - Patients with Type I diabetes had increased symptomatic periradicular disease. -Diabetic patients with preoperative periradicular Lesions had significantly reduced successful outcome.
7	Lopez-Lopez et al.	2011	To compare the prevalence of apical periodontitis and endodontic treatment in type II diabetic patients and non-diabetics.	Cross-sectional	50 patients with well controlled diabetes (Type II) pair-matched with non-diabetic patients	T-test, chi square, and logistic regression	- AP in one or more teeth was found in 74% of diabetic patients and 42% of the control group. - With regards to root canal treated teeth, the prevalence of AP was found in 46% of diabetic patients and 24% in the control. - The periapical status was significantly associated with diabetic status.
8	Falk et al.	1989	to compare the periapical lesions in patients with long and short duration insulin-dependent diabetics with pair-matched non-diabetics.	Cross-sectional	94 with long duration of Type I diabetes and 86 with short duration of Type 1 diabetes duration pair-matched with 102 non-diabetic patients	T test, Anova, Newman-Keul test, chi square	- No Significant difference detected between long term (26.4%) and short term (17.3%) diabetics compared to nondiabetics (21.4%) -In terms of number of endodontically treated teeth with periapical lesions. -Comparing long term diabetics to short term, higher percentage of periapical lesions were found in women with longer duration. However, this difference was detected in men.
9	Laukkanen et al.	2018	To investigate the effect of systemic disease (including diabetes) and tooth-based factors on the outcome of root canal treatment.	Cross-sectional	640 permanent teeth in 504 patients	Chi squared. Fischer exact test, and Hosmer and Lemeshow test	- The success rate of root canal treatment in diabetic patients was 73.2% while 85.6% in non-diabetic patients. - Diabetes decreased the success of endodontic treatment particularly in teeth with apical periodontitis.

No	Authors	Year of Publication	Aim & Objective	Type of study	Sample size	Statistics	Outcomes
10	Sisli S.	2019	To compare the prevalence of apical periodontitis in patients with controlled and uncontrolled type II diabetic to nondiabetics using cone-beam computed tomography.	Cross-sectional	53 cases with well controlled diabetes, 22 with uncontrolled diabetes, and 162 nondiabetic patients.	Chi-squared, Fisher's exact test, and sample t-tests	- Significant differences was found between the diabetic (37.3%) and the control group (28.4%) in terms of apical periodontitis. - However, no significant difference was detected between the controlled and uncontrolled groups.
11	Arya et al.	2017	to compare the reduction in periapical lesions after primary root canal treatment between type II diabetic and nondiabetic patients.	Prospective cohort study	21 diabetic and 25 non diabetic patients.	Kolmogorov -Smirnov test, Mann-Whitney U test and Chi square Test, Wilcoxon test	- A significant reduction was detected in the periapical score in both the diabetic and nondiabetic groups at 12 months after endodontic treatment. - Significantly less periapical healing was detected in the diabetic group (43%) compared with the nondiabetic group (80%) at the 12-month follow-up.

5.2 Part II: Association between Type II Diabetes and Apical Periodontitis before and after Endodontic Treatment in an Adult Population in in an Emirati Adult Population.

5.2.1 Sample Characteristics

The 50 pair-matched cases included in this research includes both genders; 78% females and 22% males. Majority of the pair-matched participants are within the age range of 55 to 65 years old (44%). While the other age groups; 45 to 55 years old account for 26%, above 65 years old accounts for 14%, 35 to 45 years old accounts for 12%, and 25 to 35 years old accounts only for 4%. No participants were within the age group of 18 to 25 years old. With regard to the medical history, 72% of the pair-matched cases were without any known medical conditions except type II diabetes in the diabetic group. Whereas, 22% of the pair-matched cases had hypertension, 4% had asthma, and 2% had congenital heart disease in addition to the type II diabetes in the diabetic group (Table 4).

In terms of the treated teeth involved in this study, 48% of the pair-matched teeth are molars, 30% are premolars, 8% are canines, and 14% are incisors. Most of the pair-matched cases involved in this study are related to primary endodontic treatment (80%), whereas secondary endodontic treatment accounts for 20%. The endodontic treatment for the included cases is mostly done in multiple visits (76%) compared to single visits (24%). The duration in which the follow up radiograph was evaluated ranged from 1 to 4 years where the majority of cases had a follow up period of 2 years (36%). The cases which had a follow up period of 1 year are 30%, 3 years 22% and 4 years 12% (Table 4).

Table 4. Background characteristics of the sample

Characteristics	number of pair-matched cases n (%)
Gender_	
male	11 (22%)
female	39 (78%)
age	
18 to 25 years old	0 (0%)
25 to 35 years old	2 (4%)
35 to 45 years old	6 (12%)
45 to 55 years old	13 (26%)
55 to 65 years old	22 (44%)
Above 65 years	7 (14%)
Medical Conditions	
Hypertension	11 (22%)
Asthma	2 (4%)
Congenital Heart Disease	1 (2%)
No other known medical condition other than diabetes	36 (72%)
Tooth type	
Incisor	7 (14%)
Canine	4 (8%)
Premolar	15 (30%)
Molar	24 (48%)
Endodontic treatment	
Primary	40 (80%)
Secondary	10 (20%)
Duration of treatment	
Single visit	12 (24%)
Multiple visits	38 (76%)
Follow up period	
1 year	15 (30%)
2 years	18 (36%)
3 years	11 (22%)
4 years	6 (12%)

The characteristic of the sample in each pair-matched group; the uncontrolled and controlled, is displayed in Table 5.

Table 5. Background characteristics of the sample in each group

Characteristics	number of pair-matched cases n (%)	
	Group I (Uncontrolled)	Group II (Controlled)
Gender		
male	8	3
female	15	24
age		
18 to 25 years old	0	0
25 to 35 years old	2	0
35 to 45 years old	2	4
45 to 55 years old	6	7
55 to 65 years old	11	11
Above 65 years	2	5
Medical Conditions		
Hypertension	2	9
Asthma	2	0
Congenital Heart Disease	1	0
No other known medical condition other than diabetes	18	18
Tooth type		
Incisor	4	3
Canine	0	4
Premolar	9	6
Molar	10	14
Endodontic treatment		
Primary	17	23
Secondary	6	4
Duration of treatment		
Single visit	4	8
Multiple visits	19	19
Follow up period		
1 year	5	10
2 years	10	8
3 years	3	8
4 years	5	1

4.2.2 PAI scores

The mean PAI score for the uncontrolled diabetic group (n=23) prior to endodontic treatment was 3.3 compared to 2.3 (Table 6) for the matched nondiabetic control group. The Wilcoxon Sign Rank test revealed that this was statistically significant (p=0.002) indicating that uncontrolled Type II diabetes influences the size of the AP lesion. These figures were reduced to a mean PAI score of 1.9 in the uncontrolled diabetic group and 1.5 in the healthy control group (Table 4) in the follow up periapical radiographs. The corresponding mean PAI value prior to endodontic treatment were

2.4 and 2.7 in the controlled diabetic patients and their matched control group respectively. The differences were not statistically significant (p=0.13). For the sample as a whole (n=50), the mean PAI value for both diabetic and non-diabetic groups reduced to 1.7 and 1.6 respectively on the post Endodontic periapical radiographs. The Wilcoxon Sign Rank test revealed a statistically significant improvement in healing in both these groups (p<0.001).

Table 6. Mean pre and post-operative PAI scores for Group I and II (pair-matched study groups)

	Mean Preoperative PAI	Mean Postoperative PAI
Group I		
Uncontrolled Diabetic	3.3	1.9
Non Diabetic	2.3	1.5
Group II		
Controlled Diabetic	2.4	1.5
Non Diabetic	2.7	1.8

Concentrating on the cases with other medical conditions, the mean preoperative PAI score of hypertensive patients was 2.6 while the mean postoperative PAI scores is 2.8 (Table 7). In asthmatic patients the mean preoperative score is 3.25 and mean postoperative score is 1.5. While in congenital heart disease, the scores were 3 and 4 respectively.

Table 7. Mean preoperative and postoperative PAI of patients with other medical diseases.

	Mean Preoperative PAI	Mean Postoperative PAI
Hypertensive	2.6	1.8
Asthma	3.25	1.5
Congenital Heart Disease	3	4

In order to show the relationship between PAI scores and controlled diabetic and non-diabetic patients before and after root canal treatment was exhibited in bar charts (Figures 7a and 7b). Similarly, the relationship between PAI scores and controlled diabetic and non-diabetic patients before and after root canal treatment is shown in bar charts (Figure 8a and 8b). Main features of the bar chart show that the uncontrolled diabetic patients have significantly larger PAI scores than non-diabetic group (Figure 7a). Both controlled and uncontrolled diabetic groups show improvement in PAI scores following root canal treatment as can be seen by the skewed nature of the charts (Figure 8a and 8b).

Figure 7. Range of PAI scores in Group I

Figure 7a. Preoperative

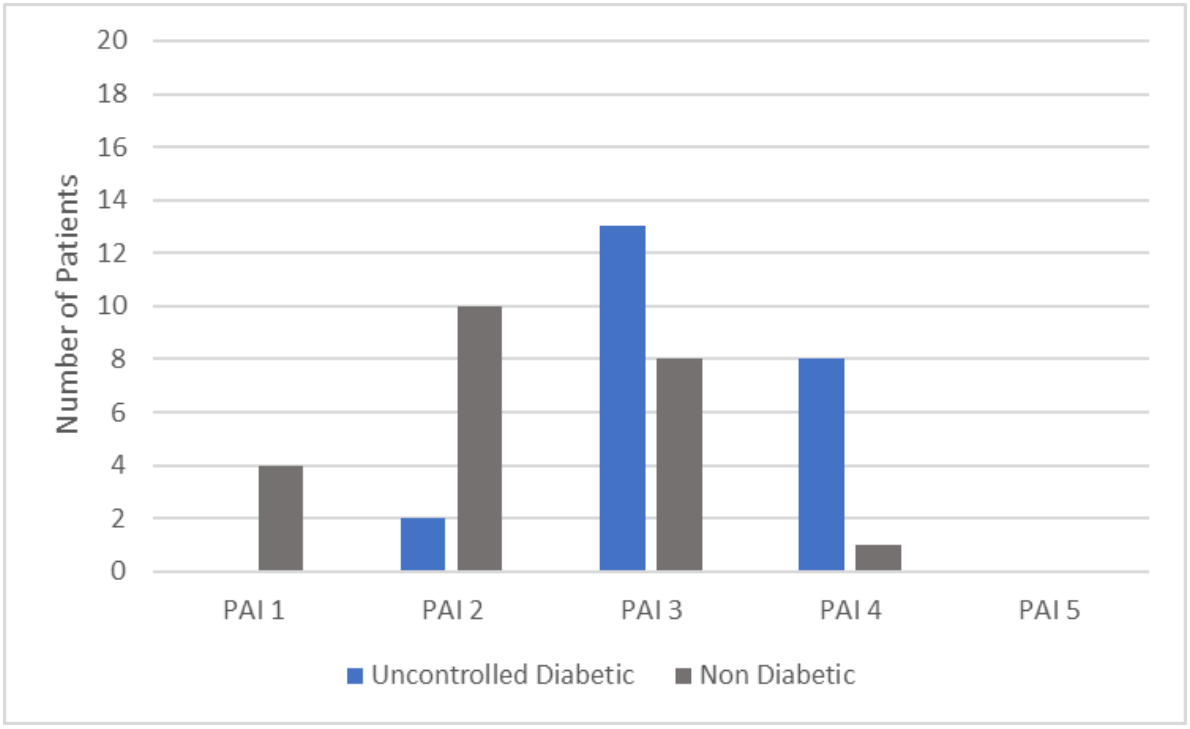


Figure 7b. Postoperative

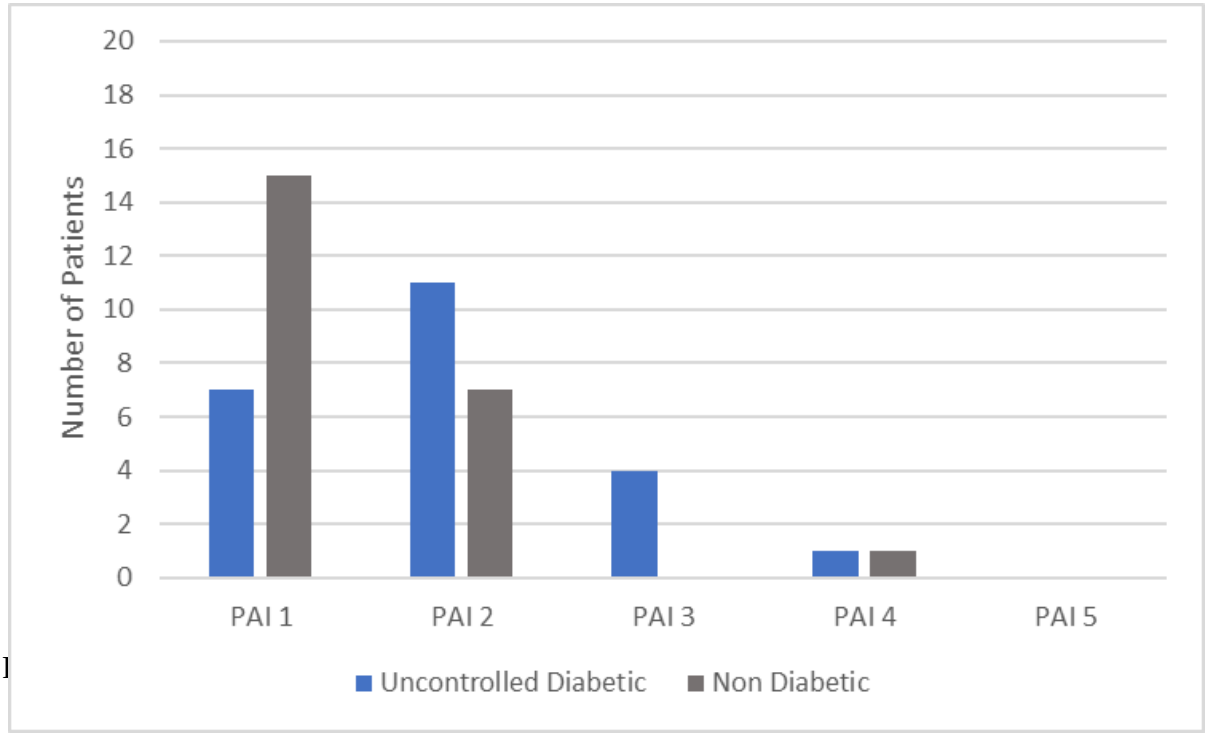


Figure 8. Range of PAI scores in Group II

Figure 8a. Preoperative

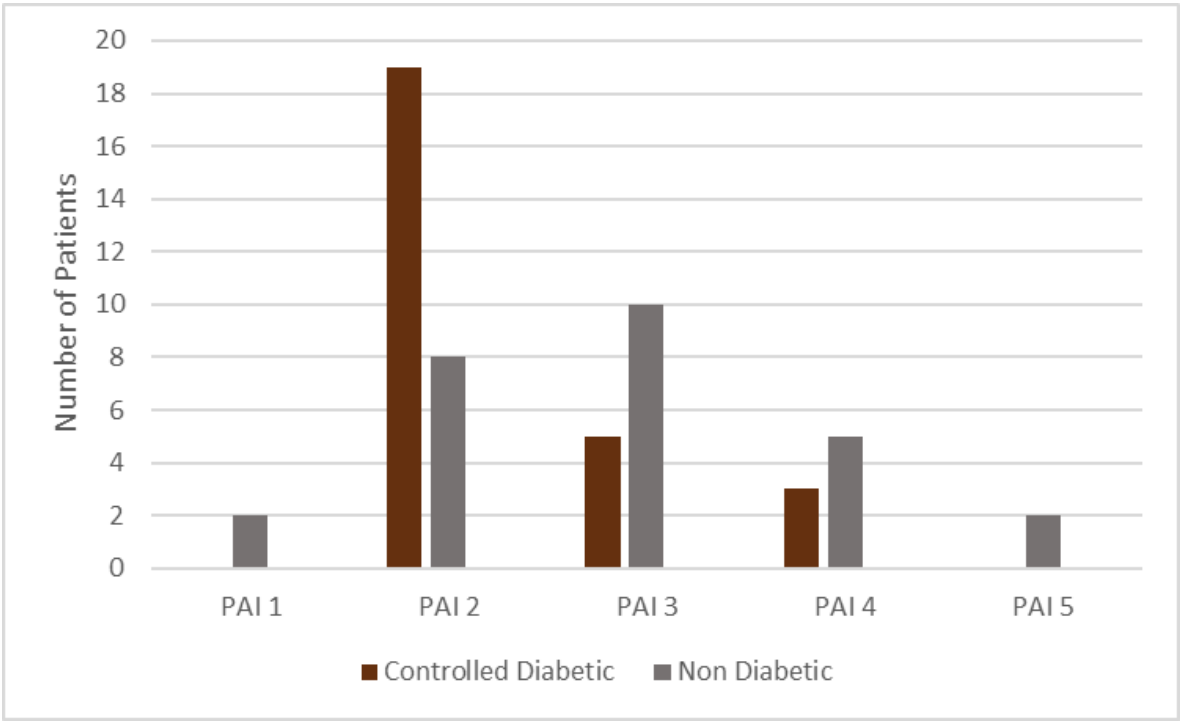
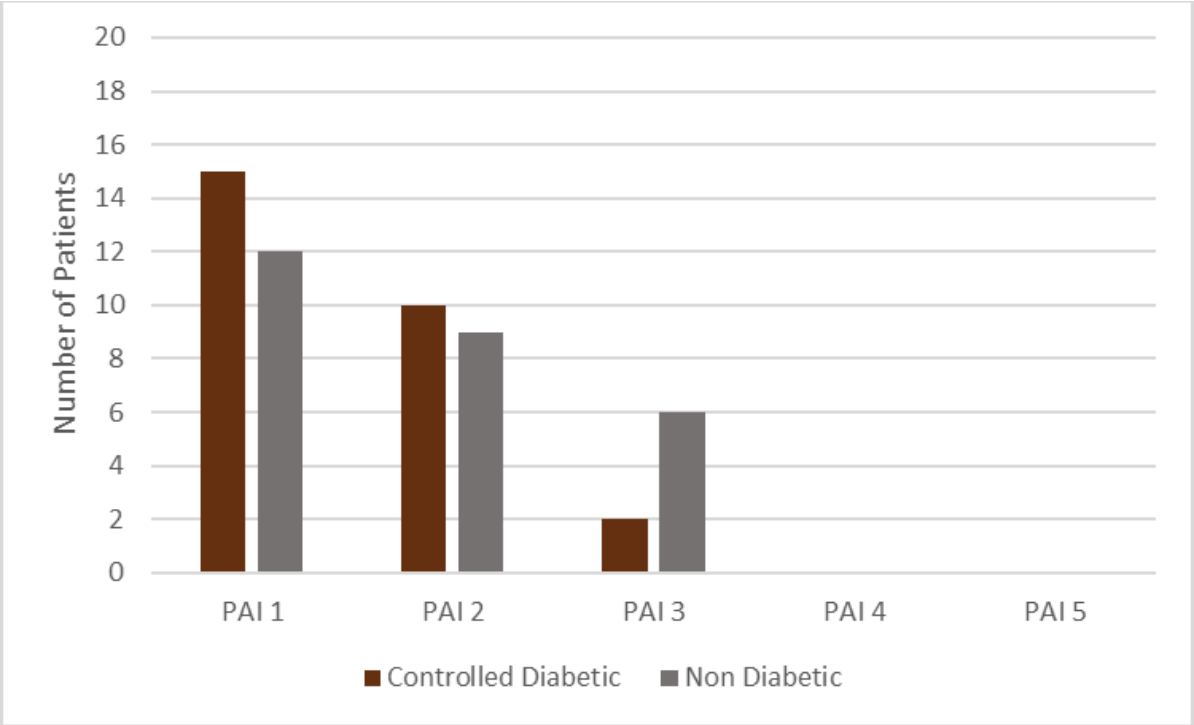


Figure 8b. Postoperative



The above data has also been displayed as two scatter plots (Figure 9 and 10). A main feature of figure 7 is a clustering of points for preoperative PAI of 3 with showing a dramatic improvement with post-operative PAI scores of 1 and 3. A similar pattern, but not dramatic, can also be seen in the scatter plot of Group II (Figure 10).

Figure 9. Scattered Plot of PAI score of Group I

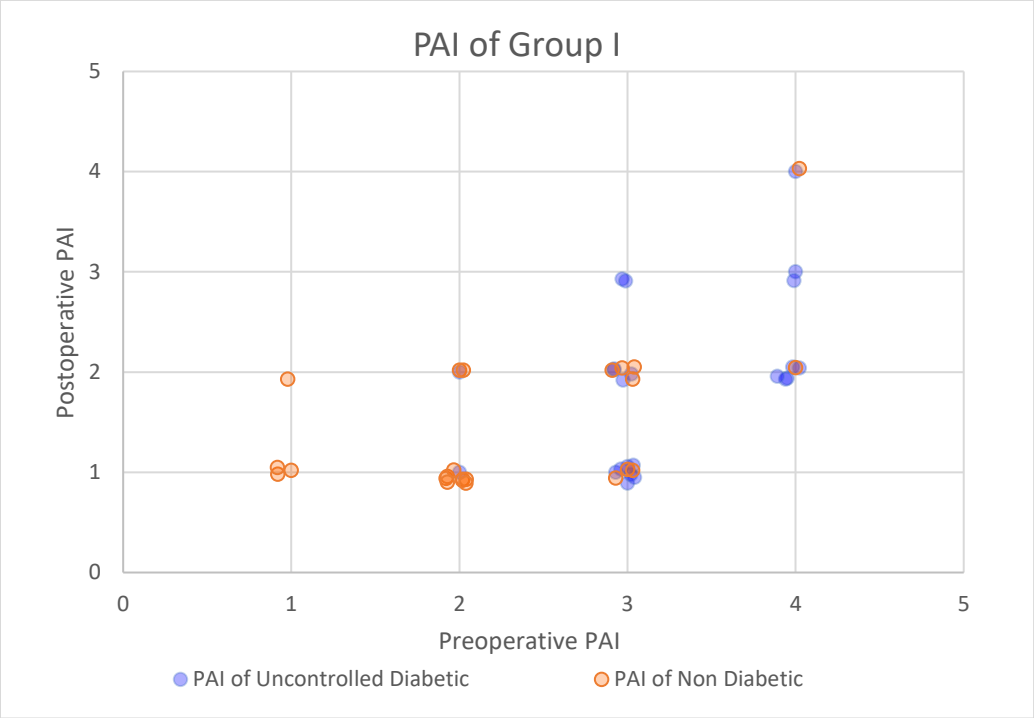
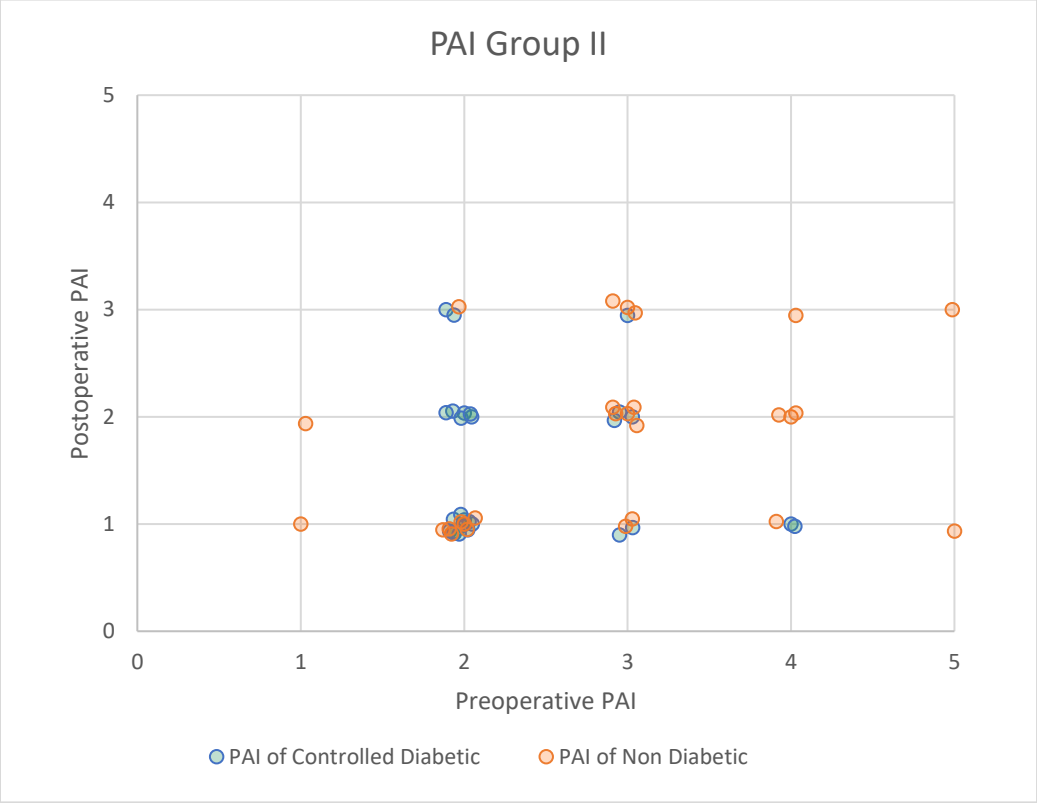


Figure 10. Scattered Plot of PAI score of Group II



5.2.3 Intra-observer and Inter-observer Reproducibility

The Cohen Kappa test revealed an intra-observer reproducibility of 0.923. Whereas the inter-observer Cohen Kappa score is 0.796. A lower inter-observer kappa score is to be expected.

6. DISCUSSION

6.1 Part I: A Critical Review of the literature

Periapical radiographs were used to assess the status of apical periodontitis in most of the studies (Segura-Egea et al. 2005, Marrota et al. 2012, Ferreira et al. 2014, Britto et al. 2003, Fouad and Burlesson 2003, Falk et al. 1989, Laukkanen et al. 2018, Arya et al. 2017). However, Lopez-Lopez et al. (2011) and Smadi (2017) used panoramic radiograph to evaluate the apical status. Apical periodontitis was assessed using the PAI index in 6 studies (Segura-Egea et al. 2005, Smadi 2017, Ferreira et al. 2014, Lopez-Lopez et al. 2011, Laukkanen et al. 2018, Arya et al. 2017), Strendberg's crietria in 2 studies (Marrota et al. 2012, Britto et al. 2003), size of the lesions measured in millimeters in 1 study (Fouad and Burlesson 2003), and detection of presence of specific signs in another study (Falk et al. 1989). Furthermore, in a recent study conducted by Sisli (2019), Cone Beam Computed Tomography was the radiographic diagnostic tool used. Thus, the CBCT periapical index was used as method of evaluation of apical periodontitis in this study.

With regards to the method of comparison between the diabetic and non-diabetic groups; one study used a pair-matched approach (Marrota et al. 2012). The groups were pair-matched according to age and gender. In two other studies, Smadi (2017) and Lopez-Lopez et al. (2011), the matched-group approach was used in which in Lopez-Lopez et al. (2011) the groups were matched according to age and gender while in Smadi (2017) the matching extended into income, BMI, presence of hypertension, education and last dental visit. Whereas the comparison in the other studies was not confined to a match (Segura-Egea et al. 2005, Ferreira et al. 2014, Britto et al. 2003, Fouad and Burlesson 2003, Falk et al. 1989, Laukkanen et al. 2018, Sisli 2019, Arya et al. 2017). However, age range and gender distribution were considered in some of these studies

(Segura-Egea et al. 2005, Britto et al. 2003, Falk et al. 1989, Arya et al. 2017). The sample size in all included studies ranged from as low as 21 and as high as 5,002 cases in a group.

They type of diabetes investigated varied among the included studies. Type II diabetes was the interest of 5 studies (Segura-Egea et al. 2005, Marrota et al. 2012, Lopez-Lopez et al. 2011, Sisli 2019, Arya et al. 2017), while Type I was the interest of 1 study (Falk et al. 1989). The remaining 5 studies included patients of both types; Type I and II, in their sample (Smadi 2017, Ferreira et al. 2014, Britto et al. 2003, Fouad and Burlesson 2003, Laukkanen et al. 2018). With regards to the status of diabetes, only 4 studies specified whether the patient has controlled or uncontrolled diabetes (Segura-Egea et al. 2005, Smadi 2017, Lopez-Lopez et al. 2011, Sisli 2019) while the status was not specified in the other studies (Marrota et al. 2012, Ferreira et al. 2014, Britto et al. 2003, Fouad and Burlesson 2003, Falk et al. 1989, Laukkanen et al. 2018, Arya et al. 2017). Moreover, a study by Falk et al. (1989) classified the status of diabetic patients into short and long duration.

The outcome of 9 studies revealed a higher percentage of apical periodontitis in diabetic patients. To elaborate, a study by Segura-Egea et al. (2005) found that 83% of type II diabetic patients had root canal treated teeth with apical periodontitis compared to 60% in non-diabetic patients. This study also found that 6% of untreated teeth in type II diabetic patients had apical periodontitis compared to 3% in non-diabetic patients. Similarly, Lopez-Lopez et al. (2011) concluded that periapical status was significantly associated with the presence of diabetes and that apical periodontitis was detected in 74% of diabetic patients compared to 42% of non-diabetic patients. In terms of root canal treated teeth, apical periodontitis was found in 46% of diabetic patients compared to 24% of non-diabetic patients however, this difference was not considered significant.

In addition, a study by Britto et al. (2003) stated that more residual lesions after endodontic treatment was associated with patients with type II diabetes.

Moreover, Sisli (2019) found a significant difference in the percentage of apical periodontitis in type II diabetic patients (37.3%) compared to non-diabetic patients (28.4%) while no significance difference was found between controlled and uncontrolled diabetes. In addition, in a study by Marrota et al. (2012), the overall prevalence of apical periodontitis in diabetic patients was considered significantly higher than non-diabetic patients. It was reported that 10% of diabetic patients had apical periodontitis in non-treated teeth while 7% in non-diabetic patients. Whereas, 46% of diabetic patients had apical periodontist in endodontically treated teeth compared to 38% in non-diabetic patients. However, the difference in endodontically treated teeth was not considered significant.

Furthermore, Smadi (2017) found that diabetic patients had a higher percentage of apical periodontitis (13.5%) than non-diabetic patients (11.9%). Nevertheless, this difference is not statistically significant. Moreover, the apical periodontitis to endodontic treatment ratio was significantly higher in the diabetic group (27.7%) than in the nondiabetic group (19.3%). The same study found that patients with uncontrolled diabetes had significantly higher apical periodontitis (18.29%) than patients with controlled diabetes (9.21%). There was also a higher apical periodontitis to endodontic treatment ratio (32% in uncontrolled diabetes and 21.8% in controlled diabetes).

According to Fouad and Burlesson (2003), diabetic patients had significantly more periodontal disease associated with endodontically treated teeth than non-diabetic patients. Preoperative apical periodontitis and peri radicular lesions in diabetic patients had also significantly reduced successful outcomes. The study also concluded that Type I diabetic patients had increased

symptomatic peri radicular lesions. Additionally, Laukkanen et al. (2018) found a lower success rate of endodontic treatment in patients with diabetes (73.2%) compared to non-diabetic patients (85.6%). The lower success rates were more clear in diabetic patients with preoperative apical periodontist. Similarly, Arya et al. (2017) found that periapical healing was significantly less in diabetic patients than in non-diabetic patients when compared at 12 months post endodontic treatment. Despite the lower healing, both groups had significantly lower PAI score in the same period. Lower success rates were also observed in a study by Ferreira et al. (2014), as diabetic patients had a success rate of 62% compared to 80% non-diabetic patients. However, the results related to apical periodontitis found in Ferreira et al. (2014) was considered inconclusive.

In contrast, according to Falk et al. (1989), no significant difference was detected in terms of periapical lesions in endodontically treated teeth between long term diabetic patients (26.4%) and short term diabetic patients (17.3%) compared to non-diabetic patients (21.4%). A difference between long term and short-term diabetes was only observed in women as women with longer duration of diabetes had a higher percentage of periapical lesions.

6.2 Part II: Association between Type II Diabetes and Apical Periodontitis before and after Endodontic Treatment in an Adult Population in in an Emirati Adult Population.

This study used a pair-matched approach to ensure that the matched cases, although different in terms of the presence of type II diabetes, yet similar in other aspects. This helped in reducing the confounding factors that may have affected the obtained results. The aspects in which the pairs were matched i.e. age, gender, medical condition, were similar to the literature (Marrota et al. 2012; Lopez-Lopez et al. 2011; and Smadi 2017) and extended to have additional aspects; duration of root canal treatment, and duration of follow-up, which were found to be relevant.

The sample used in this study (50 pair-matched cases) is within the range of the samples used in other related studies (Marrota et al. 2012; Lopez-Lopez et al. 2011, Segura-Egea et al. 2005, Arya et al. 2017, Britto et al. 2003, Ferreira et al. 2014). The sample contained more females (78%) than males (22%) participants. However, several epidemiological studies found no significant difference in terms of apical periodontitis between the two genders (Ørstavik et al. 1986, Jime´nez-Pinzo´n et al. 2004). In terms of age, most of the participants were above 45 years of age (84%), this distribution is to be expected due to the higher prevalence of diabetes in older ages (Centers of Disease Control and Prevention 2020).

Although majority of the cases (72%) had no other known systemic disease other than Type II diabetes, some cases in this study had hypertension (22%), asthma (4%), and congenital heart disease (2%). With regards to hypertensive cases, a mean PAI scores less than 3 was found preoperatively (2.6) and postoperatively (1.8). This indicates a low PAI score in hypertensive patients, which aligns with the findings in the literature that states no significance difference in prevalence of apical periodontitis between hypertensive and non-hypertensive patients (Segura-Egea et al. 2010). In contrary, patients with asthma and congenital heart disease had higher PAI score, however the number of cases within these groups were small therefore, the findings are inconclusive.

In this study, molars, which are associated with lower success rates (Ng et al. 2010) constituted 48% of the tooth type. Moreover, endodontic treatment was provided by Endodontist specialists to assure a high level of treatment provided. Most of the treatments of the included cases were carried on in multiple visits (76%). The follow up period was mainly within 1 (30%) and 2 (36%) years, with a minority of cases being reviewed within 3 (22%) or 4 (12%) years.

Moreover, the use of periapical radiograph and PAI score to assess apical periodontitis, as used in this study, were widely used in the literature (Ørstavik et al. 1986, Segura-Egea et al. 2005, Ferreira et al. 2014, Laukkanen et al. 2018, Arya et al. 2017). PAI score of 3 or more have been considered as a presence of apical periodontitis in many studies (Ørstavik et al. 1986, Segura-Egea et al. 2005, Smadi 2017, Laukkanen et al. 2018, Arya et al. 2017). The mean PAI score of 3.3 in uncontrolled diabetic cases preoperatively indicates the presence of apical periodontitis in majority of cases. However, the mean PAI score of 1.9 postoperatively indicates a reduction in the apical lesions. While in the matched non-diabetic group, both preoperative and postoperative PAI scores were less than 3; the scores were 2.3 and 1.5 respectively. In the other pair-matched group, both uncontrolled diabetic cases and non-diabetic cases had a mean PAI score less than 3, 2.4 and 2.7 respectively. The postoperative mean PAI scores of uncontrolled diabetic cases was 1.5 while in the non-diabetic matched cases the mean PAI score was 1.8. The reduction in PAI score postoperatively were observed in all the groups.

The findings of the study suggest a higher preoperative PAI score in the uncontrolled diabetes patients than in the non-diabetic pair-matched patients. While postoperatively, the findings suggest a similar concentration of PAI score between the two pair-matched groups. In details, in Group I; the number of uncontrolled diabetic patients with preoperative PAI score of 1 is 0, PAI score of 2 is 2, PAI score of 3 is 13, PAI score of 4 is 8, and PAI score of 5 is 0. Whereas the number of pair-matched non-diabetic patients with preoperative PAI score of 1 is 4, PAI score of 2 is 10, PAI score of 3 is 8, PAI score of 4 is 1, and PAI score of 5 is 0. Postoperatively, the number of uncontrolled diabetic patients with a PAI score of 1 is 7, PAI score of 2 is 11, PAI score of 3 is 4, PAI score of 4 is 1, and PAI score of 5 is 0. Whereas the number of pair-matched non-diabetic patients with postoperative PAI score of 1 is 15, PAI score of 2 is 7, PAI score of 3 is 4, PAI score

of 4 is 1, and PAI score of 5 is 0.

Whereas in the second group, the findings suggest a similar distribution between the two pair-matched groups, controlled diabetic and non-diabetic, preoperatively and postoperatively (Figure 6).In regard to Group II; the number of controlled diabetic patients with a preoperative PAI score of 1 is 0, PAI score of 2 is 19, PAI score of 3 is 5, PAI score of 4 is 3, PAI score of 5 is 0. While in non-diabetic group, the preoperative PAI score of 1 is 2, PAI score of 2 is 8, PAI score of 3 is 10, PAI score of 4 is 5, PAI score of 5 is 2. Postoperatively, the controlled diabetic patients had a postoperative PAI score of 1 is 15, PAI score of 2 is 10, PAI score of 3 is 2, PAI score of 3 is 0, and PAI score of 5 is 0. While in non-diabetic group, the postoperative PAI score of 1 is 12, PAI score of 2 is 9, PAI score of 3 is 6, PAI score of 4 is 0, and PAI score of 5 is 0.

Comparing the distribution of preoperative and postoperative PAI scores in a scattered plot revealed a shift toward a lower PAI score concentration postoperatively in both groups (Figure 7 and 8). In Group I, the concentration of uncontrolled diabetic preoperative PAI score is between 3 and 4, while postoperatively the PAI score is concentrated between 1 and 3. Whereas the concentration of non-diabetic preoperative PAI score is concentrated between 1 and 3, while postoperatively between 1 and 2. In Group II, the concentration of controlled diabetic preoperative PAI scores and non-diabetic preoperative PAI scores are similar, between 2 and 4. Postoperatively, the concentration of PAI score controlled diabetic and non-diabetic are between 1 and 3.

From the studies included in the critical review, Marrota et al. (2012) had a similar pair-matched approach to our study. However, some differences exist between the two studies. Marrota et al. (2012) had limited the cross-matching to age and gender only whereas the crossmatching in our study included additionally the tooth number, medical conditions, duration in which the root canal treatment was completed and the time of the follow-up radiograph to ensure a similar healing

period was provided for each pair-matched case. These additional matching aspects aimed to reduce the confounding factors that may affect the results. Other differences between the two studies include using Strindberg's criteria to evaluate the apical periodontitis radiographically, and not specifying the diabetes status whether controlled or uncontrolled. Moreover, the study by Marrota et al. (2012) included 30 pair-matched cases consisting of 30 type II diabetic patients and 60 non-diabetic patients; two non-diabetic patients for each diabetic case. While our study included a higher number of pair-matched cases (50 cases), but with a one control case for each diabetic case.

Nevertheless, the findings of Marrota et al. (2012) study which was based on a Brazilian population, aligns with the findings of our study. Marrota et al. (2012) concluded that the overall prevalence of apical periodontitis in diabetic patients was considered significantly higher than non-diabetic patients. However, the difference in endodontically treated teeth was not considered significant. Regardless of the diabetes control status, these findings support the higher PAI scores found preoperatively in the uncontrolled diabetic group and the non-significant difference in PAI scores found postoperatively in the two groups.

Other similar studies; Lopez-Lopez et al. (2011) and Smadi (2017), have used an approach in which the diabetic and non-diabetic groups were matched as a group; instead of a pair-matching on an individual basis. The matching in Lopez-Lopez et al. (2011) was constricted with regards to age and gender only, while in Smadi (2017) the matching extended to include income, BMI, presence of hypertension, education, and time since last dental visit. Whereas in our study, income, BMI, and education were not considered as this information could not be obtained from patient dental records considering the design of the study.

Relating the findings of these two studies to our study, Smadi (2017) states no significant

difference in terms of apical periodontitis when a group that contains both controlled and uncontrolled diabetic patients was compared with non-diabetic patients prior to endodontic treatment. In this diabetic group, the number of controlled diabetic patients (n=82) was higher than the uncontrolled (n=63). However, when comparing the diabetic groups, uncontrolled diabetes had significantly higher apical periodontitis prior to endodontic treatment than well-controlled diabetes. These findings support that result of this study and states that uncontrolled diabetic patients had significantly higher PAI values than non-diabetic patients, while no significance difference was found between controlled diabetic patients and non-diabetic patients. Similarly, this result is also supported with the finding suggested in Lopez-Lopez et al. (2011); that the prevalence of apical periodontitis was detected to be significantly higher in type II diabetic patients (74%) than in non-diabetic patients (42%) although the status of the diabetic disease is not specified. The same study also found that in terms of root canal treated teeth, the prevalence of apical periodontitis in the two groups were not statistically significant. This finding would further support the result of our study that no significant difference was found between the diabetic group; uncontrolled and controlled, and non-diabetic group.

Nevertheless, Smadi 2017 found significantly higher prevalence of apical periodontitis after endodontic treatment between non-diabetic patients and diabetic patients, as well between uncontrolled diabetic and well-controlled. This finding opposes the results found in this study; however, this difference may exist because of the use of panoramic radiograph to assess the PAI scores. Moreover, this study contained Type I and Type II diabetic patients while our study included Type II diabetic patients only which might have contributed to the difference.

Furthermore, additional articles related to Type II diabetes could be linked to findings of the study despite the different approach. In terms of apical periodontitis following endodontic treatment,

Arya et al. (2017) found that periapical healing was significantly less in diabetic patients that in non-diabetic patients when compared at 12 months post endodontic treatment. Despite the lower periapical healing in this prospective study, 90% of diabetic cases showed improved periapical status in the same period, with no cases with deteriorated apical condition. The time at which the apical condition was reviewed (12 months) differs from the follow up time allocated for the current study (1 to 4 years). However, the improvement in apical condition detected within the diabetic group in a 12-month period would indicate a better apical healing if reviewed for a longer period of time. Furthermore, this study included only molars with existing apical periodontitis, considering the lower success rates associated with non-molar tooth (Ng et al. 2010) and those with exiting apical lesions (Ng et al. 2011).

Contrary to the results of the present study, Segura-Egea et al. (2005) found well-controlled diabetic patients to have significantly more apical periodontitis (83%) after endodontic treatment than non-diabetic patients (60%). In this study, teeth with inadequate endodontic treatment were also included in the study which may have contributed to the increased apical periodontist. Moreover, absence of a cross-matching approach in this study may have led to the presence of confounding factors. For instance, the time between endodontic treatment and the radiograph was not considered in this study which means that the healing period provided for the cases may not be similar.

Similarly, Sisli (2019) found a significant difference in the percentage of apical periodontitis in type II diabetic patients (37.3%) after endodontic treatment compared to non-diabetic patients (28.4%). Both controlled and uncontrolled diabetic patient where included in this group and the evaluation was based upon CBCT examination. Although the prevalence of apical periodontitis was higher in the presence of diabetic, this does not mean that healing did not occur. Absence of

the evaluation of preoperative lesions of these cases makes it difficult to conclude whether the healing was delayed in the diabetic group or the preoperative lesions were actually larger in the diabetic group.

Additionally, Laukkanen et al. (2018) found a lower success rate of endodontic treatment in patients with diabetes (73.2%) compared to non-diabetic patients (85.6%). In this study, teeth with suboptimal root canal filling was also included in the study which accounted for 32.8% of the whole sample. The study also found that the lower success rates were more associated with tooth that had preoperative apical periodontitis in diabetic patients. Comparing these results to the current study where all the included cases had optimal root canal filling, this may infer that having an adequate root canal treatment for diabetic patients is essential for optimal healing. Moreover, the root canal treatment in the study by Laukkanen et al. (2018) was performed by undergraduate students in a university setting, while the treatment was performed by endodontic specialist in the current study. Similarly, the treatment in Segura-Egea et al. (2005) and Sisli (2019) was also performed in university settings. This may infer the need of performing root canal treatments for diabetes patients by Endodontist specialists considering their higher skills.

In terms of HBA1C test used to differentiate between controlled and uncontrolled diabetic patients. The studies mentioned used HBA1c of 6.5 to 7 as a cutoff to differentiate between the two groups as per the old guidelines. However, the current study followed the recent guidelines of the American College of Physicians in which the controlled border was raised from 7 to 8, as no significant differences was found in terms of complications between the two scores (Qaseem et al., 2018). This might explain some differences that may exist between the mentioned studies and the current study in terms of the findings related to uncontrolled diabetic patients preoperatively.

The reduced successful outcomes of endodontic treatment in diabetic patients have been reported in earlier papers (Fouad and Burlesson 2003; Britto et al. 2003). For instance, Fouad and Burlesson (2003) stated that diabetic patients had significantly more periodontal disease associated with endodontic treated teeth than non-diabetic patients. This was also mentioned by Britto et al. (2003) in which type II diabetes is associated with more residual lesions after endodontic treatment. However, the findings of the current study along with the recent studies that followed a matching approach suggest that better results could be achieved in diabetic patients following endodontic treatment with the advanced technology. Moreover, it can be concluded that studies that followed a cross-matched approach in which the confounding factors are controlled as much as possible found less discrepancies in terms of the difference in apical periodontitis between diabetic and non-diabetic patients.

7. CONCLUSION

7.1 Part I: A Critical Review of the literature

To conclude, most of the studies measured the difference in terms of apical periodontitis between diabetic and non-diabetic patients through comparing the prevalence of apical periodontitis in each group. Although all these studies concentrated on diabetes, the type of diabetes included and the status of control of the disease varied among the different studies. To elaborate, some studies included Type I diabetes, some included Type II diabetes, and some included both types. In addition, some studies clarified the status of diabetes whether controlled or not controlled, while it was not mentioned in other studies. Despite this heterogenicity, 4 studies out of 11 found a significant higher prevalence of apical periodontitis in diabatic patients compared to non-diabatic patients. Moreover, 7 studies out of 11 found significantly higher prevalence of apical periodontitis associated with endodontically treated teeth in diabatic than non-diabatic cases.

7.2 Part II: Association between Type II Diabetes and Apical Periodontitis before and after Endodontic Treatment in an Emirati Adult Population.

PAI scores, prior to Endodontic treatment, were significantly higher in the uncontrolled diabetic group compared to the controlled diabetic group. In all cases the Endodontic treatment significantly reduced the size of the AP lesions.

8. REFERENCES

1. Alba-Loureiro TC, Munhoz CD, Martins JO, Cerchiaro GA, Scavone C, Curi R, et al. Neutrophil function and metabolism in individuals with diabetes mellitus. Braz J Med Biol Res 2007; 40:1037-44
2. Alberti K. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO Consultation. Diabetic Medicine 1998, 539-553.
3. Al-Maskari AY, Al-Maskari MY, Al-Sudairy S. Oral Manifestations and Complications of Diabetes Mellitus: A review. Sultan Qaboos Univ Med J. 2011;11(2):179-186.
4. Arya S. Healing of Apical Periodontitis after Nonsurgical Treatment in Patients with Type II Diabetes. Journal of Endodontics 2017, Volume 43, Issue 10, 1623 – 1627. https://doi.org/10.1016/j.joen.2017.05.013
5. Bender IB, Seltzer S, Freedland J. The relationship of systemic diseases to endodontic failures and treatment procedures. Oral Surg Oral Med Oral Pathol 1963; 16:1102-15.
6. Britto LR, Katz J, Guelmann M, Heft M. Periradicular radiographic assessment in diabetic and control individuals. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003; 96:449-52.
7. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001; 414:813-20.
8. Brynolf I. A histological and roentgenological study of the periapical region of human upper incisors. Odontol Revy 1967; 18: Suppl. 11.
9. Casqueiro, J., Casqueiro, J., Alves, C. Infections in patients with diabetes mellitus: A review of pathogenesis. Indian Journal of Endocrinology and Metabolism, 2012;16(Suppl1), S27–S36.

10. Centers of Disease Control and Prevention. National Diabetes Statistics Report 2020. Centers of Disease Control and Prevention Website. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf Accessed April 2018
11. Chakravarthy P. Diabetes Mellitus: An Endodontic Perspective. Eur J Gen Dent 2013;2:241-5
12. Cheraskin E, Ringsdorf WM. The biology of the endodontic patient: 3. Variability in periapical healing and blood glucose. J Oral Med 1968; 23:87-90.
13. Cruz JW, Oliveira MA, Hohman TC, Fortes ZB. Influence of tolrestat on the defective leukocyte-endothelial interaction in experimental diabetes. Eur J Pharmacol 2000; 391:163-74.
14. Delmaire M, Maugendra D, Moreno M, Le Goff MC, Allanic H, Genetet B. Impaired leukocyte functions in diabetic patients. Diabet Med 1997;14:29-34.
15. De Oliveira MJ, Meyer-Pflug AR, Alba-Loureiro TC, Melbostad H, Costa da Cruz JW, Coimbra R, et al. Modulation of lipopolysaccharide-induced acute lung inflammation: Role of insulin. Shock 2006; 25:260-6.
16. Diagnosis and Classification of Diabetes Mellitus. American Diabetes Association Diabetes Care Jan 2010, 33 (Supplement 1) S62-S69; DOI: 10.2337/dc10-S062
17. Dubai Health Authority. 2nd Phase of Dubai Diabetes Survey Results Revealed. Dubai Health Authority Website https://www.dha.gov.ae/en/DHANews/pages/dhanews1111704558-14-11-2017.aspx Published 2017. Accessed March 2019
18. Echeverri AF, Tobón GJ. Autoimmune diabetes mellitus (Type 1A) In: Anaya JM, Shoenfeld Y, Rojas-Villarraga A, et al., editors. Autoimmunity: From Bench to Bedside [Internet].

Bogota (Colombia): El Rosario University Press; 2013 Jul 18. Chapter 29. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459476

19. Falk H, Hugoson A, Thorstensson H. Number of teeth, prevalence of caries and periapical lesions in insulin-dependent diabetics. Scand J Dent Res 1989; 97:198-206.

20. Fernandes M, Ataide ID. Nonsurgical management of periapical lesions. J Conserv Dent 2010; 13:240-5

21. Ferreira MM; Carrilho E; Carrilho F. Diabetes Mellitus and its Influence on the Success of Endodontic Treatment: A Retrospective Clinical Study. Acta Médica Portuguesa, [S.l.], v. 27, n. 1, p. 15-22, jan. 2014. ISSN 1646-0758

22. Filho EM, Calisto AM, Tavarez RR, Rizzi C, Segato RA, Bezerra da Silva LA. Correlation between the Periapical Index and Lesion Volume in Cone-beam Computed Tomography Images. Iranian endodontic journal 2018, 13(2), 155–158. doi:10.22037/iej.v13i2.15040

23. Fouad AF, Barry J, Caimano M, Clawson M, Zhu Q, Carver R, et al. PCR-based identification of bacteria associated with endodontic infections. J Clin Microbiol 2002; 40:3223-31.

24. Fouad AF. Diabetes mellitus as a modulating factor of endodontic infections. J Dent Educ 2003; 67, 459–67.

25. Fouad AF, Burlesson J. The effect of diabetes mellitus on endodontic treatment outcome: Data from an electronic patient record J Am Dent Assoc 2003; 134:43-51.

26. Fouad AF, Kum KY, Clawson ML, Barry J, Abenojo C, Zhu Q, et al. Molecular characterization of the presence of Eubacterium spp and Streptococcus spp in endodontic infections. Oral Microbiol Immunol 2003; 18:249-55

27. Fowler M. Microvascular and Macrovascular Complications of Diabetes. Clinical Diabetes Journal 2008 Apr; 26(2): 77-82

28. International Diabetes Federation. IDF Diabetes Atlas, 8th edition. Brussels, Belgium: International Diabetes Federation, 2017. http://www.diabetesatlas.org

29. Jime´nez-Pinzo´n A, Segura-Egea JJ, Poyato-Ferrera M, Velasco-Ortega E, Rı´os-Santos JV (2004) Prevalence of apical periodontitis and frequency of root filled teeth in an adult Spanish population. International Endodontic Journal 2004. 37,167–73.

30. Laukkanen, E, Vehkalahti, MM, Kotiranta, AK. Impact of systemic diseases and tooth-based factors on outcome of root canal treatment. International Endodontic Journal 2019, 52, 1417–1426. https://doi.org/10.1111/iej.13143

31. Leite MF, De Lima A, Massuyama MM, Otton R. In vivo astaxanthin treatment partially prevents antioxidant alterations in dental pulp from alloxan-induced diabetic rats. Int Endod J 2010; 43:959-67.

32. Lima S, Grisi D, Kogawa E, Franco O, Peixoto V, Gonçalves-Júnior J, Arruda M, Rezende T. Diabetes mellitus and inflammatory pulpal and periapical disease: a review. Int Endod J. 2013 Aug;46(8):700-9.

33. Lopez-Lopez J, Jane-Salas E, Estrugo-Devasa A, Velaso-Ortego E, Martin-Gonzalez J, Segura-Egea JJ. Periapical and endodontic status of Type II diabetic patients in Catalonia, Spain: A cross sectional study. J Endod 2011;37:598-601

34. Marotta PS, Fontes TV, Armada L, Lima KC, Rocas IN, Siquerira JF Jr. Type II diabetes mellitus and the prevalence of apical periodontitis and endodontic treatment in an adult Brazilian population. J Endod 2012;38:297-300.

35. Metzger Z, Abramovitz I, Bergenholtz G. TextBook of Edontology. Second Edition. Chapter 7 Apical Periodontitis. 2010: 113-127

36. Muller L.M, Gorter K.J, Hak E., Goudzwaard W.L, Schellevis F.G, Hoepelman A.I, & Rutten G.E, Increased Risk of Common Infections in Patients with Type 1 and Type II Diabetes Mellitus, Clinical Infectious Diseases, Volume 41, Issue 3, 1 August 2005, Pages 281–288, https://doi.org/10.1086/431587

37. Nair PN. New perspectives on radicular cysts: do they heal? International Endodontic Journal 2002, 31(3), 155–160. doi:10.1046/j.1365-2591.1998.00146.x

38. Ng YL, Mann V, Gulabivala K. A prospective study of the factors affecting outcomes of non-surgical root canal treatment: part 2: tooth survival. International Endodontic Journal 2011, 44(7), 610–625. doi:10.1111/j.1365-2591.2011.01873.x

39. Ng YL, Mann V, Gulabivala K. Tooth survival following non-surgical root canal treatment: a systematic review of the literature. International Endodontic Journal 2010, 43(3), 171–189. doi:10.1111/j.1365-2591.2009.01671.x

40. Orstavik D, Kerekes K, Eriksen HM. The periapical index: a scoring system for radiographic assessment of apical periodontitis. Endod Dent Traumatol. 1986 Feb;2(1):20-34.

41. Patterson JE, Andriole VT. Bacterial urinary tract infections in diabetes. Infect Dis Clin North Am 1997; 11:735–50

42. Qaseem A, Wilt TJ, Kansagara D, et al, for the Clinical Guidelines Committee of the American College of Physicians. Hemoglobin A_{1c} Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type II Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians. Ann Intern Med. 2018. 168:569–576. doi: 10.7326/M17-0939

43. Rayfield, E. J., Ault, M. J., Keusch, G. T., Brothers, M. J., Nechemias, C., & Smith, H. Infection and diabetes: The case for glucose control. The American Journal of Medicine 1982, 72(3), 439–450. doi:10.1016/0002-9343(82)90511-3

44. Ryan, M., Carnu, O., and Kamer, A. The influence of diabetes on the periodontal tissues. J Am Dent Assoc. 2003 Oct; 134 :34S-40S

45. Segura-Egea JJ, Castellanos-Cosano L, Machuca G, et al. Diabetes mellitus, periapical inflammation and endodontic treatment outcome. Med Oral Patol Oral Cir Bucal. 2012;17(2): e356-e361. doi:10.4317/medoral.17452

46. Segura-Egea JJ, Jimenez-Moreno E, Calvo-Monroy C, Ríos-Santos J V, Velasco-Ortega E, Sánchez-Domínguez, B, Llamas-Carreras JM. Hypertension and Dental Periapical Condition. Journal of Endodontics 2010, 36(11), 1800–1804. doi:10.1016/j.joen.2010.08.004

47. Segura-Egea JJ, Jimez-Pinzon A, Rios-Santos JV, Velasco OE, Cisneros-Cabello R, Poyato FM. High prevalence of apical periodontitis amongst Type II diabetics. Int Endod J 2005;38:564-9.

48. Segura-Egea J., Martin-Gonzalez, J., Cabanillas-Balsera, D., Fouad, A., Valasco-Ortega E., Lopez-Lopez J. Association between diabetes and the prevalence of radiolucent periapical lesions in root filled teeth: systematic review and meta-analysis. Clin Oral Invest 2016 ;20:1133-114

49. Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care 2003;26:510–3

50. Sherwani, S. I., Khan, H. A., Ekhzaimy, A., Masood, A., & Sakharkar, M. K. Significance of HbA1c Test in Diagnosis and Prognosis of Diabetic Patients. Biomarker insights 2016; 11, 95–104. doi:10.4137/BMI.S38440

51. Siddiqui, A., Siddiqui, SA., Ahmad, S., Siddiqui, S., Ahsan, I., Sahu, K. Diabetes: Mechanism, Pathophysiology and Management-A Review. Int. J. Drug Dev. & Res., April-June 2013, 5(2): 1-23

52. Sisli SN. Evaluation of the Relationship between Type II Diabetes Mellitus and the Prevalence of Apical Periodontitis in Root-Filled Teeth Using Cone Beam Computed Tomography: An Observational Cross-Sectional Study. Med Princ Pract. 2019;28(6):533–538. doi:10.1159/000500472

53. Smadi L. Apical Periodontitis and Endodontic Treatment in Patients with Type II Diabetes Mellitus: Comparative Cross-sectional Survey. J Contemp Dent Pract. 2017 May 1;18(5):358-362

54. West IC. Radicals and oxidative stress in diabetics. Diabet Med 2000; 17:171-80.

55. World Health Organization. Diabetes Fact Sheet. World Health Organization Website. http://www.who.int/mediacentre/factsheets/fs312/en/ Published 2018. Accessed May 2019

56. World Health Organization. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus Abbreviated Report of a WHO Consultation. Geneva: WHO; 2011 https://www.who.int/diabetes/publications/report-hba1c_2011.pdf Accessed April 2019

57. Yosipovitch G, Hodak E, Vardi P, et al. The prevalence of cutaneous manifestations in IDDM patients and their association with diabetes risk factors and microvascular complications. Diabetes Care 1998;21: 506–9.

9. APPENDICES

APPENDIX 1: Data collection sheets

Table 1a Data Collection Sheet- Diabetic Group: Patient Information

Case	Patient ID	DOB	Age	Gender	Medical Condition	Other relevant Patient Information
1 .... n=50						

Table 1b Data Collection Sheet- Diabetic Group: Information related to root filled tooth

Case	Patient ID	Tooth Number	Date RCT commenced	Date RCT completed	Date follow up Radiograph	De novo RCT/Retreatment	Periapical Pathosis (PAI:1-5)	Other relevant Information relating to root canal treatment provided.
1 .... n=50								

Table 2a Data Collection Sheet- Control Group (cross matched to diabetic group): Patient Information

Case	Patient ID	DOB	Age	Gender	Medical Condition	Other relevant Patient Information
1 .... n=50						

Table 2b Data Collection Sheet- Control Group (cross matched to diabetic group): Information related to root filled tooth

Case	Patient ID	Tooth Number	Date RCT commenced	Date RCT completed	Date follow up Radiograph	De novo RCT/Retreatment	Periapical Pathosis (PAI:1-5)	Other relevant Information relating to root canal treatment provided.
1 .... n=50								

APPENDIX 2: Ethical approval obtained from the Ethics Committee in Hamdan Bin Mohammed College of Dental Medicine – MBRU

MBRU
جامعة محمد بن راشد للطب والعلوم الصحية
MOHAMMED BIN RASHID UNIVERSITY OF MEDICINE AND HEALTH SCIENCES

Date: 06/05/2018

Dear Dr Alaa

Re: Your research protocol

Titled: Relationship between diabetes and periapical lesions ……

Thank you for submitting your research protocol to the Research and Ethics committee of the Hamdan Bin Mohammed College of Dental Medicine, MBRU.

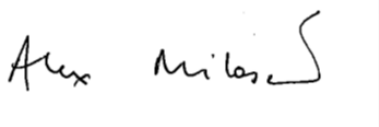
It was considered at the meeting held on 06/05/2018 and subsequently revised by you on 19/05/18

I have made one minor change. On top of page 6, you have written 'pseudonymised' which I think is meant to be 'anonymised'.

The protocol is now approved, and the REC wishes you every success with your study.

With best wishes

Yours sincerely,



Prof A Milosevic

Chair, Research and Ethics Committee, HBMCDM

APPENDIX 3: Ethical approval obtained from the Ethical Committee in Dubai Health Authority

GOVERNMENT OF DUBAI

DUBAI SCIENTIFIC RESEARCH ETHICS COMMITTEE APPROVAL LETTER

DUBAI HEALTH AUTHORITY

From :	Dubai Scientific Research Ethics Committee (DSREC) Dubai Health Authority	**Date :**	28 OCT 2018
To :	Ms. Alaa Tariq AlMutawa, Student, Mohammed Bin Rashid University of Medicine and Health Sciences	**Ref :**	DSREC-SR-10/2018_10
Study Site	Al Dental Department, DHA		

Subject: Approval for the research proposal, ***"The Prevalence of Chronic Apical Periodontitis and Its Association with Diabetes in Root Filled Teeth in an Adult UAE Population"***

Dear Student Researcher,

Thank you for submitting the above mentioned research proposal to Dubai Scientific Research Ethics Committee, DHA. The Dubai Scientific Research Ethics Committee has been organized and operates in accordance with the ICH/GCP guidelines and the committee is registered with the Office for Human Research Protection (OHRP).

Your request was discussed with Dubai Scientific Research Ethics Committee. We are pleased to advice you that the committee has granted ethical approval for the above mentioned study to be conducted in Dubai Health Authority. However, you will have to approach the Medical Director of the Hospitals to secure permission to review any hospital records and to carry out your study in the hospital.

Please note that it is DSREC's policy that the principal investigator should report to the committee of the following:

1. Anything which might warrant review of ethical approval of the project in the specified format, including:
   - any serious or unexpected adverse events and
   - unforeseen events that might affect continued ethical acceptability of the project
2. Any proposed changes to the research protocol or to the conduct of research
3. Any new information that may affect adversely the safety of the subjects
4. If the project is discontinued before the expected date of completion (reason to be specified)
5. Annual report to DSREC about the progress of the study
6. A final report of the finding on completion of the study

The approval for the study expires on **28 OCT 2019**. Should you wish to continue the study after this date, please submit an application for renewal together with the Annual Study site progress report no later than 30 days prior to the expiry date.

APPENDIX 4: Collected data of the pair-matched cases

No	Diabatic/ Non Diabatic	Tooth	age	gender	Medical history	Time from start to end of treatment	Time in which follow up xray was taken	Denovo /retretament	Preoperative PAI score	Postoperative PAI score	Status of diabetes
1	Diabatic Non-Diabatic	15 15	61 59	F F	Asthma Asthma	2 weeks 2 weeks	1 year 1 year	Denovo Denovo	4 2	3 2	Uncontrolled
2	Diabatic Non-Diabatic	13 13	64 65	F F		One visit One visit	1 year 1 year	Denovo Denovo	3 4	2 2	Controlled
3	Diabatic Non-Diabatic	15 15	64 64	F F		One visit One Visit	2 years 2 years	Retreatment Retreatment	2 3	2 2	Controlled
4	Diabatic Non-Diabatic	27 17	37 35	F F		2 weeks 2 weeks	1 year 1 year	Denovo Denovo	3 2	2 1	Controlled
5	Diabatic Non-Diabatic	45 35	36 37	F F		One visit One Visit	1 year 1 year	Denovo Denovo	4 3	1 1	Controlled
6	Diabatic Non-Diabatic	34 44	37 39	F F		3 weeks 3 weeks	3 years 3 years	Denovo Denovo	4 5	1 1	Controlled
7	Diabatic Non-Diabatic	11 11	55 52	F F	Hypertension Hypertension	One visit One Visit	1 year 1 year	Denovo Denovo	3 3	2 1	Controlled
8	Diabatic Non-Diabatic	36 46	52 53	F F	Hypertension Hypertension	3 weeks 2 weeks	1 year 1 year	Retreatment Retreatment	2 4	1 3	Controlled
9	Diabatic Non-Diabatic	35 45	59 60	M M		3 months 3 months	2 years 2 years	Denovo Denovo	2 1	2 2	Controlled
10	Diabatic Non-Diabatic	37 37	28 30	M M		3 weeks 3 weeks	4 years 4 years	Denovo Denovo	4 1	3 1	Uncontrolled
11	Diabatic Non-Diabatic	45 35	54 52	F F		2 weeks 1 week	4 years 4 years	Denovo Denovo	2 1	1 2	Uncontrolled
12	Diabatic Non-Diabatic	47 47	47 47	F F		One visit One visit	1 year 1 year	Denovo Denovo	2 2	2 1	Uncontrolled
13	Diabatic Non-Diabatic	16 16	49 46	F F		1 week 1 week	4 years 4 years	Denovo Denovo	2 3	1 2	Controlled
14	Diabatic Non-Diabatic	17 17	59 56	M M	Hypertension Hypertension	2 weeks 2 weeks	4 years 4 years	Denovo Denovo	3 3	1 2	Uncontrolled
15	Diabatic Non-Diabatic	47 47	60 63	M M	Hypertension Hypertension	1 month 1 month	2 years 2 years	Denovo Denovo	3 4	1 2	Uncontrolled
16	Diabatic Non-Diabatic	36 46	60 59	F F	Hypertension Hypertension	1 year 1 year	2 years 2 years	Denovo Denovo	2 2	3 1	Controlled
17	Diabatic Non-Diabatic	21 11	60 63	F F	Hypertension Hypertension	1 week 1 week	2 years 2 years	Denovo Denovo	2 4	2 1	Controlled
18	Diabatic Non-Diabatic	22 22	60 57	F F	Hypertension Hypertension	One visit One Visit	2 years 2 years	Denovo Denovo	2 5	3 3	Controlled
19	Diabatic Non-Diabatic	23 13	60 58	F F	Hypertension Hypertension	One visit One Visit	2 years 2 years	Denovo Denovo	2 4	2 2	Controlled
20	Diabatic Non-Diabatic	26 16	45 43	F F		2 weeks 2 weeks	3 years 3 years	Retreatment Retreatment	3 2	2 2	Uncontrolled
21	Diabatic Non-Diabatic	27 27	45 48	F F		6 months 5 months	2 years 2 years	Denovo Denovo	3 3	1 1	Uncontrolled
22	Diabatic Non-Diabatic	24 24	45 43	F F		1 week 1 week	3 years 3 years	Denovo Denovo	3 3	1 1	Uncontrolled
23	Diabatic Non-Diabatic	45 45	45 46	F F		3 weeks 3 weeks	1 year 1 year	Retreatment Retreatment	4 2	2 1	Uncontrolled
24	Diabatic Non-Diabatic	46 46	57 55	F F		2 weeks 2 weeks	2 years 2 years	Denovo Denovo	4 2	2 1	Uncontrolled

25	Diabatic Non-Diabatic	11 11	26 29	M M		One visit One Visit	2 years 2 years	Denovo Denovo	3 3	1 2	Uncontrolled
26	Diabatic Non-Diabatic	26 26	68 66	F F		2 weeks 2 weeks	1 year 1 year	Denovo Denovo	2 2	2 1	Controlled
27	Diabatic Non-Diabatic	16 16	69 66	M M	Congenital Heart Disease Congenital Heart Disease	2 weeks 2 weeks	2 years 2 years	Retreatment Retreatment	3 4	3 4	Uncontrolled
28	Diabatic Non-Diabatic	17 27	67 65	F F		2 weeks 2 weeks	3 years 3 years	Denovo Denovo	2 2	1 3	Controlled
29	Diabatic Non-Diabatic	16 16	70 68	F F		1 week 1 week	4 years 4 years	Denovo Denovo	2 3	1 3	Controlled
30	Diabatic Non-Diabatic	15 15	56 57	F F		2 weeks 2 weeks	1 year 1 year	Denovo Denovo	2 2	1 1	Controlled
31	Diabatic Non-Diabatic	37 37	56 58	F F	Hypertension Hypertension	1 week 1 week	2 years 2 years	Denovo Denovo	2 2	1 1	Controlled
32	Diabatic Non-Diabatic	14 24	56 55	F F	Hypertension Hypertension	2 weeks 2 weeks	3 years 3 years	Denovo Denovo	2 3	2 3	Controlled
33	Diabatic Non-Diabatic	14 14	49 50	F F		1 week 1 week	2 years 2 years	Denovo Denovo	3 3	2 2	Uncontrolled
34	Diabatic Non-Diabatic	16 16	49 51	F F		2 weeks 3 weeks	3 years 3 years	Retreatment Retreatment	4 3	1 3	Controlled
35	Diabatic Non-Diabatic	36 46	48 48	F F		1 week 1 week	2 years 2 years	Denovo Denovo	2 3	1 2	Controlled
36	Diabatic Non-Diabatic	36 36	56 59	F F		1 month 1 month	4 years 4 years	Denovo Denovo	3 2	3 1	Uncontrolled
37	Diabatic Non-Diabatic	31 31	59 57	F F		1 month 1 month	1 year 1 year	Denovo Denovo	3 3	2 2	Uncontrolled
38	Diabatic Non-Diabatic	42 42	61 63	F F		One visit One Visit	2 years 2 years	Retreatment Retreatment	4 2	4 1	Uncontrolled
39	Diabatic Non-Diabatic	17 17	51 48	F F		3 weeks 3 weeks	1 year 1 year	Denovo Denovo	2 2	1 1	Controlled
40	Diabatic Non-Diabatic	23 23	38 35	F F		One visit One Visit	1 year 1 year	Denovo Denovo	2 3	1 2	Controlled
41	Diabatic Non-Diabatic	41 41	59 56	F F		1 week 1 week	1 year 1 year	Denovo Denovo	4 1	2 1	Uncontrolled
42	Diabatic Non-Diabatic	44 44	78 75	M M		1 week 2 weeks	2 years 2 years	Retreatment Retreatment	4 3	2 1	Uncontrolled
43	Diabatic Non-Diabatic	16 16	55 58	F F		2 weeks 3 weeks	4 years 4 years	Denovo Denovo	3 2	1 1	Uncontrolled
44	Diabatic Non-Diabatic	26 26	68 65	M M	Hypertension Hypertension	2 weeks 2 weeks	2 years 2 years	Denovo Denovo	2 1	1 1	Controlled
45	Diabatic Non-Diabatic	46 36	45 41	F F		2 weeks 3 weeks	3 years 3 years	Retreatment Retreatment	3 4	1 2	Controlled
46	Diabatic Non-Diabatic	24 14	54 50	F F		One visit One Visit	2 years 2 years	Denovo Denovo	3 1	2 1	Uncontrolled
47	Diabatic Non-Diabatic	27 17	68 65	M M		3 weeks 3 weeks	4 years 4 years	Denovo Denovo	2 2	1 1	Controlled
48	Diabatic Non-Diabatic	13 13	55 56	F F		One visit One Visit	3 years 3 years	Denovo Denovo	3 3	2 2	Controlled
49	Diabatic Non-Diabatic	45 45	61 57	M M		2 weeks 3 weeks	2 years 2 years	Retreatment Retreatment	4 2	2 1	Uncontrolled
50	Diabatic Non-Diabatic	14 24	61 59	M M		1 month 3 weeks	3 years 3 years	Denovo Denovo	3 2	1 1	Uncontrolled