Diabetes Mellitus and the Prevalence of Periapical Periodontitis in a Scottish Subpopulation

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Declarations

Candidate Declaration

I declare that this thesis, presented for the degree of Master of Dental Science, was composed by myself, and that the work contained herein is my own except where explicitly stated otherwise in the text. I confirm that this thesis has not been submitted for any other degree or professional qualification.

Name..RYAN HIGGINS.....

Signed.....R Higgins.....

Date.....17/8/17.....

Supervisor Declaration

I declare that the conditions of the relevant Ordinance and Regulations have been fulfilled in the presentation of this thesis for the degree of Master of Dental Science.

Name...PROF DAVID RICHARDS

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Summary

This investigation aims to assess the prevalence of periapical periodontitis in patients with diabetes mellitus, compare this against patients without a diagnosis of diabetes mellitus, and to evaluate the relationship between periapical periodontitis and glycosylated haemoglobin levels.

This is a cross-sectional case-controlled study which has examined the medical and dental records for 503 patients with diabetes mellitus (DM) and 503 control patients. Dental panoramic radiographs (DPRs) were assessed for periapical periodontitis (PP) using a modified periapical index score. Number of teeth, horizontal alveolar bone level, and number of root canal fillings were also assessed from these radiographs. In the diabetic group, glycosylated haemoglobin (HbA1c) levels were reviewed and analysed with the data obtained from the radiographs. Statistical analyses were undertaken using Cohen's κ test, analysis of variance, independent *t*-tests (95% CI), and multiple regression.

The key results of this investigation were that the diabetic group had a mean number of teeth with periapical periodontitis of 1.14 (95% CI; 0.92, 1.32) per patient, compared with 0.87 (95% CI; 0.75, 0.99) in the control group ($p = 0.021$). In diabetic patients with HbA1c levels ≥ 9% the mean number of teeth with periapical periodontitis was 1.8, compared with 1.0 in diabetic patients with HbA1c levels < 9% ($p = 0.002$). The mean number of teeth per patient was 18.57 in the diabetic group and 20.51 in the control group ($p = 0.003$).

The findings of this investigation indicate that, on average, patients with DM have fewer teeth, but a greater proportion of teeth with PP, when compared with non-diabetic patients. In addition to this, as a group, diabetic patients with high levels of glycosylated haemoglobin (HbA1c $\geq$ 9%) have a greater number of teeth with PP than those with lower levels.

1. LITERATURE REVIEW

1.1 Introduction

This literature review will explore the disease processes of diabetes mellitus (DM) and periapical periodontitis (PP). It will discuss the systemic effects of DM, how disease control is monitored, and the relationship between these factors. It will consider how chronic periodontitis (CP) can be affected by DM, and the similarities between CP and PP. The use of radiography to identify PP will be reviewed along with the range of other radiographic findings which may impact on development of PP. All these factors will be considered with particular emphasis on their relevance to the population of Tayside, Scotland, where this investigation has been undertaken.

1.1.1 Background - Diabetes Mellitus

DM refers to a group of disorders which result in elevated levels of glucose circulating in the blood. This can lead to complications which affect a range of body systems, organs and tissues. These complications can result in significant morbidity and potentially mortality for patients. DM has been shown to have a negative effect on quality of life (1) and life expectancy (2), which have been largely attributed to its associated co-morbidities.

DM has been classified into subtypes including type 1, type 2, and gestational DM. Although the pathogenesis of each subtype is different, there can be accompanying features in disease aetiology, symptoms, and treatment provided. The hormone insulin

has a predominant effect in all subtypes of DM. In healthy patients insulin helps regulate blood glucose levels by signalling liver, muscle, and fat cells to metabolise glucose circulating in the blood. Cells use glucose as an energy source and the majority of tissue cells require insulin to obtain glucose from the blood.

1.1.2 Diabetes Mellitus in Tayside, Scotland and Globally

The prevalence of diagnosed DM in the population of Tayside in 2013 was 5.2% (21,428). In the same year, there were 268,154 people (5.0%) across Scotland who had been diagnosed with DM (3). Of these, 88.2% were identified as type 2 DM and 10.9% were type 1 DM. The prevalence of type 2 DM has increased in Tayside, throughout other regions in Scotland, and in the majority of more economically developed countries. It has been predicted that the prevalence of type 2 DM will continue to increase in the future, linked to high kilojoule diet, low levels of physical activity, and increased levels of obesity (4). The financial cost of DM to the National Health Service (NHS) in Scotland was approximately £1,000,000,000 in 2010-2013 (5). In 2012, DM was linked directly to the deaths of 1.5 million individuals world-wide (19).

It is likely that the prevalence of DM is underestimated because of a significant proportion of undiagnosed individuals (6). A study in Tayside which looked at 7,596 known diabetic patients also identified 701 patients with recent history of hyperglycaemia who were not recognised to be diabetic by their general practitioners (7).

1.1.3 Type 1 Diabetes Mellitus

Type 1 DM, also referred to as immune-mediated DM, accounts for approximately 5–10% of the diabetic population. It refers to an absolute insulin deficiency, resulting from cellular-mediated autoimmune destruction of the insulin producing β-cells in the pancreas. This disease has a largely genetic aetiology, having been linked to DQA, DQB and DRB genes (8). There may also be environmental factors related to type 1 DM progression, but these are not currently fully understood.

Type 1 DM most commonly presents in childhood or adolescence but can be diagnosed at any age (9). The range in age presentation is related to variable rates of β-cell destruction. When destruction is rapid, patients will commonly present with symptoms of ketoacidosis at a young age. Some patients may retain residual β-cell function that can delay the presentation of symptoms for a number of years. The treatment for type 1 DM involves a combination of glucose monitoring and provision of genetically engineered insulins. Insulin can be delivered either by subcutaneous injection or use of an insulin pump (10).

1.1.4 Type 2 Diabetes Mellitus

Type 2 DM accounts for approximately 90% of diabetic patients and it was historically associated with disease onset in adulthood. Individuals with type 2 DM have developed increased cellular resistance to the actions of insulin, rather than a deficiency. The specific aetiology is not known, but destruction of β-cells in the pancreas does not occur in these individuals (11).

The majority of patients in this group are either clinically obese or have an increased percentage of body fat, which is commonly distributed around the abdominal region. Other risk factors for developing type 2 DM include increasing age, lack of physical activity, females who have had gestational DM, hypertension, and a genetic predisposition. The insulin resistance may improve with weight reduction or pharmacological treatment, although it is not common for it to return to a normal range. Historically type 2 DM was recognised as a disease which increased in prevalence with increasing age (12). Its prevalence has been increasing in young adulthood and childhood, and this has largely been attributed to increased levels of obesity. The prevalence of type 2 DM in a younger population is predicted to increase in future years (4).

1.1.5 Other Types of Diabetes Mellitus

There are a range of genetic defects which are associated with several forms of DM. These present at an early age and are referred to as maturity onset diabetes of the young (MODY). They are autosomal dominant and are characterized by impaired insulin secretion. Separate to MODY, there can be genetic defects which affect the action of insulin, where mutations of insulin receptors can result in impaired glucose uptake and subsequent DM.

Gestational DM is defined as any glucose intolerance which has an onset during pregnancy. This will often resolve following delivery, but in some cases can persist. This classification is therefore limited as it may not account for undiagnosed type 2 DM in pregnant women (13).

1.1.6 Diabetes Mellitus – Diagnostic Criteria and Monitoring

DM has been measured through observation of clinical signs and symptoms, and by using a range of blood tests. The current diagnostic criteria of the American Diabetes Association (ADA) for DM measures the fasting plasma glucose (FPG) and the 2 hour plasma glucose (2-h PG).

The following thresholds indicate a positive diagnosis for DM:

$$\text{FPG} \geq 126 \text{ mg/dl } (7.0 \text{ mmol/l})$$

$$\text{2-h PG} \geq 200 \text{ mg/dl } (11.1 \text{ mmol/l})$$

Glycosylated haemoglobin (HbA1c) is a blood test taken to measure chronic hyperglycaemia, using the red blood cells that circulate for around 100-120 days. It is used as a biomarker to reflect average blood glucose levels over a period of months. An HbA1c level $\geq 6.5\%$ has been recommended by the ADA and an International Expert Committee as the diagnostic threshold for DM (14).

HbA1c is advantageous as a diagnostic test as it does not require patients to undergo a period of fasting, making it more convenient. Furthermore, transient variations which may occur as a result of short term periods of stress or illness will have less of an effect on the result. The disadvantage of this test is that it may not identify rapidly developing DM. In the current investigation, the long-term effects of both DM and PP are assessed. The use of HbA1c is therefore preferable, as it will evaluate glycaemic control in individuals with DM over a longer period of time.

1.1.7 Diabetes Mellitus – Scottish Database

The Scottish Care Information Diabetes Collaboration (SCI-DC) was commissioned by the Scottish Executive Health Department in 2001 to provide central support for information technology to improve diabetes care in Scotland. The SCI-DC Network for each of the Health Boards within Scotland migrated to a single system in 2013, called SCI-Diabetes. SCI-Diabetes provides an electronic network with a wealth of data on all patients who have been diagnosed with DM in Scotland.

The main features of this network are:

- Real-time data entry (data is available immediately)
- Full patient contact record
- Fully integrated diabetes patient record (whether the patient has been seen in primary or secondary care)
- Single shared electronic record regardless of geographic location

The SCI-Diabetes register underpins national programmes and surveys, including SIGN clinical guideline support, the Diabetes Retinal Screening Programme, and the Scottish Diabetes Survey (15) .

1.1.8 Diabetes Mellitus – Systemic Manifestations

There are five classical complications of DM; retinopathy, nephropathy, neuropathy, macrovascular disease, and poor wound healing. Individuals with DM have depressed

leukocyte adherence, decreased chemotaxis, reduced phagocytosis, impaired cytokine production, and an increased adherence of microorganisms to their cells (16).

Retinopathy in DM involves changes to vascular permeability, capillary degeneration and excessive neovascularization. Hyperglycaemia can cause the death of some cells in the neural retina and occlusion of retinal capillaries can result in ischaemia. Angiogenic factors are released and new blood vessels proliferate and this can result in an accumulation of fluid within the retinal tissue layers, known as macular oedema. This can contribute to visual impairment and can lead to retinal detachment (17).

Diabetic nephropathy is characterised by the development of proteinuria and a subsequent decline in glomerular filtration rate, which progresses over a long period of time. Nephropathy is a risk factor for macrovascular complications, particularly in type 2 DM. DM may also affect other functional aspects of the kidney, including release of hormones, activation of vitamin D, and the maintenance of fluid balance and blood pressure.

Neuropathy is thought to eventually develop in over half of all individuals with DM (18), and advanced neuropathy carries a risk of limb amputation. It is thought to occur because of vascular abnormalities, including basement membrane thickening and endothelial hyperplasia. These may reduce oxygen tension and result in hypoxia. Nerve fibre deterioration can occur in advanced neuropathy and can result in hyperalgesia, paraesthesia, and allodynia. Pain is a common complaint in individuals with DM and clinical signs of neuropathy (19).

Macrovascular disease in diabetes can include reduction in cardiac function, development of atherosclerosis, stroke, and myocardial infarction. The likely mechanisms through which these occur are: altered vascular permeability, ischaemia, and hypertension.

Healthy wound healing occurs as a cellular response to injury which is co-ordinated by growth factors and cytokines. Poor wound healing in diabetes has been related to over 100 physiological factors, including impaired growth factor production, impaired macrophage function, impaired angiogenic response, collagen accumulation, insufficient quantity of granulation tissue, impaired fibroblast migration and proliferation, and impaired bone healing (20).

1.1.9 Diabetes Mellitus: Mechanisms

The exact pathological mechanisms for the complications of DM are not fully understood, however the following processes have been identified as having a contributory role.

Cells of the retina, kidney, and nervous tissues are insulin-independent and glucose can cross their cell membrane freely. Glucose is used to produce energy through phosphorylation, a process which requires the enzyme hexokinase. When there are large amounts of circulating blood glucose, hexokinase becomes saturated and glucose that has not been utilised will enter the polyol (sorbitol-aldose reductase) pathway (Figure 1). In this pathway, the enzyme aldose reductase reduces glucose to sorbitol. However, in hyperglycaemia, aldose reductase has a greater affinity for glucose,

resulting in greater production and subsequent accumulation of sorbitol. The build-up of sorbitol has been found to cause osmotic damage to cells.

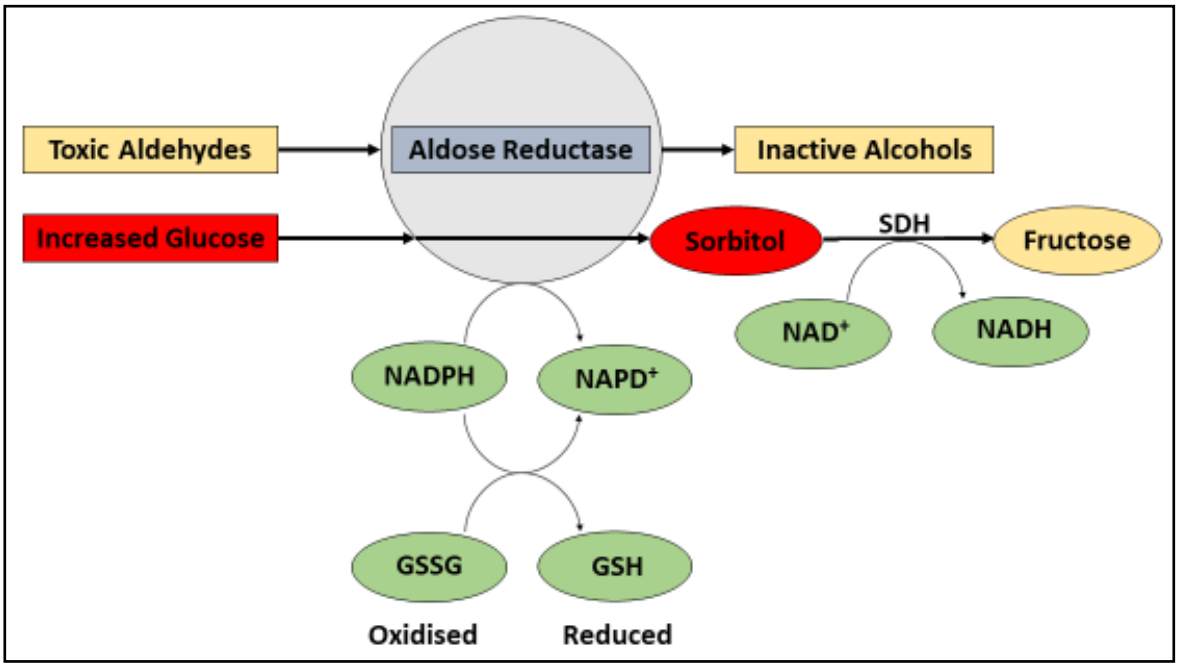

Figure 1 Polyol (sorbitol aldose-reductase) pathway. The enzyme aldose reductase reduces glucose to sorbitol, however in hyperglycaemia sorbitol can accumulate, and NADPH levels can become insufficient. Both of these can result in cellular damage.

Another mechanism that can result in DM complications involves nicotinamide adenine dinucleotide phosphate ($NADP^+$), a cofactor used in cellular metabolism in its reduced form, NADPH. Insufficient levels of NADPH have been shown to lead to cell damage, a reduced capacity for repair, and haemolysis (21).

Advanced glycation end products (AGEs) are proteins or lipids that become glycated when they are exposed to excess glucose. AGEs have been associated with a number of

pathological effects including increased oxidative stress, inhibition of vascular dilation, increased vascular permeability, increased arterial stiffness, and altered cytokine secretion from a range of cells (22). These effects contribute to the pathogenesis of complications including retinopathy, nephropathy, neuropathy, and cardiomyopathy (23).

AGEs bind to a specific cellular receptor (RAGE) which is found on monocytes and endothelial cells. This stimulates a series of pro-inflammatory events because binding to the endothelial cell surface causes expression of capsular cell adhesion molecule 1, which attracts monocytes to the region and perpetuates the inflammatory response (24).

Oxidative stress is thought to have a damaging effect on proteins in DM. Free radicals generated by the autoxidation reactions of sugars, and autoxidation of unsaturated lipids in plasma and membrane proteins can cause defects in the structural cross links of collagen, resulting in tissue damage (25), and this can result in further free radical production.

Altered lipid metabolism occurs in DM and tends to lower levels of high density lipoprotein (HDL) cholesterol and raises levels of low density lipoprotein (LDL) and triglycerides. This increases the risk for macrovascular diseases (26).

1.2 Diabetes Mellitus – Oral Health

The systemic effects of DM have been shown to have a negative impact on oral health in a number of ways. Individuals with DM suffer from xerostomia (dry mouth) to a greater degree than those without DM. Chronic periodontitis is more prevalent in patients with poorly controlled DM and it also progresses to an advanced stage more rapidly (27, 28).

There may be a relationship between DM and some oromucosal lesions, such as lichen planus and recurrent aphthous stomatitis, although the current level of evidence for this is not conclusive (29, 30). The prevalence of oral candidiasis has been shown to be greater in patients with DM (31). The relationship between dental caries and DM is complex and no specific association has been confirmed.

The oral environment has a wide range of diverse micro-organisms which live in a dynamic relationship with host defences. It is therefore not always clear how much of an effect DM has on the oral health of an individual. Diet, medications, oral hygiene, and smoking status are a few of the potential confounding factors which may also contribute to changes in the oral tissues.

1.2.1 Diabetes Mellitus – Oral Manifestations

Many of the oral manifestations of DM appear to occur through similar mechanisms to the five classical complications. Dental caries, however, appears to have a complex and unclear relationship with the presence of DM. Children and adolescents with type 1

DM are often given diets that will restrict their intake of carbohydrate rich, cariogenic foods. Individuals with type 2 DM, which is more commonly associated with obesity, may have had a high kilojoule diet consisting of many carbohydrate rich foods. These potential confounding factors have resulted in no clear consensus on the relationship between caries and DM (32).

The effect of DM on salivary flow rate (SFR) may further confound the results of studies which have assessed the progression of caries with DM. A reduction in SFR has been reported in individuals with type 1 DM who also suffer from neuropathy (33). The perception of a dry mouth may be affected by prescribed medications, increasing age, and severity of neuropathy. At this stage, a definitive quantifiable relationship has not been proven, although some association has been indicated. Disturbances in taste have also been reported in diabetic patients, particularly those on haemodialysis (34).

Oromucosal lesions, such as lichen planus and aphthous stomatitis have been reported to have a greater prevalence in diabetic individuals (28, 35). It is difficult to ascertain whether this is a true representation as the disease processes are common and often asymptomatic. It is possible that diabetic patients are more likely to report painful symptoms from these conditions, which could be related to a degree of neuropathy. Oral candidiasis has been a consistent finding in diabetics. The increased circulating glucose may act as a substrate to microorganisms when tissue breakdown occurs. A reduction in SFR could also impede the removal of pathogenic microorganisms (31).

It is possible that concurrent retinopathy and peripheral neuropathy in individuals can affect their hands, and thus limit their ability to undertake adequate oral hygiene

measures. In these situations there would be a greater risk of developing gingivitis and dental caries, in addition to other oral manifestations.

1.2.2 Diabetes Mellitus and Periodontal Diseases

Chronic periodontitis (CP) describes a chronic inflammation of the periodontal tissues which occurs as a result of an excessive immune response to polymicrobial dental plaque. It is recognised as a disease process linked with DM, and Loe (1993) even described it as the sixth complication of diabetes (36).

CP is a disease which can be influenced by many variables and there have been multiple studies exploring its relationship with DM. A systematic review by Taylor and Borgnakke (2008) indicated that there was a greater prevalence and severity of CP in patients with DM. This study also identified CP as a possible risk factor for poor glycaemic control in people with DM (32). Tsai et al (2002) reviewed over 4000 adults aged 45-90 and found that adults with poorly controlled diabetes had an odds ratio of 2.9 for having CP (37).

1.2.3 Periodontal Diseases and Periapical Periodontitis

The periapical and periodontal tissues have similar cells, constituents, blood supply and innervation (38). The inflammatory response in both periodontal and periapical tissues occurs by a similar mechanism (39). Periapical and periodontal disease are both

initiated by a polymicrobial biofilm. A predominance of similar gram negative anaerobic species has been associated with increased severity of both diseases (40), (41). Inflammation in the periapical tissues in individuals with DM may have a similar relationship to inflammation which has been observed within periodontal tissues of diabetics.

1.2.4 Chronic Periapical Periodontitis in Tayside and Globally

When assessing the radiographic prevalence of PP in an adult population within the Tayside region, a study by Saunders and Saunders (1998) found that 41-47% of the patients had at least one affected tooth. This increased to 60-72% when only elderly patients were considered. 3-5% of all the teeth examined were found to have radiographic signs of PP, which rose to 31-61% when only root canal treated teeth were assessed (42). This is particularly relevant to the current investigation as it highlights a high prevalence of PP in the same geographic region. Furthermore, this study found a higher prevalence of PP with increasing age. Prevalence of type 2 DM has also been linked to increasing age. An aging population may therefore have a greater risk of developing both diseases and it would be beneficial to evaluate any potential relationship between them.

A more recent study in the Tayside region, using cone-beam computed tomography to detect radiological signs of PP, found 5.8% of all teeth were affected. This study again included only adult patients and had an age range of 18 to 85 years. 47% of root canal treated teeth had signs of PP, and over 50% of these were judged to have been

inadequately root filled (43). There have been a number of studies globally which have attempted to identify the prevalence of PP within a population, with results ranging from 27-80% (Table 1). While the prevalence of teeth affected by PP appears to be generally low, the number of patients with at least one tooth with PP has been reported to be higher. The significance of this is not currently known when considering potential systemic effects of PP.

1.3 Periapical Periodontitis

Periapical periodontitis (PP), apical periodontitis and periradicular periodontitis are terms which have all been used to describe the inflammatory process of endodontic aetiology, which can occur in the tissues surrounding the root of a tooth. This process can result in destruction of the periradicular tissues. The reported prevalence of this disease process has varied between studies and can be considered either as a prevalence by subject, or a prevalence by tooth (Table 1). When considering the prevalence within a population, it refers to the number of subjects investigated who were found to have at least one tooth with PP. The number of individual teeth with PP in the population studied considers prevalence by tooth. It is worth considering that there is a wide variation in the possible number of teeth with PP in each patient. One patient could have multiple teeth with PP, or only one tooth with PP. Prevalence should therefore be considered in terms of both prevalence by tooth, and prevalence by patient. Environmental and patient factors are likely to play a role in the progression of this disease, which makes it less likely that there will be an even spread of disease over a population.

Study	Country	Radiograph Type	Sample Size (Subjects)	Total Number of Teeth	Prevalence PP by Patient	Prevalence by Tooth	Prevalence of RFT by Patient	Prevalence of RFT by Tooth
Eriksen & Bjertness, 1991 (44)	Norway	DPR	119	2940	-	3.5%	-	6.0%
Saunders et al, 1997 (42)	UK	Full-mouth periapicals	340	8420	27%	5.6%	54%	-
Marques et al, 1998 (45)	Portugal	DPR	179	-	27%	-	-	-
Sidaravicius et al, 1999 (46)	Lithuania	DPR	147	3892	70%	-	71.4%	8.2%
Kirkevang et al, 2001 (47)	Denmark	Full-mouth periapicals	614	15984	-	3.4%	-	4.8%
Jimenez-Pinzon et al, 2004 (48)	Spain	Full-mouth periapicals	180	-	61%	-	40.6%	2.1%
Kabak & Abbott, 2005 (49)	Belarussia	DPR	1423	31212	80%	12%	-	-
Gulsahi et al, 2007 (50)	Turkey	DPR	1000	24433	-	1.4%	-	3.3%
Tavares et al, 2009 (51)	France	Periapicals	-	1035 RCTd teeth	-	-	-	33%
Peters et al, 2010 (52)	Netherlands	Periapicals	-	4594	-	2.5%	-	4.8%

Table 1 Summary of studies assessing the prevalence of periapical periodontitis and root-filled teeth in various countries. Prevalence is shown as measured by patient and by tooth.

1.3.1 Periapical Periodontitis – Pathogenesis

Periapical periodontitis develops when the dental pulp becomes infected and necrotic. Infection of the dental pulp can occur as a result of dental caries, trauma, dental procedures, periodontal disease and tooth wear (53, 54, 55, 56). Bacterial species are the major microbial agents in the development of pulpal inflammation and PP (57), although fungi and viruses have also been identified and may have a contributory role (58, 59).

A healthy dental pulp is contained within the root canal system in a sterile environment. In contrast, the environment of the main oral cavity contains many microbial species. The pulp therefore, has mechanisms to protect itself from microbial colonization. One of the main protective methods is stimulation of an outward flow of dentinal fluid through the dentinal tubules, to prevent an influx of microbes.

When the pulpal tissue is exposed or inflamed, microbial species and their by-products may enter the root canal system. These stimulate formation of micro-abscesses within the pulp and localised foci of necrosis will occur. As the foci increase in size and number, they will coalesce and the remaining vital pulp has a reduced capacity to stimulate outward flow of dentinal fluid. At this point, further bacteria can spread unhindered through the dentinal tubules, increasing the insult to the remaining vital pulp tissue and increasing the microbial load within the root canal system. When the entire dental pulp has become necrotic, the apical and lateral foramina provide points of communication between the microbial community within the root canal system and the periapical tissues.

The host mounts an array of defences including several types of cells, intercellular messengers, and antibodies. The microbial factors and host defences encounter and destroy the periapical tissues, resulting in PP (60). Destruction of bone in the periapical region permits radiographic identification of PP, as the localised area of reduced bone density has a radiolucent appearance.

1.3.2 Periapical Periodontitis – Dental Factors

The presence of PP is inextricably linked to the status of the remaining root and coronal tooth structure. There are therefore a number of dental factors which can affect the likelihood that PP may be present.

Deep coronal restorations have been identified as a risk factor for the development of PP (61). This can be as a result of previous deep caries having caused irreversible inflammation in the pulp, which subsequently can become necrotic. Alternatively, inflammation in the pulp may have occurred during removal of deep caries. In these cases the pulp may have been mechanically heated beyond its capacity to repair, or it may have been exposed to bacteria in the oral environment (55, 62). The diameter of dentinal tubules is greater closer to the pulp (63). Mechanical and thermal components of dental procedures in deep dentine can therefore have a greater effect on pulpal inflammation. Similarly, bacteria and their by-products are more likely to account for an increased inflammatory response when they progress into a deeper layer of dentine. The wider diameter of dentinal tubules in this region facilitates these pathogens to transfer towards the pulp at a greater rate.

The presence of metal and fibre posts have been linked to an increased prevalence of PP (43, 64). There are a number of potential factors that could permit the passage of bacteria to the apical tissues in these cases. Placement of a post in a tooth may alter the direction in which occlusal forces are transmitted and can cause a vertical root fracture. A post may be placed in a tooth because coronal tooth structure has previously been lost because of trauma. In these cases there could be an undetected crack along which bacteria can spread. Procedural errors can occur during preparation and placement of a post, and perforation of the root is a known complication, which could facilitate bacterial ingress.

The presence of a crown on a tooth has similarly been associated with an increased prevalence of PP (42). The thermal and mechanical stress placed on a dental pulp are again considered to be the factors which ultimately lead to pulpal necrosis and PP. The concept of a stressed-pulp syndrome has been suggested by Abou-Rass (1982) (65). This theory speculates that the dental pulp has a limited inflammatory capacity and repeated insults on a previously inflamed pulp may cause the pulp to become stressed beyond the level where the inflammation can resolve. In cases where a tooth has been exposed to these types of stress, subsequent pulpal necrosis and PP would be considered more likely to occur.

Teeth serving as abutments for bridges have been found to have a greater progression to pulpal necrosis than those of a single unit crown (66, 67). Preparation of a tooth for conventional fixed-fixed bridge abutments generally requires the removal of more dentine to produce abutment preparations with parallel walls. These preparations will

be more extensive than those of single crowns and will therefore result in a greater insult to the pulp of each bridge abutment.

Periodontal disease has been investigated as a factor which may lead to pulpal inflammation and necrosis. It has been demonstrated that the pulp can become inflamed because of bacterial by-products in a periodontal pocket entering through lateral canals (68, 69). However, the current available evidence indicates that a tooth will not develop pulp necrosis until an infected periodontal pocket extends to the main apical foramen (70).

A history of dental trauma is a risk factor for developing pulpal necrosis and PP (54). Unfortunately it is not often possible to definitively ascertain from a DPR whether a tooth has previously suffered trauma.

1.3.3 Periapical Periodontitis – Identifying and Monitoring

PP can occur with or without symptoms and its presence can be detected through clinical and radiographic assessment (71). Clinical signs may include the presence of a sinus tract adjacent to the affected tooth, tenderness of the mucosa overlying the tooth apex, tenderness on percussion of the tooth, and negative responses to an electric pulp test and thermal tests. These findings may be combined with the presence of gross caries, an extensive coronal restoration, or a history of dental trauma.

Periapical radiographs are recommended for endodontic treatment during assessment, intra-operatively, and to monitor disease following treatment (72, 73). They will

generally provide sufficient information on the morphology of teeth, their roots, root canals, and the periradicular tissues. An index for classifying PP has been developed to measure the level of disease adjacent to the root of a tooth (74). The limitation of this method is that a radiograph is a two dimensional representation of a three dimensional object. The radiographic image will therefore not always accurately represent the level of disease which is present.

A dental pantomographic radiograph (DPR), also known as an orthopantomogram and panoral radiograph, has been used to identify the prevalence of PP in a number of studies (44-46). This method of assessing PP is less sensitive than periapical radiography, but in population studies it is advantageous as it provides information on the entire dentition.

A study by Carlos Estrela (2008) compared the sensitivity of cone-beam computed tomography (CBCT), periapical radiographs and DPRs when assessing PP in 888 imaging examinations (75). CBCT identified a significantly higher prevalence of PP and the sensitivity for periapical radiographs was found to be 0.55, compared with 0.28 for DPRs. Estrela (2008) undertook a further study where 596 patients had a combination of periapical radiographs and CBCT scans taken and the accuracy of each was compared. PP was identified in 60.9% of cases by CBCT and 39.5% for periapical radiographs (76). CBCT would therefore be the optimal current method for assessing PP, although there are comparatively limited numbers of scans available for analysis as this imaging technique has been introduced more recently.

1.4 Diabetes Mellitus and Pulpal Inflammation

The dental pulp is a highly vascularized connective tissue that has capacity for repair following an injury. Its reparative process requires an absence of bacterial contamination and in optimal conditions the pulp can form a dentine bridge over an exposed area. Unfortunately, an exposed pulp will most often encounter the complex microflora of the oral environment and inflammation progresses to necrosis.

There have been a number of studies carried out on the dental pulps of rats, where diabetes was induced with an injection of Streptozotocin. When these were compared with the pulpal tissue of healthy controls, the pulps were shown to have differing levels of a number of markers including nitrite, kalikrein, myeloperoxidase and alkaline phosphatase. The concentration of collagen in the pulp was also found to be lower in diabetic rats (77). Catalase is an enzyme involved in the decomposition of hydrogen peroxide and is therefore important in protecting cells from oxidative damage. The activity of catalase has been found to be enhanced in the pulp of diabetic rats (78). In addition to this, it has been reported that dentine bridge formation was inhibited in repaired pulp exposures of diabetic rats (79). It seems plausible that the pulp of a diabetic rat may therefore have an increased inflammatory response, less collagen, and a reduced capacity to repair.

A study by Cintra et al (2017) assessed the pulpal response to bleaching of normoglycaemic and diabetic rats (80). Diabetic rats which underwent tooth bleaching had a greater pulpal inflammatory response, a wider layer of reactionary dentine, and more mature collagen fibres. These factors could adversely affect the capacity for the

pulp to repair and may increase the risk of pulpal necrosis, should a tooth be exposed to further insult. These animal studies should be interpreted with caution as similar data from humans is not currently available.

1.5 Diabetes Mellitus and Periapical Periodontitis

It has been suggested that patients with poorly controlled DM do not respond to endodontic treatment as well as their healthy counterparts (81). An increase in circulating glucose levels has been shown to directly impact the healing of periradicular lesions (82). There are a number of possible mechanisms which could cause this. The effect of DM on the immune system, inflammatory response, bone resorption, and resistance to infection may all play a role.

Research with mice indicated a greater incidence of both caries and alveolar bone resorption in the diabetic group (83). A separate study showed that diabetic rats developed more severe apical inflammation, more apical root resorption, more alveolar bone resorption, and larger apical lesions than the control group (84). In another study, a group of non-obese diabetic mice with infected teeth and PP were found to have greater morbidity and mortality than equivalent healthy mice (85).

A study in humans reviewed the medical histories and endodontic treatment data for 540 cases with follow-up data for two years, of which 73 were patients with DM. Diabetic patients were found to have a reduced likelihood of success in cases where a pre-operative apical lesion was present. They also had increased periodontal disease on teeth with PP (86).

A number of studies, from a variety of geographical regions have compared the prevalence of PP in diabetic and non-diabetic patients. These studies have used either periapical or panoral radiographs and have assessed prevalence both by individual and by tooth. A summary of the findings of these studies is outlined in Appendix 1.

The previous studies have generally been carried out in small sized groups with limited data relating to the level of control of diabetes for each patient. It is therefore difficult to draw definitive conclusions.

1.6 Summary

PP and DM are both common disease processes which affect a significant proportion of the population of Tayside. The available literature would suggest that progression of pulpal inflammation to PP may be more likely in patients with DM. It also suggests that lesions of PP may be more extensive and more prevalent in diabetics. Records of HbA1c levels will provide an indication of the diabetic control of patients over a relatively long period of time. Progression of PP also occurs over a longer period of time and so this measurement is the most appropriate. To ascertain the prevalence of lesions of PP it is necessary to obtain images of all the teeth of a patient. DPRs readily provide this, although it is noted that they are not the most sensitive radiographic technique for detecting periapical radiolucencies.

2. AIMS AND NULL HYPOTHESES

2.1. Aims

1. To assess the prevalence of periapical periodontitis within diabetic and non-diabetic patient groups.
2. To assess the relationship between HbA1c and the presence of periapical periodontitis in diabetic patients.
3. To compare the number of teeth and root canal fillings between the diabetic and non-diabetic patients.
4. To compare the periapical health of root canal treated teeth in diabetic and non-diabetic patients.

2.2. Null Hypotheses

1. There is no statistical difference in the prevalence of periapical periodontitis within diabetic and non-diabetic patient groups.
2. No statistically important relationship exists between the prevalence of periapical periodontitis and increased levels of circulating glycosylated haemoglobin for patients with diabetes.

3. MATERIALS AND METHODS

3.1 Study Design

This retrospective observational case-controlled study was designed to assess whether factors related to DM could be associated with PP. The cases in this study were adult patients with either type 1 or type 2 DM, and the controls were age and sex matched patients who had not been diagnosed with DM. All subjects included in the study had a digital DPR available on an NHS database, which was taken between 31st July 2007 and 31st July 2013. DPRs for both groups were analysed by blinded assessors.

To identify the relationship between DM and PP a radiograph was used that provided information on the full dentition of each individual. Data related to the control of patient's DM was also considered and for this study the HbA1c was selected as the most appropriate measure of this. The data sets were collected separately and then collated following individual analysis of each data subset.

Approval was obtained from the Caldicott Guardian for NHS Tayside to access the radiographs and data related to patient diabetic status (Ref number: CSAppRH21062013).

3.3 Data Collection

Subject data was gathered from patient data stored in the NHS CHI number system, PACS radiograph database, and SCI-Diabetes database.

These included:

1. Sex.
2. Age.
3. Diabetic status and type.
4. HbA1c blood test results.
5. DPR measurements.

Data was stored on password protected computers and within encrypted files. Data was collated by Data Analysts at the Health Informatics Centre, University of Dundee. DPRs were analysed separately by blinded assessors, who were unaware of each subject's diabetic status. Subjects were therefore assigned an anonymised identifying number by the HIC Data Analysts. When analyses of DPRs were completed, this data was sent to the Data Analysts at HIC for anonymization. Data related to the diabetic status of the diabetic group was then accessed via a secure password-protected virtual desktop, called Safe Haven.

3.3 SCI-Diabetes

SCI-Diabetes is a national database set up to record and monitor diabetic patients. The data recorded for these patients includes their diabetic diagnoses, type of diabetes, blood investigations results, medications prescribed to patients, record of admissions to

Accident and Emergency Departments, and demographic data. For the purposes of this study the factors from SCI-Diabetes which were assessed included the presence of a diabetes diagnosis for DM, type of DM, and the diabetic control of a patient measured from their HbA1c blood investigation result.

SCI-Diabetes has access to a vast volume of data related to patients with DM. The data required for the patients in this study was condensed to the following variables:

- Type of DM
- HbA1c (mean, median, maximum, minimum, number of readings)

All values were taken for results dating back to 31st July 2007 or the first results available following diagnosis of DM, if the patient was diagnosed after this time.

3.4 Recruitment

Subjects identified for this study were made up of two groups; a group of patients with DM, and a group of patients without DM.

Every patient who has accessed care in the NHS is assigned a unique patient identifying number, called a CHI number. An electronic list of CHI numbers was generated for all patients who had a DPR taken and stored on the PACS digital radiograph system in the Tayside region between 31st July 2007 and 31st July 2013. SCI-Diabetes is a national database used across the NHS within Scotland, which records data for every patient who has been diagnosed with DM within the NHS. Data recorded on SCI-Diabetes for each patient includes type of DM, blood tests results, medication prescriptions, and

patient demographic information. The entire list of patients with DPRs was then cross-referenced against the SCI-Diabetes database to identify which DPRs were from patients who had been diagnosed with DM.

3.5 Subjects

There were 521 patients who both had a DPR and were on the SCI-Diabetes database with a diagnosis of DM. A control patient was selected for each case from the original full list of all patients who had ever had a DPR taken and stored on the PACS database. This group also therefore contained 521 patients. Control cases were age- and sex-matched.

3.5.1 Inclusion/Exclusion Criteria

The inclusion criteria for the case subjects were:

- Registered as diagnosed with DM on SCI (Diabetes) database.
- Good quality full DPR available on the PACS database.
- Aged 18 years or more at the time the DPR was taken.

Control subjects were selected from the remaining group of patients who had a DPRs available. The inclusion criteria for the control subjects were:

- Not registered as having been diagnosed with DM on SCI (Diabetes) database.
- Good quality full DPR available on the PACS database.
- Aged 18 years or more at the time the DPR was taken.
- Age and sex matched to a case subject.

Patients were discounted for reasons related to their radiographs:

- 22 patients were discounted as there was not a radiograph on the PACS system.
- 7 patient was discounted as the radiograph showed condyles only.
- 28 patients were discounted as their radiograph was a ½ DPR.
- 37 patients were discounted as their radiographs were deemed to be of inadequate diagnostic quality for the purposes of this study.

Therefore from 1100 patients, 94 were discounted. The remaining 1006 patients were available for analysis. A flow chart of case and control selection is displayed in Figure 2.

3.5.2 Assessment of Radiographs

All radiographs were analysed independently by two separate assessors, both postgraduates undertaking specialist training in endodontics within Dundee Dental Hospital. Each radiograph was assessed as being either of adequate or inadequate quality with only adequate radiographs being included in the study. Assessors were blinded to DM status, as well as each other's findings.

Intra-observer reproducibility was assessed on 206 DPRs viewed by Assessor 1 that were re-analysed after a two week lapse. Inter-observer reproducibility was assessed on 442 DPRs analysed by both assessors. To obtain the results for the final radiographic analyses, both assessors reviewed all radiographs where there was any disagreement and reached a consensus. The remaining 592 DPRs not been previously analysed were assessed by Assessor 1.

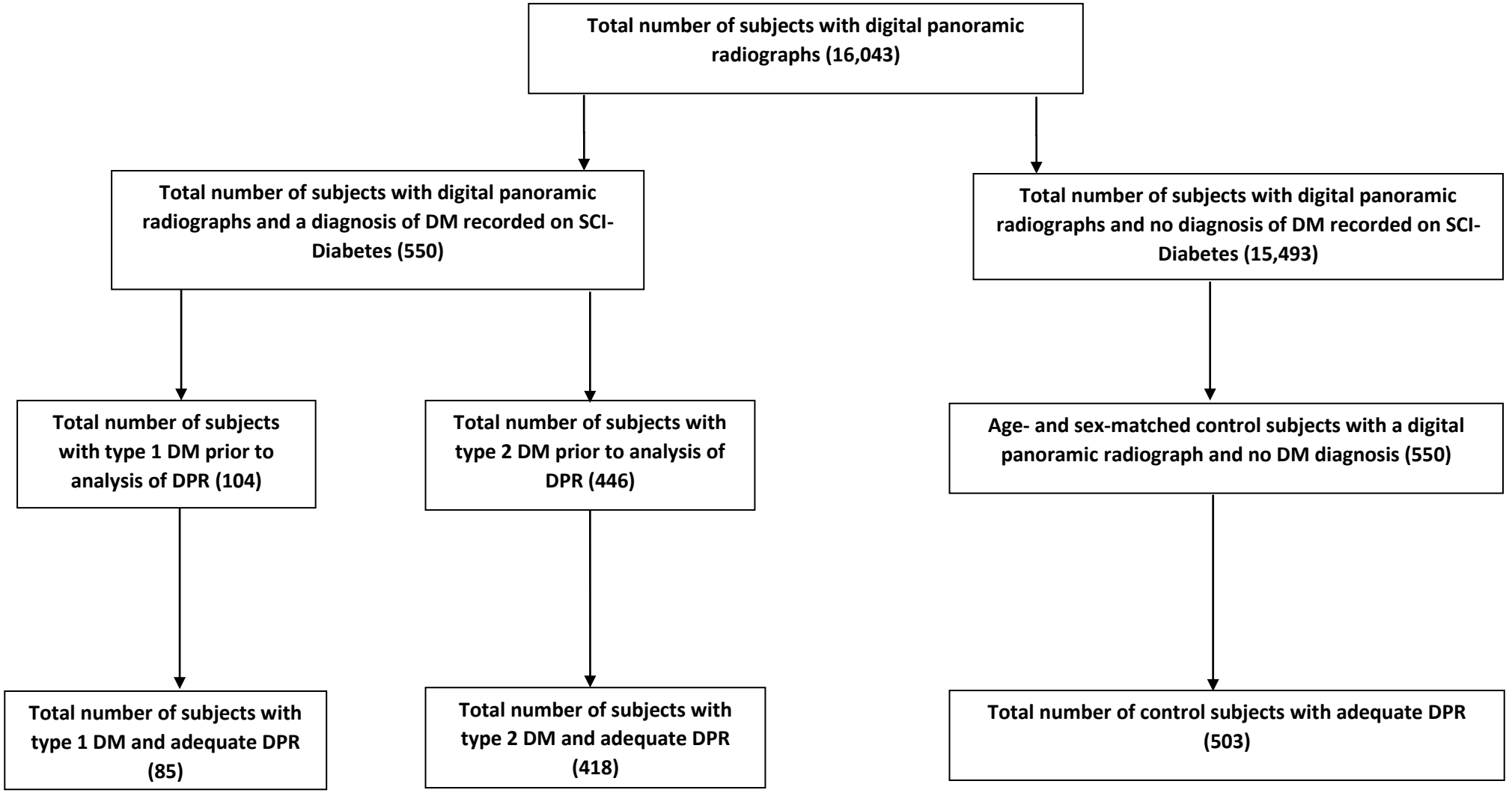

Figure 2 Flow chart of case and control selection through inclusion criteria.

DPRs were assessed for the following features:

- Total number of teeth.
- Total number of teeth with PP.
- Number of teeth with a root canal filling.
- Number of teeth with a root canal filling and PP.
- Number of teeth with PP lesions measuring over 5mm in diameter.
- Number of teeth with PP lesions measuring over 10mm in diameter.
- Number of teeth with a post-core and crown.
- Number of teeth with PP which also have a post-core and crown.
- Presence of horizontal alveolar bone loss.
- Number of teeth with a combined periodontal-endodontic lesion.

Number of teeth, number of teeth with root canal fillings, and number of teeth with a post-core and crown were assessed by a direct count from the DPR.

When assessing the DPRs for presence of PP, a simplified periapical index (PAI) scoring system was used (Table 2). The PAI system scores teeth from 1–5 based on the radiographic appearance of the periapical tissues. This includes small changes in bone structure which would be too subtle to reproducibly identify on a DPR. The scoring system was therefore simplified to include:

1. Normal periapical structures
2. Periapical periodontitis with a well-defined radiolucent area

In the simplified PAI system, the original PAI scores of 1-3 were graded as 1, whereas scores of 4-5 were graded as 2. This simplified system was used because of the lower sensitivity of DPRs for detecting PP.

Description of Radiographic Findings	PAI Score	Simplified PAI Score
Normal periapical structures	1	1
Small changes in bone structure	2	1
Changes in bone structure with some mineral loss	3	1
Periodontitis with well-defined radiolucent area	4	2
Severe periodontitis with exacerbating features	5	2

Table 2 Periapical Index and Simplified Periapical Index Scoring System.

DPRs were all viewed through digital software with a measurement tool for assessing the size of radiographic features. When PP was identified, the associated radiolucency was measured and if the diameter was greater than 5mm or 10mm this was also recorded.

A measurement for horizontal bone loss was taken from the cemento-enamel junction to the crestal bone for a molar tooth and anterior tooth in each subject. Measurements were taken with the measuring tool in the digital radiograph viewing software. Identification of bone height loss of more than 3mm at either point was recorded as being positive for the presence of horizontal alveolar bone loss (HABL). In cases where

there were not posterior and anterior teeth present, measurements were taken from two sites where teeth were present. If only one tooth was present it was measured alone.

Radiographs were additionally assessed if they contained teeth which had root canal fillings. The teeth which had undergone this treatment were further assessed and graded in relation to this. This grading system scored the quality of root canal filling as adequate or inadequate and whether PP was present in relation to this. A root canal filling was graded as adequate if it extended to within 2mm of the radiographic apex, there were no evidence of voids or an inappropriate root fillings material, and a coronal restoration with no clear defective margins was present. If any of these features were not present the root canal filling was graded inadequate. Where more than one DPR was available for a subject, the more recent radiograph was assessed.

3.6 Statistical analyses

Statistical analyses were undertaken using statistical software from IBM SPSS Version 24.0. Data was analysed to identify any statistically significant relationship between the data related to DM and the data related to DPRs.

Scatter plots were charted to assess distribution of data for each category being investigated and parametric analyses of data were undertaken where appropriate. Analyses of differences between means in the case and control groups was undertaken using *t*-tests for the following factors:

- Sex distribution
- Age distribution
- Number of teeth
- Age distribution and number of teeth
- Presence of horizontal alveolar bone loss
- Prevalence of PP by tooth
- Prevalence of PP by subject
- Prevalence of PP by subject and age
- Prevalence of teeth with PP lesions greater than 5mm and 10mm
- Prevalence by tooth of combined periodontal-endodontic lesions
- Prevalence of teeth with root canal fillings
- Prevalence of subjects with root canal fillings
- Prevalence of teeth with root canal fillings and PP
- Prevalence of subjects with root canal fillings and PP
- Glycaemic control and dental parameters

All comparisons of means were analysed with 95% confidence intervals using the standard error of the mean.

Multiple regression analyses was then undertaken to ascertain whether there was a relationship between the prevalence of PP by tooth and subject, diabetic status, presence of horizontal alveolar bone loss, prevalence of root canal fillings by tooth and by subject, and number of teeth. A mean, median, high, and low value were recorded for all subjects. Standard deviations were also calculated for this variable.

4. RESULTS

4.1 Subject Grouping

Subjects were assessed in the following groups for analyses:

- Subjects without diabetes mellitus (No DM)
- All subjects with diabetes mellitus (All DM)
- Subjects with type 1 diabetes mellitus (T1 DM)
- Subjects with type 2 diabetes mellitus (T2 DM)
- All subjects included in the study (All Subjects)

The study included 1,006 subjects in the final analyses, 503 with a diagnosis of DM and 503 without a diagnosis of DM. Of the DM group, 85 had type 1 DM and 481 had type 2 DM. All *p* values were calculated with 95% confidence intervals with the standard error of the mean.

4.2 Intra- and Inter-observer Agreement

The intra-observer reproducibility for radiographic measurements is displayed in Table 3. Both unweighted and weighted Cohen's kappa coefficients show a very high degree of agreement with the scores of greater than 0.9 for all measurements.

	No. of Teeth	Horizontal Bone Loss	Number of Teeth with PP	No of Teeth with RF	No. of RFT with PP	No. of Post-Crowns	No. of Perio-Endo Lesions
Unweighted kappa coefficient	**0.985**	**0.971**	**0.950**	**0.975**	**0.939**	**0.968**	**0.944**
Weighted kappa coefficient	**0.964**	**0.971**	**0.977**	**0.986**	**0.957**	**0.981**	**0.973**

Table 3 Intra-assessor unweighted and weighted Cohen's kappa coefficients for variables assessed in radiographic analysis of 206 DPRs by Assessor 1.

The inter-observer reproducibility for radiographic measurements is displayed in Table 4. Both unweighted and weighted Cohen's kappa coefficients show a high degree of agreement with the scores of greater than 0.85 for all measurements. The variable, Radiographic Quality, was also reviewed independently by both assessors. 450 radiographs were assessed as part of this and the unweighted Cohen's kappa coefficient was 0.855, which again indicates a high level of agreement between assessors.

	No. of Teeth	Horizontal Bone Loss	Number of Teeth with PP	No of Teeth with RF	No. of RFT with PP	No. of Post-Crowns	No. of Perio-Endo Lesions
Unweighted kappa coefficient	0.969	0.873	0.888	0.966	0.905	0.958	0.936
Weighted kappa coefficient	0.996	0.873	0.938	0.985	0.928	0.973	0.956

Table 4 Inter-assessor unweighted and weighted Cohen's kappa coefficients for variables assessed in radiographic analysis of 442 DPRs by Assessor 1 and Assessor 2.

4.2 Sex Distribution

Sex distribution by each subgroup is displayed in Table 5. No statistically significant differences were found between the number of males and females in each subgroup. The investigation had a total of 531 male subjects and 475 female subjects.

	No DM	All DM	T1 DM	T2 DM	All Subjects
Male	268 (53.2%)	263 (52.3%)	40 (47.1%)	223 (53.3%)	531 (52.8%)
Female	235 (46.7%)	240 (47.7%)	45 (52.9%)	195 (46.7%)	475 (47.2%)
Total	503 (100%)	503 (100%)	85 (100%)	418 (100%)	1006 (100%)

Table 5 Sex distribution by subgroup

4.3 Subject Age

The age range and mean are displayed by each subgroup are in Table 6 and Figure 4. The age range for the All DM and No DM groups were 19–97 and 19–96 years respectively, with no statistically significant difference between mean ages (p = 0.86). The T1 DM group had a mean age of 41.79 years, which was significantly lower than the T2 DM group mean of 62.78 years (p = 0.0001).

	No DM	All DM	T1 DM	T2 DM	All Subjects
Number of Subjects	503	503	85	418	1,006
Mean Age (Yrs)	59.07	59.23	41.79	62.78	59.15
Median Age (Yrs)	60	60	40	62	60
SD (Yrs)	15.39	15.36	15.89	12.59	15.37
SE Mean (Yrs)	0.69	0.69	1.72	0.62	0.48
Age Max (Yrs)	96	97	83	97	97
Age Min (Yrs)	19	19	19	24	19

Table 6 Subject age range and mean grouped by DM status

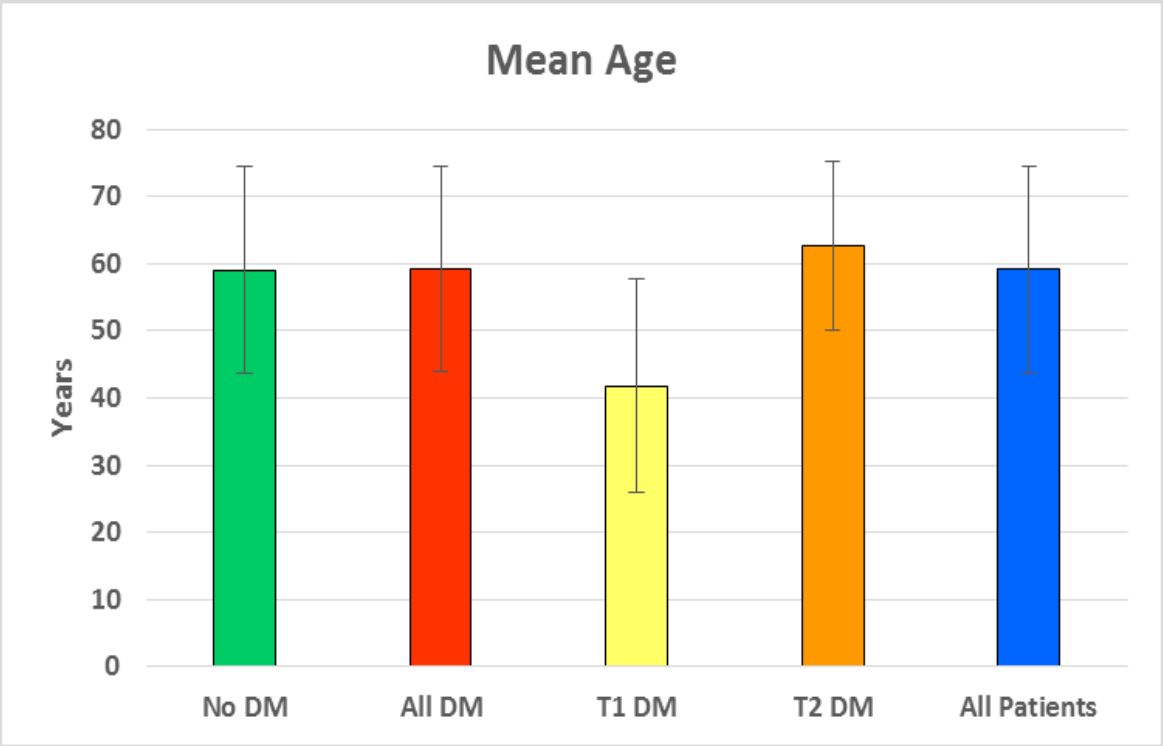

Figure 4 Mean of subject age grouped by DM status grouped by DM status with 95% confidence intervals based on standard error of the mean

4.4 Number of Teeth

The number of teeth per subject is displayed by each subgroup in Table 7 and Figure 5. The total number of teeth present when including the subjects in all groups was 19,809 of maximum possible of 32,192 (if every subject had 32 teeth). There were a total of 9,490 teeth in the All DM group compared with 10,319 teeth in the No DM group. This translated to a mean number of teeth of 18.87 (18.07, 19.67) in the All DM group, which was significantly lower than the mean of 20.51 (19.76, 21.26) in the No DM group (p = 0.003). The T1 DM group had a mean number of teeth per subject of 23.05 (21.17, 24.93), which was significantly higher than the mean of 18.02 (17.16, 18.88) in the T2 DM group (p = 0.0001). The higher mean number of teeth in the No DM group

was found to have a statistically significant difference when compared with the lower number in the T1 DM group ($p = 0.015$) and the T2 DM group ($p = 0.0001$).

	No DM	All DM	T1 DM	T2 DM	All Subjects
Number of Subjects	503	503	85	418	1,006
Total Number of Teeth	10,319	9,490	1,959	7,531	19,809
Mean Number of Teeth (Per Subject)	20.51	18.87	23.05	18.02	19.69
SD	8.63	9.19	8.8	9.04	8.95
SE of Mean	0.39	0.41	0.96	0.44	0.28
Max Number of Teeth	32	32	32	32	32
Min Number of Teeth	0	0	0	0	0

Table 7 Number of teeth for all subjects and grouped by DM status

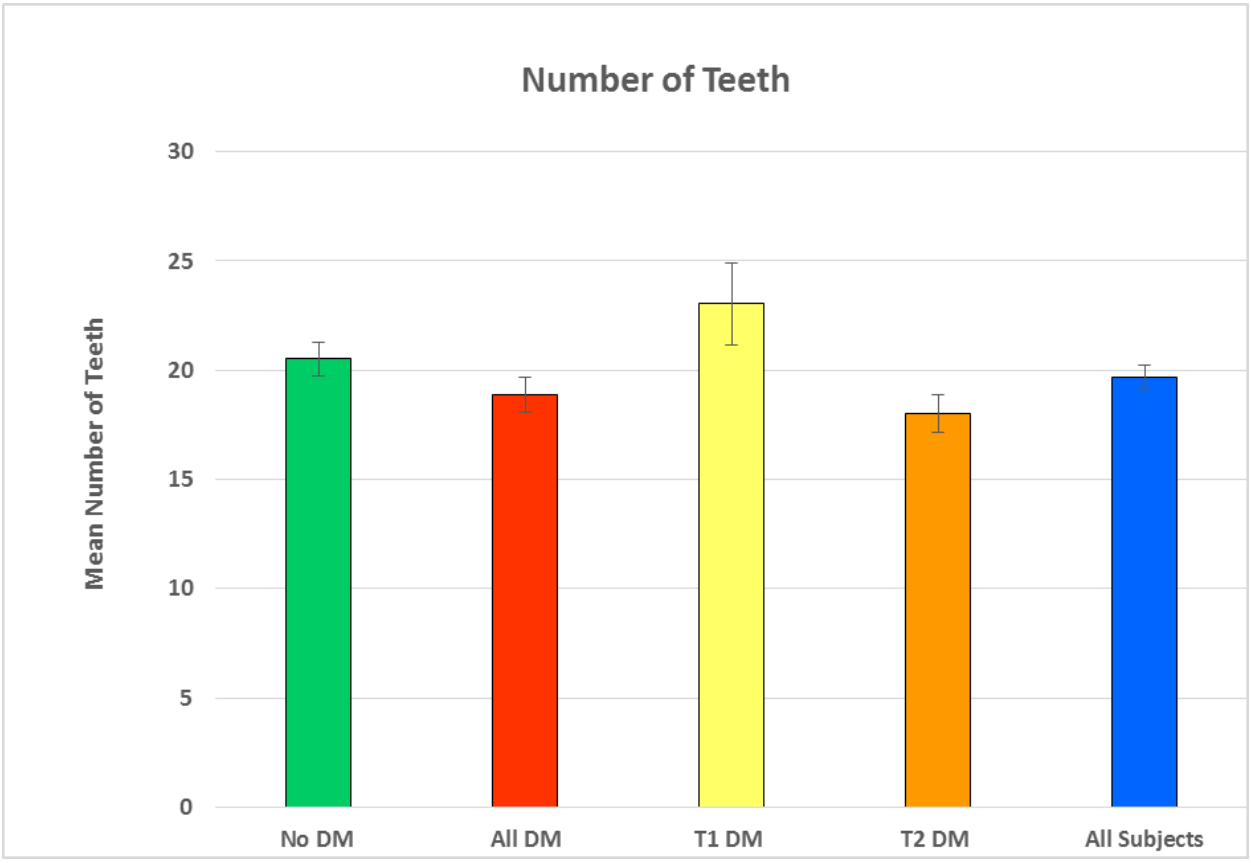

Figure 5 Mean number of teeth for all subjects grouped by DM status with 95% confidence intervals based on standard error of the mean

4.5 Age Range and Number of Teeth

The number of teeth in the No DM and All DM groups, stratified into 10 year age subgroups, are displayed in Table 8 and Figure 6. A steady decline in the mean number of teeth is evident as age increases in both the No DM and All DM groups. The mean age for number of teeth remained above 27 for both groups until age 39. Other than the 89-98 years age group, the No DM group had more teeth in each of the age subgroups over 38 years. This was only statistically significant for the 69-78 years age group where the mean number of teeth were 17.23 in the No DM group and 13.05 in the All DM group (p = 0.004).

	No DM			All DM		
Age (Yrs)	**Mean No. of Teeth**	**No. of Subjects**	**SE of Mean**	**Mean No. of Teeth**	**No. of Subjects**	**SE of Mean**
19-28	27.63	24	0.77	28.74	23	0.74
29-38	27.46	26	0.71	27.76	25	0.77
39-48	25.06	64	0.61	23.84	63	0.79
49-58	22.43	111	0.62	20.29	118	0.64
59-68	19.30	139	0.72	18.63	131	0.72
69-78	17.23	86	1.00	13.05	91	1.04
79-88	13.39	51	1.36	11.98	47	1.36
89-98	0	2	0	9.40	5	3.83
All Groups	20.51	503	0.39	18.87	503	0.41

Table 8 Mean number of teeth grouped by DM status and stratified by age

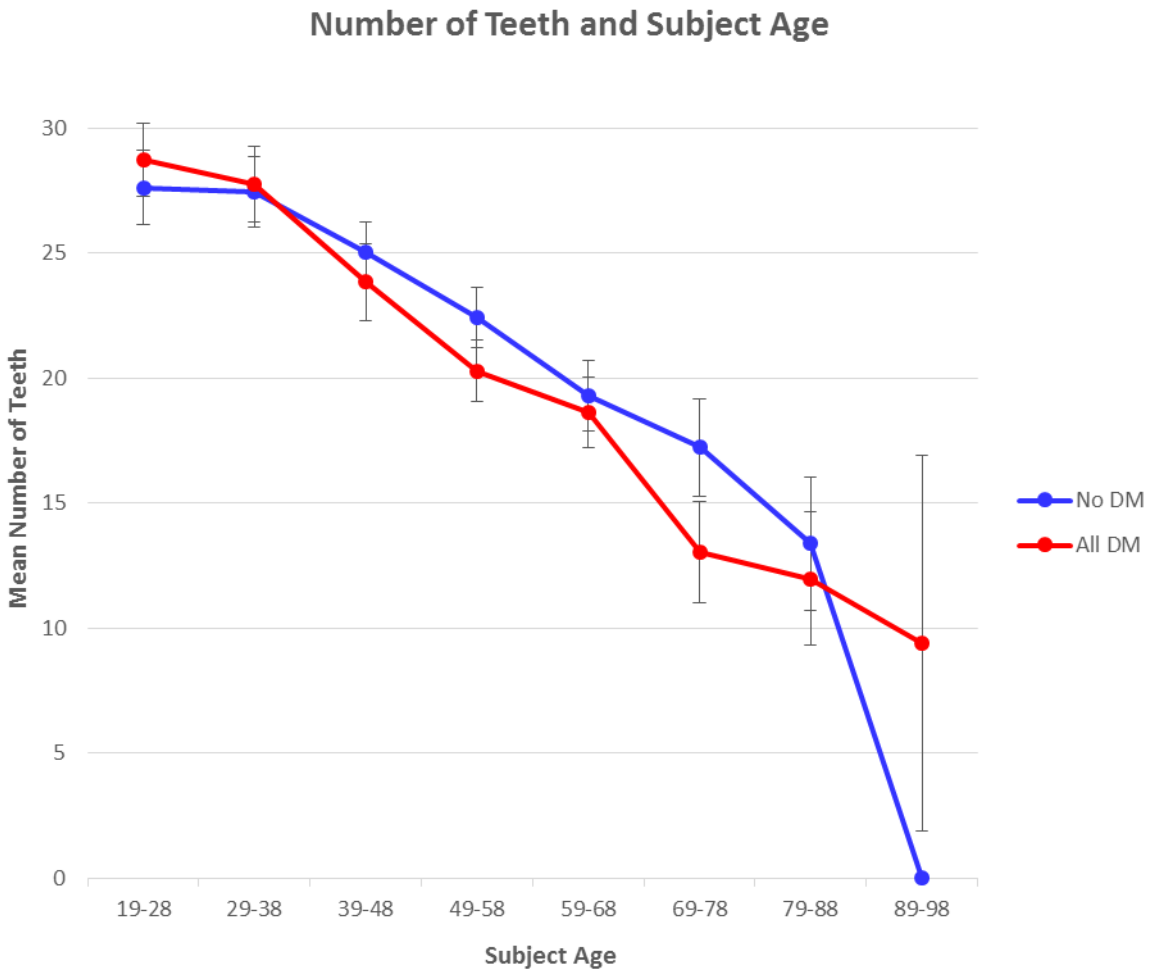

Figure 6 Mean number of teeth grouped by DM status and stratified by age with 95% confidence intervals based on standard error of the mean

4.6 Horizontal Alveolar Bone Loss

The presence of horizontal alveolar bone loss (HABL), arranged by each subgroup, is displayed in Table 9 and Figure 7. No statistical difference was found between HABL in the All DM and No DM groups ($p = 0.488$). 27% of the T1 DM group had HABL which was statistically significantly lower when compared with 53% HABL in the T2 DM group ($p < 0.001$). When the DM subgroups were compared individually against the No DM group the differences were found to be statistically significant; the T1 DM

group had a lower proportion of subjects with HABL (p = 0.001), and the T2 DM group had a higher proportion of subjects affected (p = 0.048).

	No DM	All DM	T1 DM	T2 DM	All Subjects
Number of Subjects	503	503	85	418	1,006
Total Subjects with Bone Loss Present	233	259	23	221	477
Percentage of Subjects with Bone Loss Present	46	49	27	53	47
SD	50	50	45	50	50
SE of Mean	2.2	2.2	4.8	2.4	1.6

Table 9 Presence of horizontal alveolar bone loss grouped by DM status

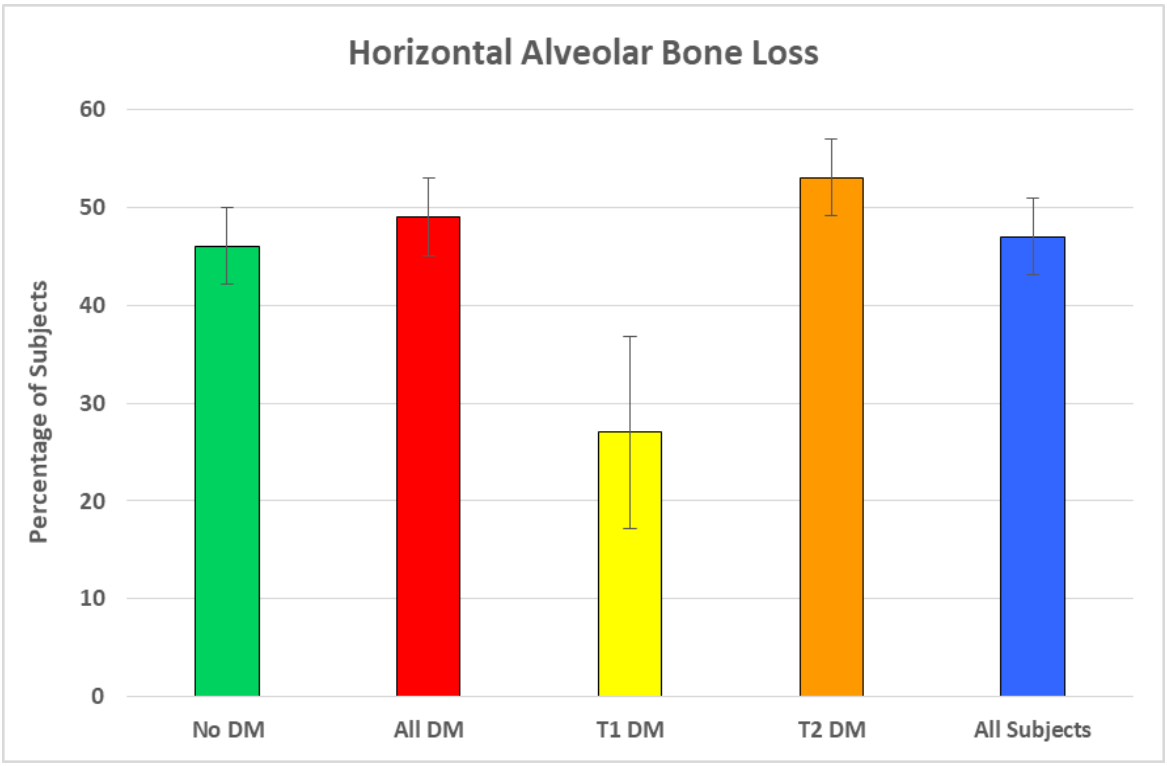

Figure 7 Presence of horizontal alveolar bone loss grouped by DM status with 95% confidence intervals based on standard error of the mean

4.7 Number of Teeth with Periapical Periodontitis

The number of teeth with periapical periodontitis (PP), arranged by each subgroup, is displayed in Table 10 and Figure 8. This data indicates the prevalence of PP per tooth. The mean number of teeth with PP was 1.01 when all subjects were included. The mean number of teeth with PP was 1.14 in the All DM group compared with the statistically significantly lower value of 0.87 in the No DM group ($p = 0.021$). In the DM subgroups, the T1 DM group had a mean of 1.59 teeth with PP compared with the statistically significantly lower value of 1.05 teeth in the T2 DM group ($p = 0.04$). It was also found to be a statistically significant when the mean number of teeth affected by PP in the T1 DM group, of 1.59, was compared with 0.87 teeth in the No DM group ($p = 0.001$). The difference between the T2 DM group and No DM group was not statistically significant ($p = 0.089$).

	No DM	All DM	T1 DM	T2 DM	All Subjects
Total Number of Teeth	10,319	9,490	1,959	7,531	19,809
Total Number of Teeth with PP	437	564	135	429	1,001
Mean Number of Teeth with PP	0.87	1.14	1.59	1.05	1.01
SD	1.43	2.198	3.65	1.76	1.86
SE of Mean	0.06	0.10	0.40	0.09	0.06
Max (Teeth with PP)	9	22	22	11	22
Min (Teeth with PP)	0	0	0	0	0
Absolute Risk (%)	0.17	0.22	1.87	0.25	0.1

Table 10 Mean number of teeth with periapical periodontitis grouped by DM status

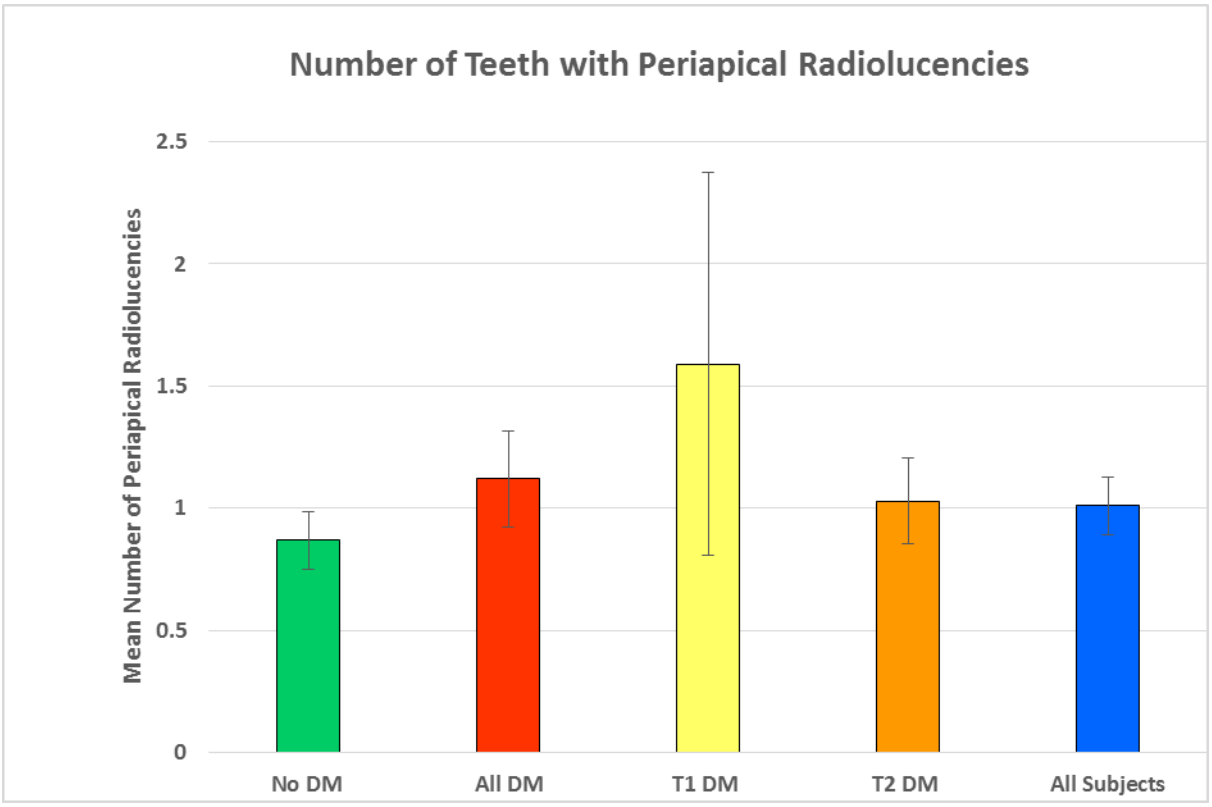

Figure 8 Mean number of teeth with periapical periodontitis grouped by DM status with 95% confidence intervals based on standard error of the mean

4.8 Number of Subjects with Periapical Periodontitis

The number of subjects who had at least one tooth with periapical periodontitis, arranged by each subgroup, is displayed in Table 11 and Figure 9. This data indicates the prevalence of PP per subject. The mean number of subjects with PP in at least one tooth was 43% when all subjects were included. No statistical differences were found when comparing PP prevalence by subject between any of the groups of DM presence and type. The prevalence of PP by subject in the All DM group was 44% compared with 42% in the No DM group (p = 0.445). In the DM subgroups, the T1 DM group had a prevalence of PP in at least one tooth of 45% compared with 44% in the T2 DM group (p = 0.876).

	No DM	All DM	T1 DM	T2 DM	All Subjects
Number of Subjects	503	503	85	418	1,006
Number of Subjects with PP	209	221	38	183	430
Mean Subjects with PP	0.42	0.44	0.45	0.438	0.43
SD	0.493	0.497	0.50	0.497	0.495
SE of Mean	0.02	0.02	0.05	0.02	0.016
Absolute Risk (%)	41.6	43.9	44.7	43.8	42.7

Table 11 Mean number of subjects with periapical periodontitis grouped by DM status

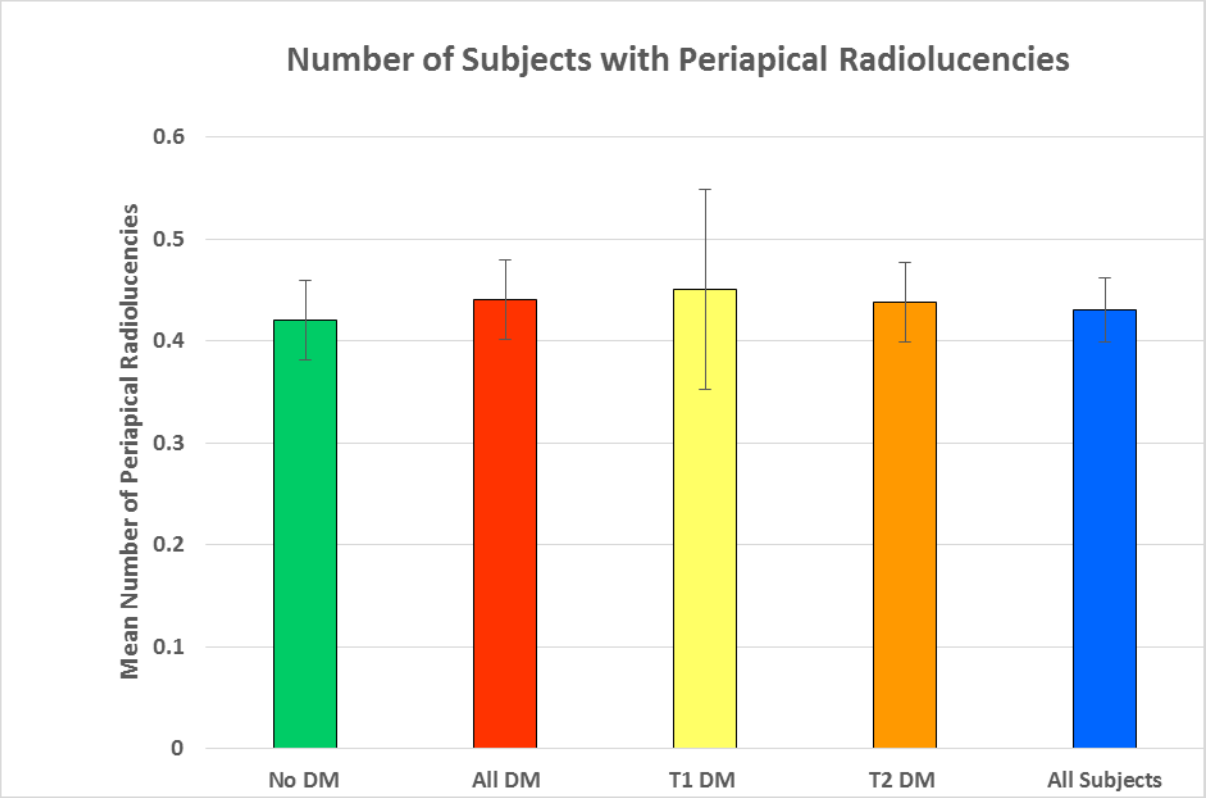

Figure 9 Mean number of subjects with periapical periodontitis grouped by DM status with 95% confidence intervals based on standard error of the mean

4.9 Mean Number of Subjects with Periapical Periodontitis Stratified by Age

The number of subjects with periapical periodontitis by each subgroup, stratified into 10 year age groups is displayed in Table 12 and Figure 10. The All DM group has a greater number of teeth with PP in every age range when compared with the No DM group, although none of these differences were found to be statistically significant.

	No DM			All DM		
Age (Yrs)	**Mean No. Teeth with PP**	**No. of Subjects**	**SE of Mean**	**Mean No. Teeth with PP**	**No. of Subjects**	**SE of Mean**
19-28	0.00	24	0.00	1.83	23	0.845
29-38	0.96	26	0.39	1.40	25	0.879
39-48	0.91	64	0.151	1.30	63	0.279
49-58	1.05	111	0.146	1.17	118	0.170
59-68	0.88	139	0.123	1.02	131	0.151
69-78	0.79	86	0.128	1.05	91	0.193
79-88	0.92	51	0.242	0.96	47	0.290
89-98	0.00	2	0.00	0.60	5	0.400
All Groups	0.87	503	0.064	1.14	503	0.098

Table 12 Mean number of subjects with periapical periodontitis grouped by DM status and stratified by age

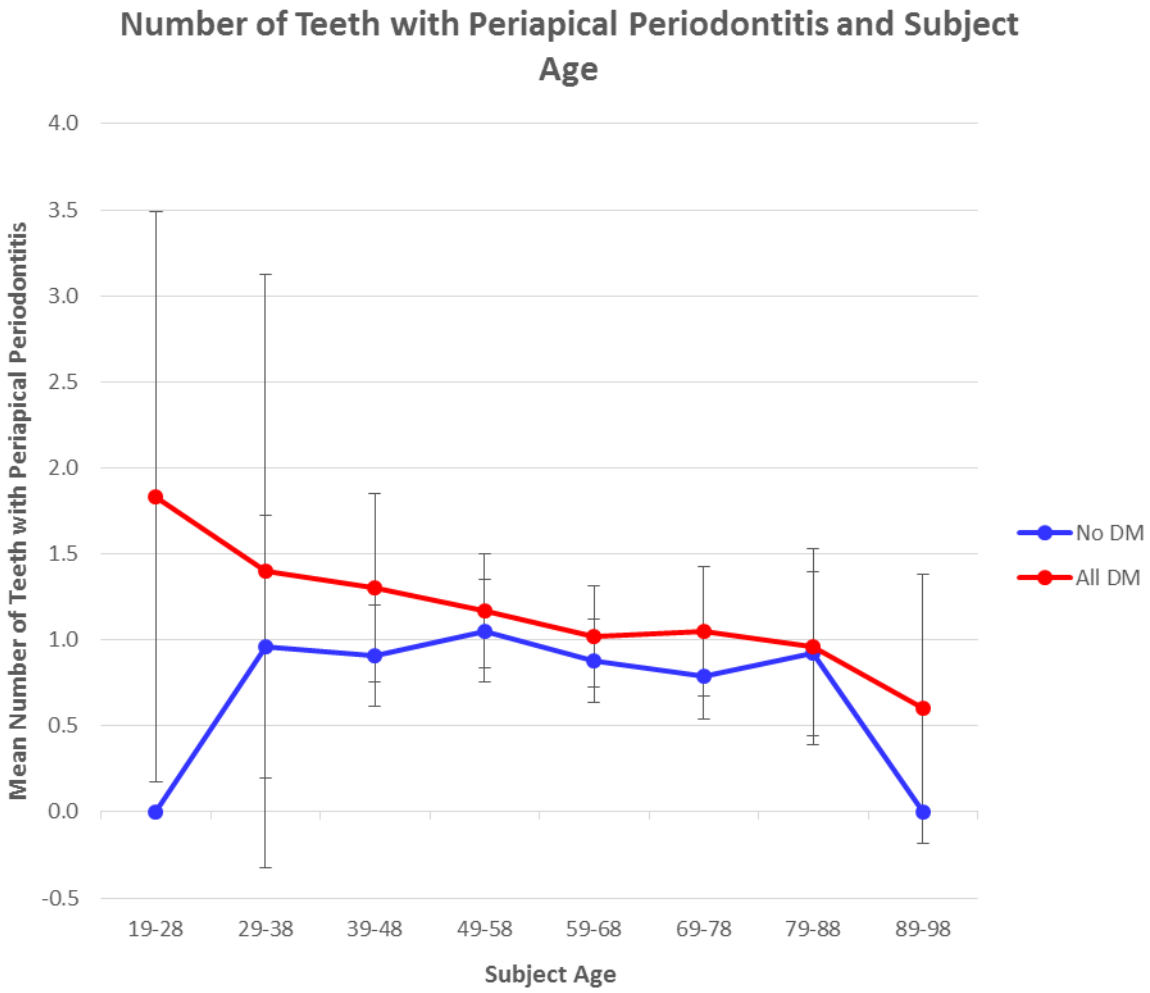

Figure 10 Mean number of subjects with periapical periodontitis grouped by DM status and stratified by age with 95% confidence intervals based on standard error of the mean

4.10 Number of Teeth with a Periapical Radiolucency Greater than 5mm

The number of teeth with a periapical radiolucency greater than 5mm in diameter, arranged by each subgroup, is displayed in Table 13 and Figure 11. None of the differences between any of the groups were found to be statistically significant for this measurement. In the All DM group the mean number of teeth with a radiolucency >5mm was 0.26 compared with 0.23 in the No DM group (p = 0.45). For the same

measurement, the T1 DM and T2 DM subgroups had a mean of 0.31 and 0.25 teeth respectively ($p = 0.52$).

	No DM	All DM	T1 DM	T2 DM	All Subjects
Total Number of Teeth	10,319	9,490	1,959	7,531	19,809
Number of Teeth with PP > 5mm	115	131	26	105	246
Mean	0.23	0.26	0.31	0.25	0.24
SD	0.62	0.71	1.17	0.58	0.668
SE of Mean	0.028	0.032	0.126	0.028	0.021
Max	4	8	8	4	8
Min	0	0	0	0	0

Table 13 Mean number of teeth with periapical radiolucencies greater than 5mm grouped by DM status

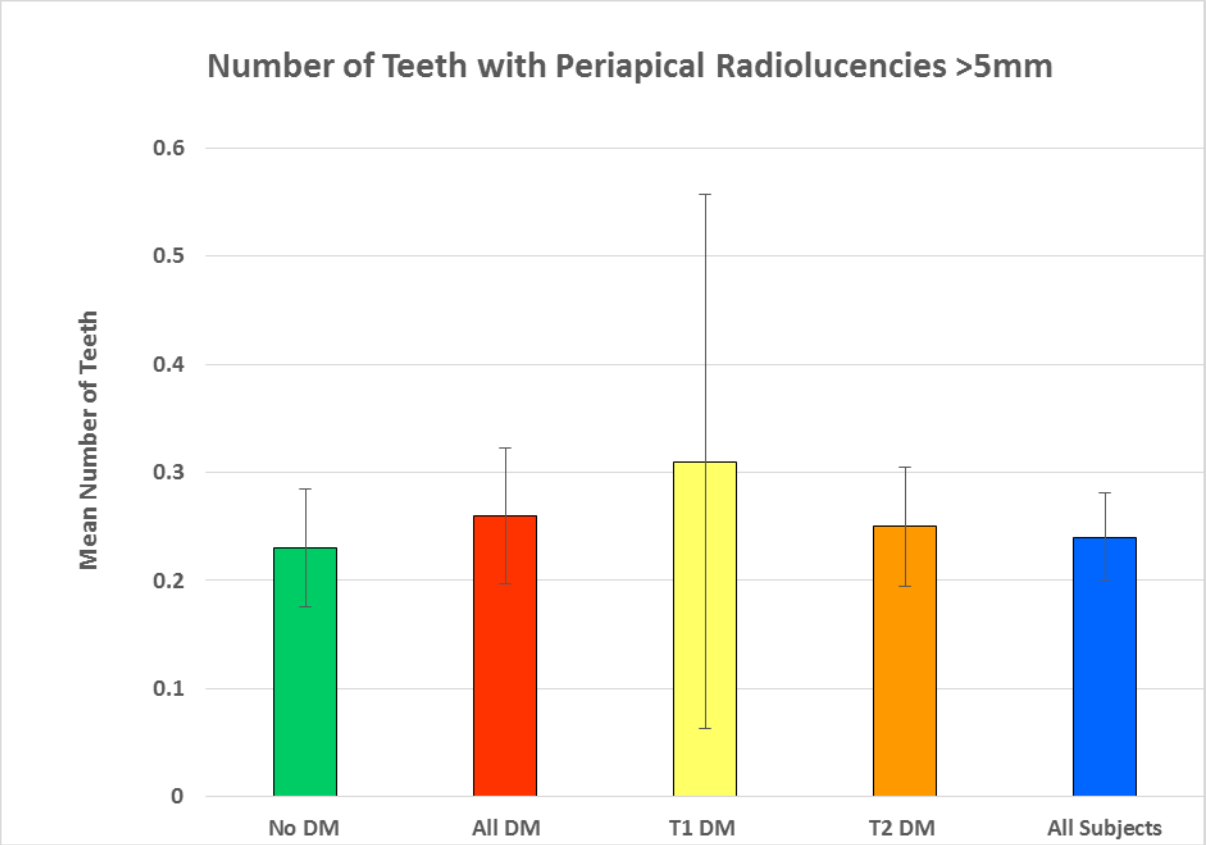

Figure 11 Mean number of teeth with periapical radiolucencies greater than 5mm grouped by DM status with 95% confidence intervals based on standard error of the mean

4.11 Number of Teeth with a Periapical Radiolucency Greater than 10mm

The number of teeth with a periapical radiolucency greater than 10mm in diameter, arranged by each subgroup, is displayed in Table 14 and Figure 12. In all of the subgroups the mean number of teeth with a radiolucency >10mm was 0.06. No differences between groups were therefore identified at the level this category was measured.

	No DM	All DM	T1 DM	T2 DM	All Subjects
Total Number of Teeth	10,319	9,490	1,959	7,531	19,809
Number of Teeth with PP > 10mm	32	31	5	26	63
Mean	0.06	0.06	0.06	0.06	0.06
SD	0.28	0.26	0.28	0.26	0.273
SE of Mean	0.013	0.012	0.031	0.013	0.009
Max	2	2	2	2	2
Min	0	0	0	0	0

Table 14 Mean number of teeth with periapical radiolucencies greater than 10mm grouped by DM status

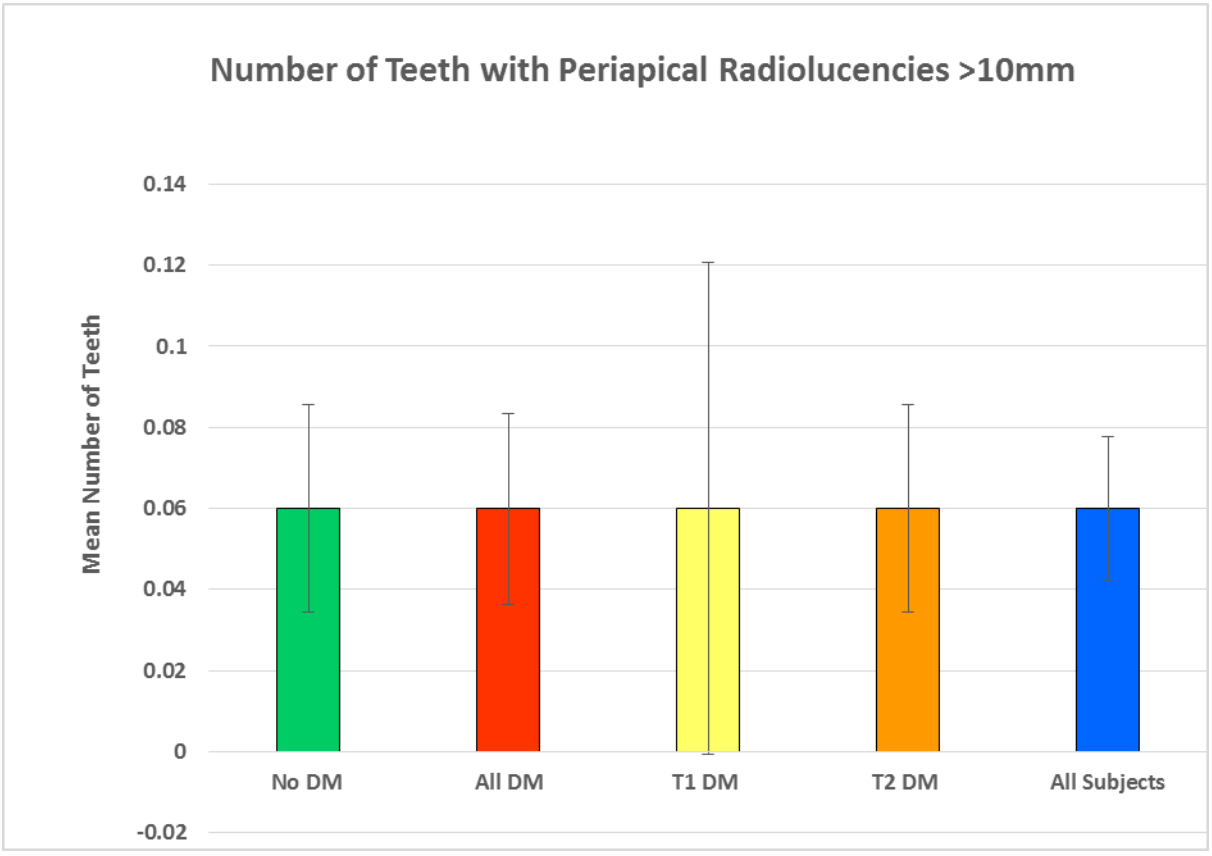

Figure 12 Mean number of teeth with periapical radiolucencies greater than 10mm grouped by DM status with 95% confidence intervals based on standard error of the mean

4.12 Number of Teeth with Combined Periodontal-Endodontic Lesions

The mean number of teeth with combined periodontal-endodontic lesions, arranged by each subgroup, is displayed in Table 13 and Figure 13. In the All DM group the mean number of teeth with a combined periodontal-endodontic lesion was 0.37 which was a higher value when compared with 0.23 in the No DM group. This difference was found to be statistically significant ($p = 0.024$). For the same measurement the T1 DM and T2 DM subgroups had mean values of 0.40 and 0.36 respectively, which was not statistically significant ($p = 0.784$).

	No DM	All DM	T1 DM	T2 DM	All Subjects
Total Number of Teeth	10,319	9,490	1,959	7,531	19,809
Total Number of Teeth with Perio-Endo Lesions	118	185	34	151	203
Mean Number of Teeth with Perio-Endo Lesions	0.23	0.37	0.40	0.36	0.30
SD	0.78	1.06	1.21	1.03	0.933
SE of Mean	0.035	0.047	0.132	0.05	0.029
Max	8	8	7	8	8
Min	0	0	0	0	0

Table 15 Mean number of teeth with combined periodontal-endodontic lesions grouped by DM status

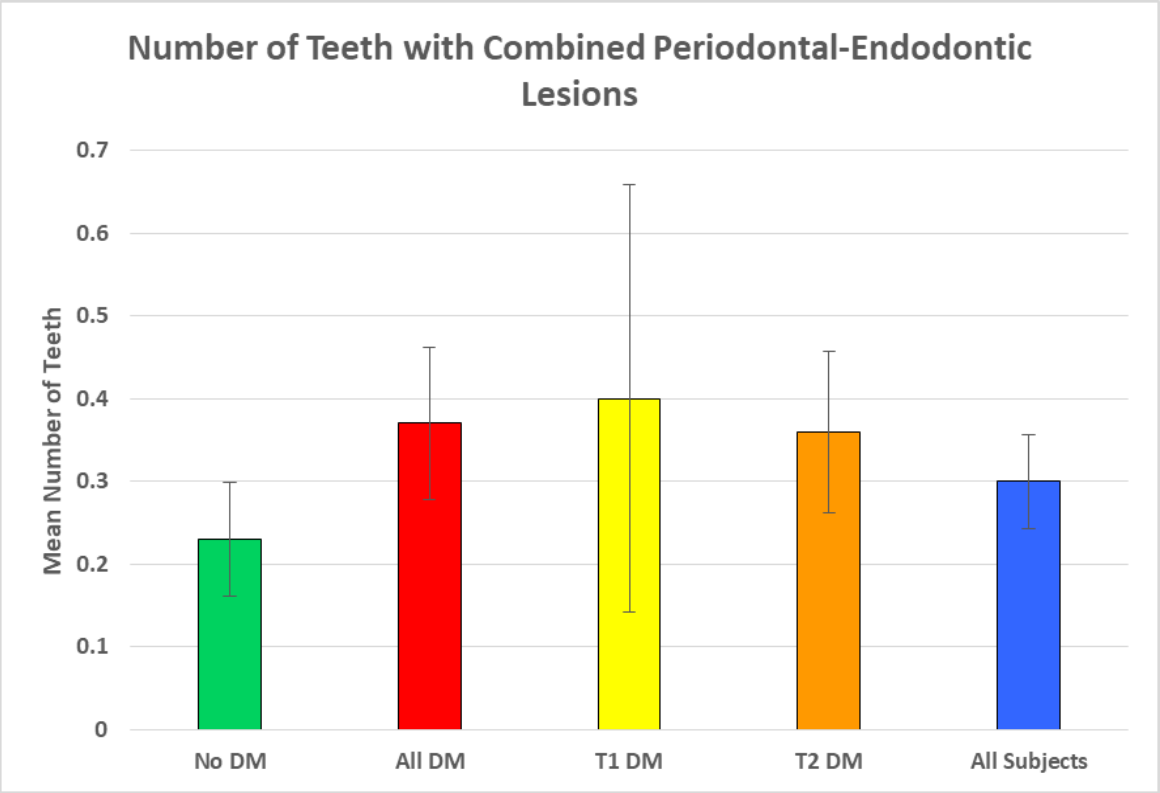

Figure 13 Mean number of teeth with combined periodontal-endodontic lesions grouped by DM status with 95% confidence intervals based on standard error of the mean

4.12 Number of Teeth with Root Canal Fillings

The number of teeth with root canal fillings, arranged by each subgroup, is displayed in Table 16 and Figure 14. No statistically significant differences were found between any of the subgroups for this measurement. In the All DM group the mean number of teeth with root canal fillings was 0.84 compared with 0.92 in the No DM group (p = 0.072). Comparison between the T1 DM and T2 DM subgroups identified means of 0.74 and 0.87 teeth respectively (p = 0.463).

	No DM	All DM	T1 DM	T2 DM	All Subjects
Total Number of Teeth	10,319	9,490	1,959	7,531	19,809
Total Number of Teeth with Root Fillings	461	425	63	362	886
Mean Number of Teeth with Root Fillings	0.92	0.84	0.74	0.87	0.88
SD	1.47	1.5	1.40	1.52	1.487
SE of Mean	0.066	0.067	0.153	0.074	0.047
Max	10	10	3	10	10
Min	0	0	0	0	0

Table 16 Mean number of teeth with root canal fillings grouped by DM status

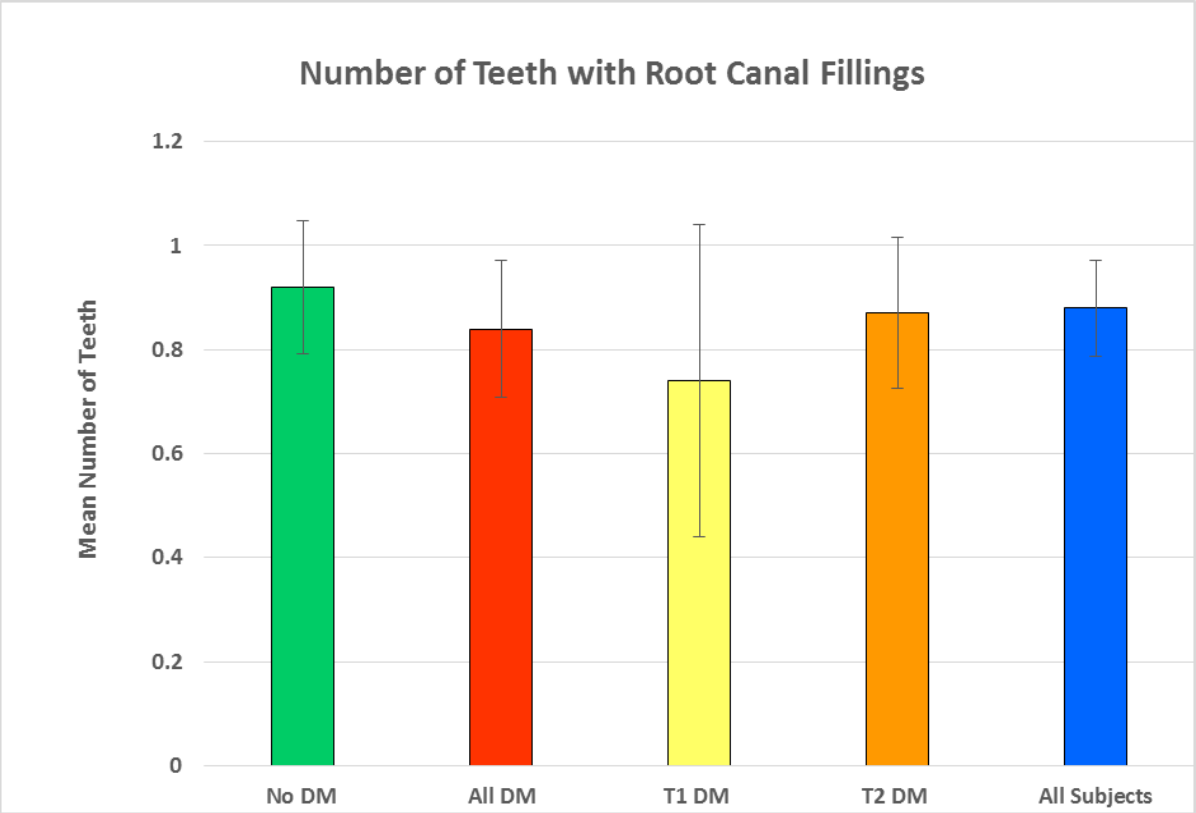

Figure 14 Mean number of teeth with root canal fillings grouped by DM status with 95% confidence intervals based on standard error of the mean

4.13 Number of Subjects with Root Canal Fillings

The proportion of subjects with a least one root canal filling, arranged by each subgroup, is displayed in Table 17 and Figure 15. No statistically significant differences were identified between any of the subgroups, for this measurement. In the All DM group the percentage of patients with root canal fillings was 37% compared with 41% in the No DM group (p = 0.245). Comparison between the T1 DM and T2 DM subgroups identified means of 33% and 38% teeth respectively (p = 0.355).

	No DM	All DM	T1 DM	T2 DM	All Subjects
Number of Subjects	503	503	85	418	1006
Total Number of Subjects with Root Canal Fillings	206	188	28	160	394
Percentage of Subjects with RFs	41%	37%	33%	38%	39%
SD	49	48	47	49	49
SE of Mean	2.195	2.159	5.128	2.38	1.5

Table 17 Number of subjects with root canal filling with root canal fillings in at least one tooth, grouped by DM status

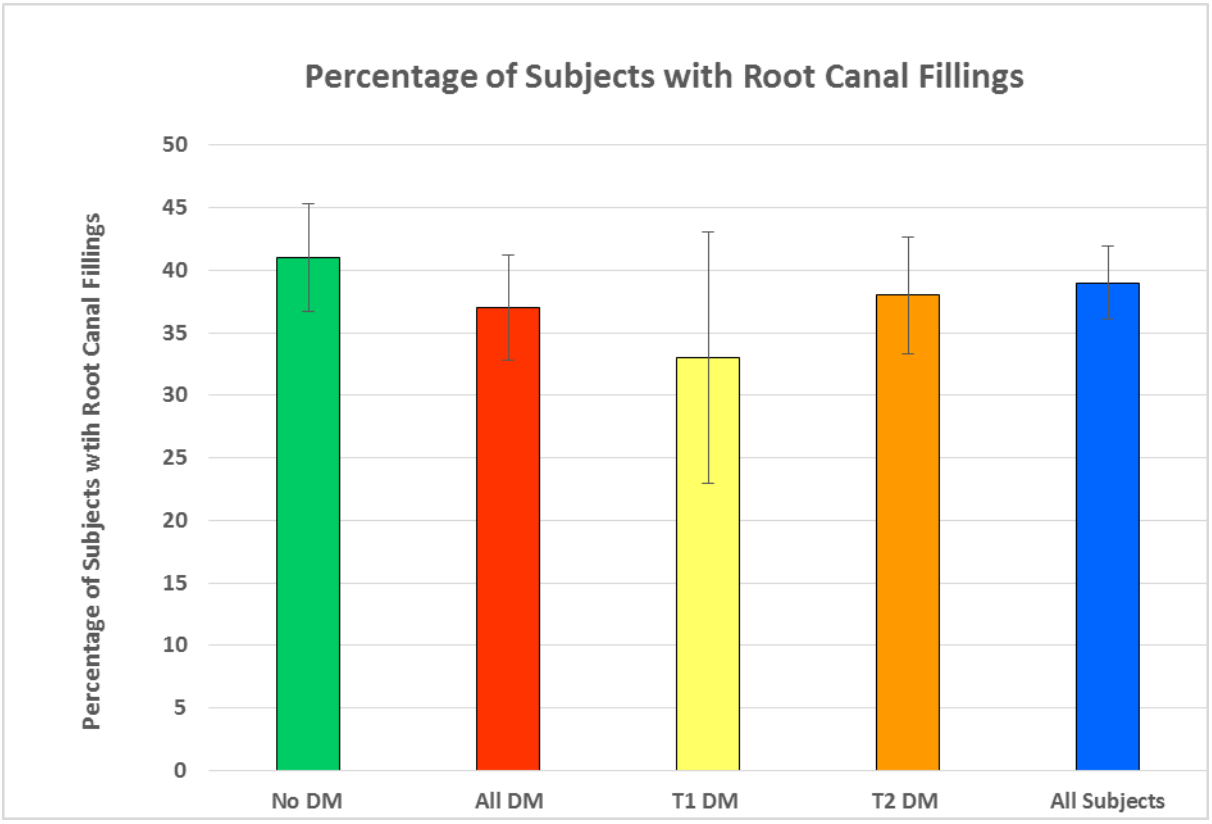

Figure 15 Percentage of subjects with root canal fillings grouped by DM status with 95% confidence intervals based on standard error of the mean

4.14 Number of Teeth with Root Canal Fillings and Periapical Periodontitis

The mean number of teeth with root canal fillings that also have periapical periodontitis, arranged by each subgroup, is displayed in Table 18 and Figure 16. No statistically significant differences were found between the groups for this measurement. In the All DM group the mean number of teeth with root canal fillings and periapical periodontitis was 0.21 compared with 0.26 in the No DM group (p = 0.206). Comparison between the T1 DM and T2 DM subgroups identified means of 0.22 and 0.21 teeth respectively (p = 0.877).

	No DM	All DM	T1 DM	T2 DM	All Subjects
Total Number of Teeth	10,319	9,490	1,959	7,531	19,809
Total Number of Teeth with Root Fillings and PP	130	108	19	89	138
Mean Number of Teeth with Root Fillings and PP	0.26	0.21	0.22	0.21	0.24
SD	0.6	0.54	0.59	0.54	0.573
SE of Mean	0.027	0.024	0.063	0.026	0.018
High	4	3	3	3	4
Low	0	0	0	0	0

Table 18 Mean number of teeth with root canal fillings and periapical periodontitis grouped by DM status

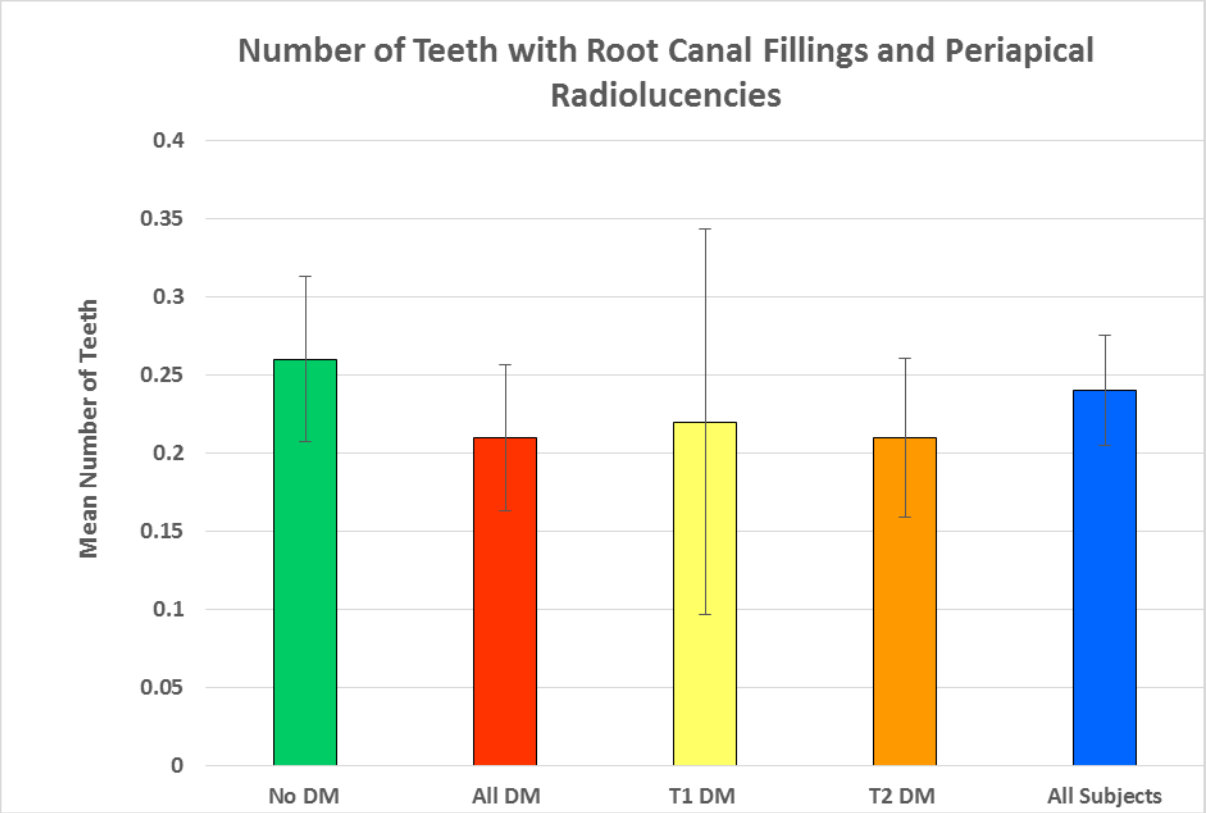

Figure 16 Mean number of teeth with root canal fillings and periapical periodontitis grouped by DM status with 95% confidence intervals based on standard error of the mean

4.15 Number of Subjects with Root Canal Fillings and Periapical Periodontitis

The percentage of subjects with one or more teeth with a root canal filling that also has concurrent periapical periodontitis, arranged by subgroup, is displayed in Table 19 and Figure 17. No statistically significant differences were found for this measurement between the different groups. In the All DM group, the percentage of subjects with at least one tooth that has both a root canal filling and periapical periodontitis was 16%, compared with 19% in the No DM group (p = 0.217). Comparison between the T1 DM and T2 DM subgroups for this measurement identified that 16% of subjects were affected in each group.

	No DM	All DM	T1 DM	T2 DM	All Subjects
Number of Subjects	503	503	85	418	1006
Total Number of Subjects with Root Fillings and PP	96	82	14	68	178
Percentage of Subjects with Root Fillings and PP	19%	16%	16%	16%	18%
SD	39	37	37	37	38
SE of Mean	1.76	1.649	4.047	1.807	1.206

Table 19 Percentage of subjects with one or more teeth with a root canal filling and concurrent periapical periodontitis, grouped by DM status

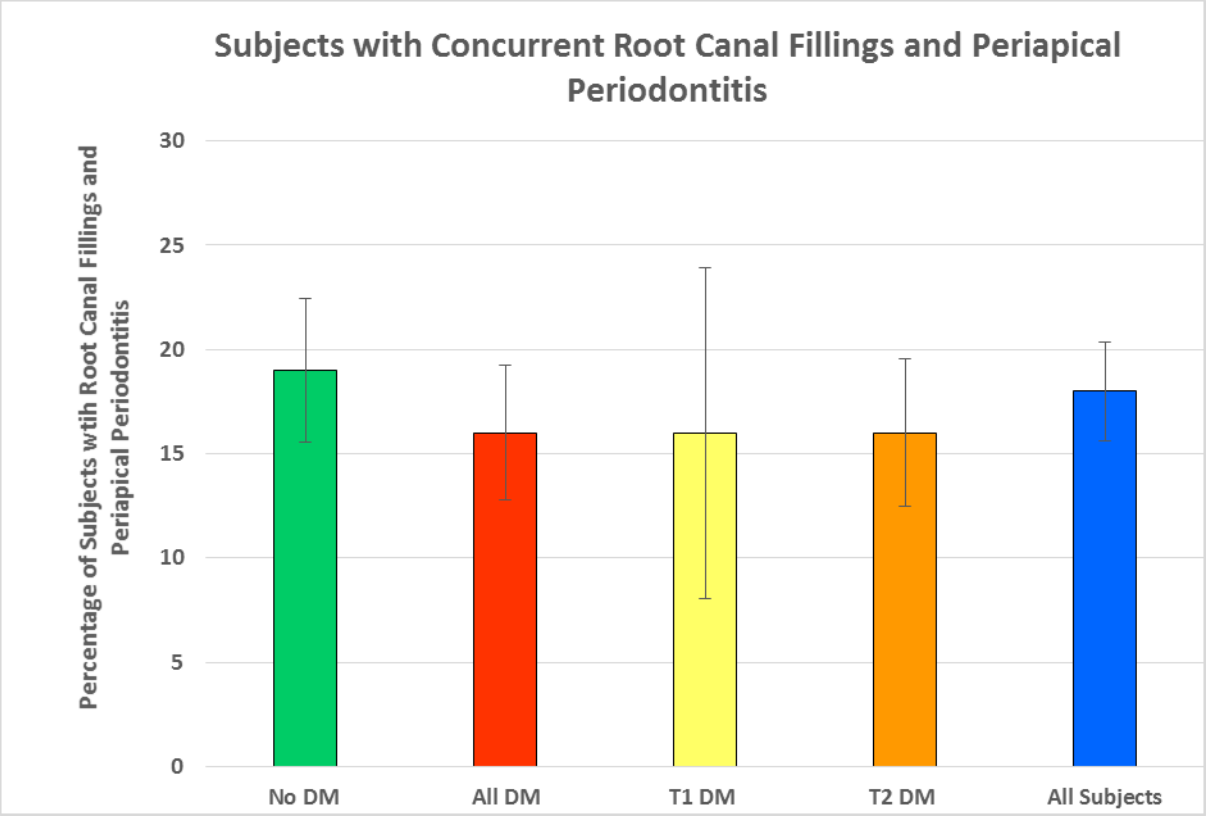

Figure 17 Percentage of subjects with one or more teeth with root canal fillings and concurrent periapical periodontitis, grouped by DM status with 95% confidence intervals based on standard error of the mean

4.16 Glycaemic Control and Dental Parameters

The results for the main radiographic measurements for the All DM group have been split depending on different levels of glycaemic control, assessed by HbA1c test values. The results of these are displayed in Table 20 and Figures 18, 19, 20, and 21. The All DM group has been split into two subgroups four times, at the HbA1c levels of 7.5, 8, 8.5, and 9%. Results are shown for mean number of teeth with PP, presence of horizontal alveolar bone loss, mean number of teeth, and mean number of root canal fillings.

The mean number of teeth with PP when the All DM group is split by HbA1c into two groups at the 7.5, 8, 8.5, and 9% points is displayed in Figure 18. The mean number of teeth with PP is greater in the group with a higher HbA1c level at each separation point; 7.5, 8, 8.5, and 9%. The subgroup with HbA1c equal or above 8.5% had a mean of 1.53 teeth with PP, which was statistically significantly greater than the subgroup below 8.5%, which had a mean of 1.03 teeth with PP ($p = 0.036$). The subgroup with HbA1c equal or above 9% had a mean of 1.8 teeth with PP, which was statistically significantly greater than the subgroup below 9%, which had a mean of 1.00 teeth with PP ($p = 0.002$).

HbA1c	Mean Number of Teeth with PP	Presence of Horizontal Bone Loss	Mean Number of Teeth	Mean Number of Teeth with Root Fillings
<7.5 (N=217)	1.11 (0.12)	0.51 (0.03)	18.17 (0.62)	0.96 (0.11)
=>7.5 (N=216)	1.23 (0.18)	0.44 (0.03)	19.60 (0.63)	0.69 (0.09)
P	0.580	0.110	0.110	0.540
<8 (N=264)	1.07 (0.11)	0.52 (0.03)	18.34 (0.55)	0.89 (0.10)
=>8 (N=169)	1.33 (0.12)	0.41 (0.04)	19.73 (0.74)	0.72 (0.10)
P	0.36	0.03	0.13	0.22
<8.5 (N=311)	1.03 (0.10)	0.52 (0.03)	18.15 (0.52)	0.87 (0.09)
=>8.5 (N=122)	1.53 (0.29)	0.36 (0.04)	20.75 (0.84)	0.70 (0.12)
P	0.036	0.003	0.009	0.240
<9 (N=339)	1.00 (0.09)	0.5 (0.03)	18.24 (0.50)	1.55 (0.08)
=>9 (N=94)	1.8 (0.37)	0.36 (0.05)	21.19 (0.90)	1.17 (0.12)
P	0.002	0.014	0.005	0.134

Table 20 Glycaemic control levels compared against mean number of teeth, presence of horizontal alveolar bone loss, mean number of teeth, and mean number of teeth with root canal fillings. Standard error of the mean is shown in parentheses for each value. Presence or absence of statistical significance between groups is indicated with *p* values displayed directly below each HbA1c subgroup.

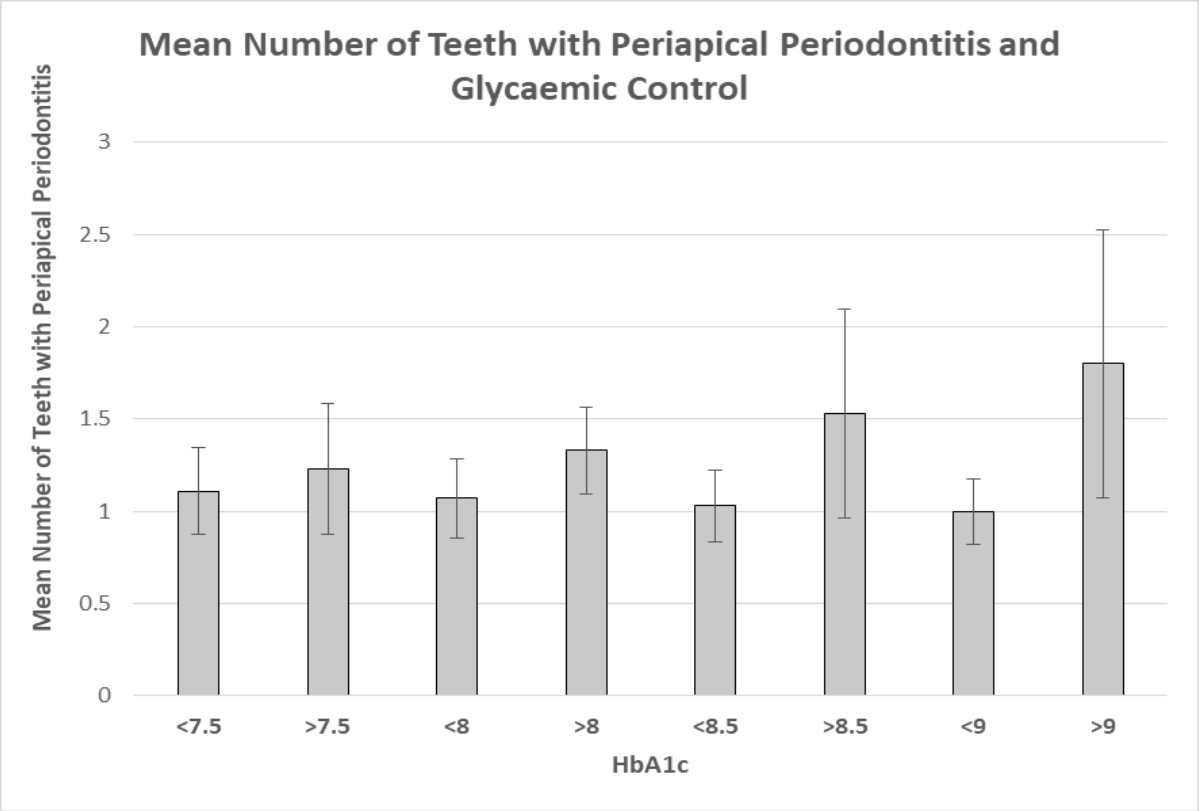

Figure 18 Mean number of teeth with periapical periodontitis when comparing subgroups separated at different HbA1c levels, with 95% confidence intervals based on standard error of the mean

The percentage of subjects with horizontal bone loss when the All DM group is separated by HbA1c is displayed in Figure 19. The percentage of subjects with HABL is less in the group with a higher HbA1c at every separation point. The subgroup with HbA1c levels equal or above 8% had 41% subjects with HABL, which was statistically significantly less than the subgroup with HbA1c levels below 8%, where 52% were affected ($p = 0.03$). The subgroup with HbA1c levels equal or above 8.5% had 36% with HABL, which was statistically significantly less than the subgroup with HbA1c levels below 8.5%, where 52% were affected ($p = 0.003$). In the subgroup separated by HbA1c at 9%, 36% of the subgroup equal or above 9% had HABL loss, which again was statistically significantly less than those with HbA1c below 9%, where 50% were affected ($p = 0.05$).

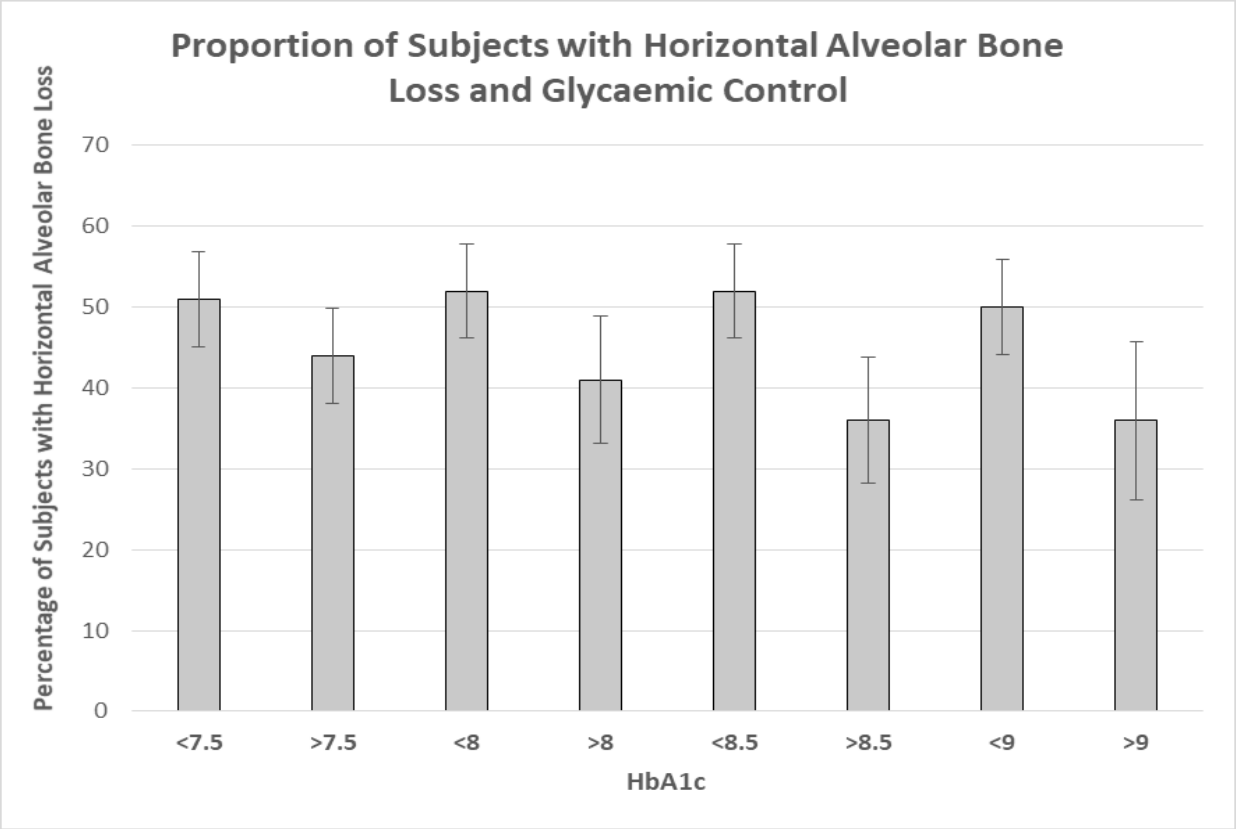

Figure 19 Percentage of subjects with horizontal alveolar bone loss when comparing subgroups separated at different HbA1c levels, with 95% confidence intervals based on standard error of the mean

The mean number of teeth present when the All DM group is separated by HbA1c levels is displayed in Figure 20. The mean number of teeth was greater in the group with a lower HbA1c at every separation point. The subgroup with HbA1c levels below 8.5% had a mean of 20.75 teeth, which was statistically significantly greater than the subgroup with HbA1c levels equal to or greater than 8.5%, which had a mean of 18.15 teeth ($p = 0.009$). The subgroup with HbA1c levels below 9% had a mean of 21.19 teeth, which was statistically significantly greater than the subgroup with HbA1c levels equal to or greater than 9%, which had a mean of 18.24 teeth ($p = 0.005$).

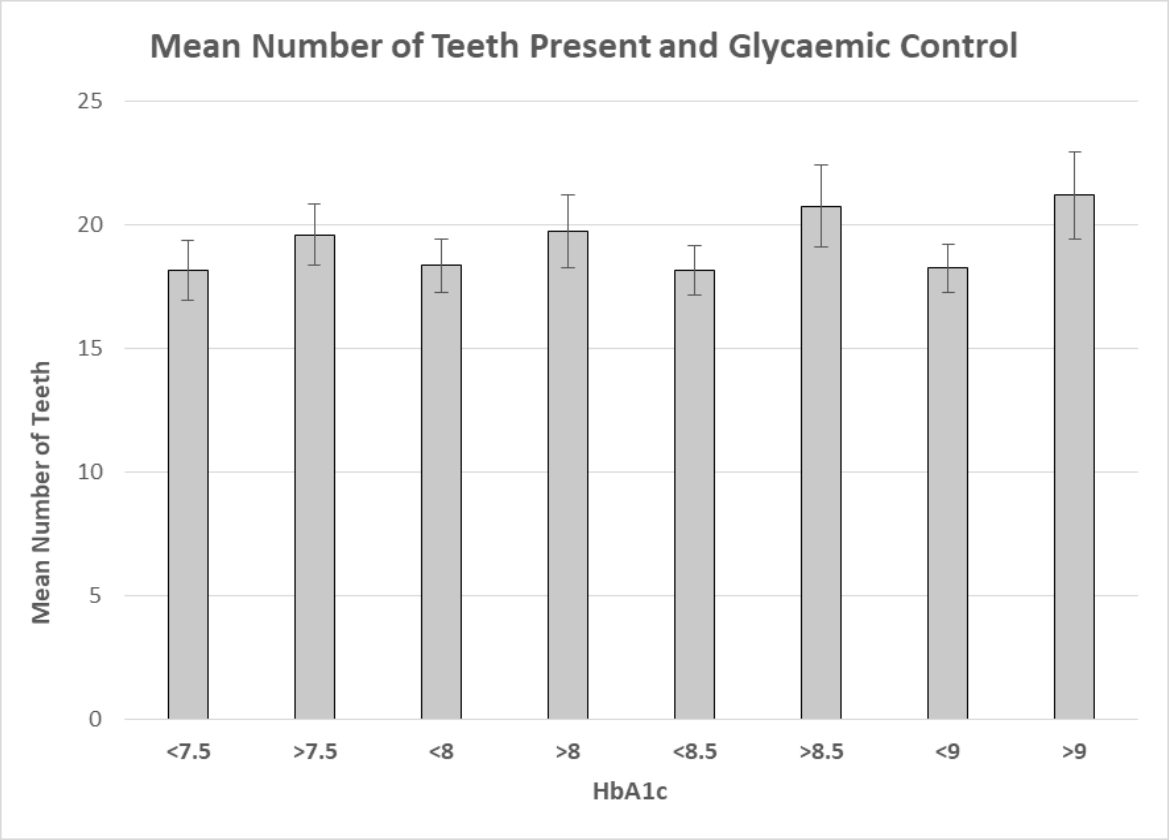

Figure 20 Mean number of teeth present when comparing subgroups separated at different HbA1c levels, with 95% confidence intervals based on standard error of the mean

The mean number of teeth with root fillings present when the All DM group is separated by HbA1c levels is displayed in Figure 21. The mean number of teeth with root fillings was greater in the group with a lower HbA1c at every separation point, although this was not statistically significant at any stage. The subgroup with HbA1c equal or above 7.5% had a mean of 0.69 teeth with root fillings, which was less than the subgroup below 7.5%, which had a mean of 0.96 teeth with root fillings ($p = 0.54$). The subgroup with HbA1c levels equal or above 9% had a mean of 1.17 teeth with root fillings, which was again less than the subgroup below 9%, which had a mean of 1.55 teeth with root fillings ($p = 0.134$).

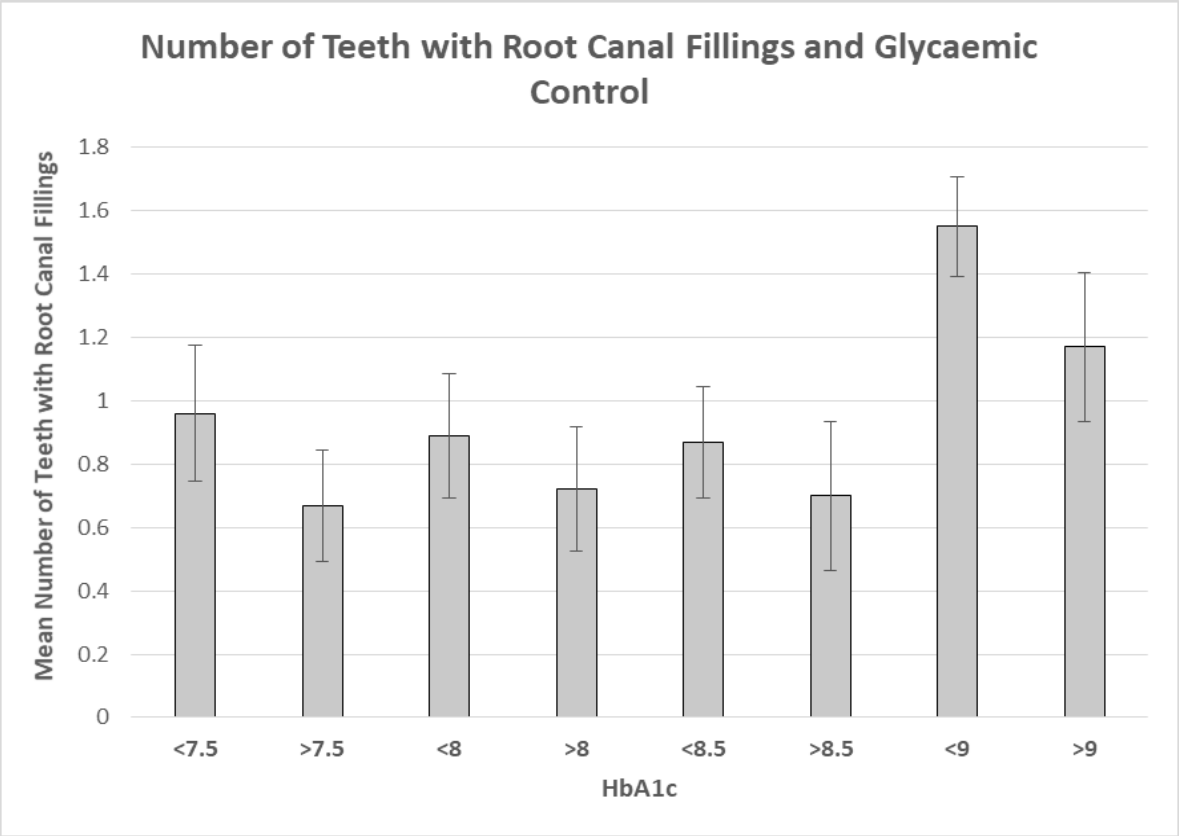

Figure 21 Mean number of teeth with root canal fillings when comparing subgroups separated at different HbA1c levels, with 95% confidence intervals based on standard error of the mean

4.17 Multiple Linear Regression Analyses

Separate multiple linear regression analyses were undertaken for the dependent variables; mean number of teeth with PP (Tables 21 and 22), and prevalence of subjects with PP (Tables 23 and 24).

4.17.1 Mean Number of Teeth with Periapical Periodontitis

A multiple regression model was run to predict the mean number of teeth with PP, from the variables; age, horizontal alveolar bone loss, number of teeth, subjects with DM, and number of teeth with root canal fillings.

The values used to determine how well the regression model fits the data are displayed in Table 21. The *R* value of 28.5% does not indicate a high level of prediction. The R^2 value indicates the proportion of variance in the dependent variable; mean number of teeth with PP, which can be explained by the independent variables; age, horizontal alveolar bone loss, number of teeth, subjects with DM, and number of teeth with root canal fillings. The independent variables explain 8.1% of the variability in the dependent variable; mean number of teeth with PP. The *F*-ratio tests whether the overall regression model is a good fit for the data. Therefore, this regression model is a good fit for the data as the independent variables statistically significantly predict mean number of teeth with PP ($F = 17.67$, $p < 0.000$).

	R	R-square	Adjusted R-square	F	Regression *p* value
Model Summary	28.5%	8.1%	7.7%	17.67	<0.000

Table 21 Model summary for multiple linear regression analysis with mean number of teeth with PP as the dependent variable

Table 22 shows that the independent variables; horizontal alveolar bone loss ($p <$ 0.000), subjects with DM ($p = 0.015$), and number of teeth with root canal fillings ($p <$ 0.000) added statistically significantly to the prediction.

Variable	Regression *p* value
Age	0.123
Horizontal Alveolar Bone Loss	<0.000
Number of Teeth	0.482
Subjects with DM	0.015
Number of Teeth with Root Canal Fillings	<0.000

Table 22 Independent variable *p* values for multiple linear regression analysis with mean number of teeth with PP as the dependent variable

4.17.2 Prevalence of Subjects with Periapical Periodontitis

A multiple regression model was made to predict the prevalence of subjects with PP from the variables; age, horizontal alveolar bone loss, number of teeth, subjects with DM, and subjects with root canal filling.

The values which are used to determine how well the regression model fits the data is displayed in Table 23. The *R* value of 38.6% does not indicate a high level of prediction. The R^2 value indicates the proportion of variance in the dependent variable, prevalence of subjects with PP, which can be explained by the independent variables; age, horizontal alveolar bone loss, number of teeth, subjects with DM, and subjects with root canal filling. These independent variables explain 14.9% of the variability in

prevalence of subjects with PP. The *F*-ratio tests whether the overall regression model is a good fit for the data. This regression model is therefore a good fit of the data as the independent variables statistically significantly predict mean number of teeth with PP ($F = 35.04$, $p < 0.000$).

	R	R-square	Adjusted R-square	F	Regression *p* value
Model Summary	38.6%	14.9%	14.5%	35.04	<0.000

Table 23 Model summary for multiple linear regression analysis with prevalence of subjects with PP as the dependent variable

The independent variables of horizontal alveolar bone loss ($p < 0.000$), and subjects with root canal filling ($p < 0.000$) added statistically significantly to the prediction, displayed in Table 24.

Variable	Regression *p* value
Age	0.503
Horizontal Alveolar Bone Loss	<0.000
Number of Teeth	0.169
Subjects with DM	0.254
Subjects with Root Canal Filling	<0.000

Table 24 Independent variable *p* values for multiple linear regression analysis with prevalence of subjects with PP as the dependent variable

5. DISCUSSION

This investigation aims to assess the relationship between periapical periodontitis prevalence and the presence of DM. It further aims to evaluate whether the control of DM has an effect on PP prevalence. The variables of number of teeth, horizontal alveolar bone levels, and number of root canal fillings were also assessed as part of the investigation.

The main findings from the results of this investigation were that the subjects with DM had the greater mean number of teeth with periapical periodontitis of 1.14, compared with 0.87 in non-diabetic subjects (p = 0.021). Previous studies have also found a higher mean number of teeth with PP in subjects with DM, so the results of this study have similarities with existing published studies (Appendix 1).

Other statistically significant differences between subjects with DM and without DM were found for the variables; number of teeth, and horizontal bone loss. The mean number of teeth per patient was 18.57 in the diabetic group and 20.51 in the control group (p = 0.003).

When glycaemic control was assessed in diabetic subjects, statistically significant results were found for prevalence of PP by tooth, when groups were split at HbA1c levels of 8.5% and 9%. There is a paucity of data assessing prevalence of PP in relation to glycaemic control, although a study by Sanchez-Dominguez (2015) also found a greater prevalence of PP in patients with higher HbA1c values (87).

5.1 Radiographs

DPRs were selected as the method for observing disease prevalence in this study for a number of reasons. They give a complete image of the whole dentition, dental restorations, alveolar bone levels, and the surrounding periradicular tissues. This is beneficial as it allows for periapical radiolucencies to be assessed along with the majority of other relevant dental findings. Another advantage of a DPR giving an image of the entire dentition is that it will allow full analysis of prevalence. An image which does not display all teeth could allow teeth which have PP to not be assessed, leading to an underestimate in disease prevalence. These reasons may be a reason why DPRs have been frequently used in studies measuring PP prevalence (Appendix 1).

DPRs have a focal trough which is designed with the aim of capturing images of the jaws and teeth, but adjacent structures can obscure or alter the appearance of some features. This can be particularly evident in the anterior maxilla and mandible in the region of incisor teeth. This could have a negative effect on the investigation results and it is possible that false positive or negative results could be recorded in these regions. Matching cases with controls should mean any effect this may have had would be present in both groups, and should have minimal effect on differences between the groups.

Periapical radiographs have been shown to be more sensitive than DPRs for assessing the presence of periapical radiolucencies (75), but these were rarely available for a patient's entire dentition. Use of periapical radiographs would therefore not have allowed assessment of the number of teeth in each subject's dentition. Teeth with no

radiographs may also have had undetected PP, but this would be missed from the analyses. Assessment of horizontal alveolar bone loss may also be underdiagnosed if limited numbers of periapical radiographs are used.

All radiographs taken in the UK are required to meet the justification standards of IR(ME)R (Ionising Radiation (Medical Exposure) Regulations). All DPRs that have been taken and stored on the PACS system are therefore required to be justified following a clinical assessment. The Faculty of General Dental Practitioners has published a selection criteria for the use of DPRs (88), this is outlined in Appendix 2.

Adherence to IR(ME)R regulations and the suggested criteria for panoramic radiography will therefore have introduced a degree of selection bias. Patients who have had DPRs are likely to fall into categories of specific conditions, where this radiographic investigation is clinically indicated. It will therefore not represent a random selection taken from the observed population. In this case of the current study, the DPRs were most likely taken to inform for assessments in a secondary care setting. Common justifications for DPRs in secondary care include investigations for oral surgery, periodontal disease, and dental caries (in patients unable to tolerate alternative radiographs). These factors could lead to biases related to age and co-morbidities. Assessment for removal of third molars is a common justification for DPRs. A study in England and Wales found the mean age of patients having surgery for third molars has increased from 25.5 years in 1989/1990 to 31.8 years in 2009/2010 (89). Both of these mean ages are lower than would be expected for a random sample of a population. Conversely, increasing age has been found to be significantly linked with the presence of periodontal disease (90,91). DPRs taken for assessment of periodontal health may

therefore preselect an older population. In this study subjects were age-matched in an attempt to reduce bias on age, but it was not possible to reduce bias based on radiographic justification.

5.1.1 Sample Size

The largest available sample of subjects with DM and a DPR was selected to attempt to reduce the margin of error and increase the confidence level. The sample size of 1,006 for this investigation was larger than the majority of previous similar studies, with the exception of Fouad and Burleson (2003) who had a sample of 5,244. However, only 242 of this sample were subjects with DM, compared with 503 in this investigation. It is challenging to obtain data on both the PP and DM status of patients, as both are chronic conditions which may develop over many years and in the absence of symptoms. Furthermore, monitoring of the progression of these diseases requires justification and is expensive. These factors make obtaining large sample sizes challenging and may account for the paucity of prospective studies in this area.

A cross-sectional study by Sanchez-Dominguez et al (87) reviewed the prevalence of PP in 83 patients with type 2 DM and compared this against their glycaemic control, measured with HbA1c levels. This study assessed radiographic periapical status based on DPRs. DPRs were also used to assess the periapical and endodontic status of type 2 DM patients in a cross-sectional study by Lopez-Lopez et al (92). This study had a sample of 50 subjects with type 2 DM and 50 age-and sex-matched control subjects with no history of DM. A retrospective cohort study by Britto et al (93) investigated the prevalence of radiographic periradicular radiolucencies in patients with and without

diabetes. This involved evaluation of the records of 30 subjects with DM and 23 control subjects. All records included a full-mouth series of periapical and panoramic radiographs. Marotta et al (94) also investigated the prevalence of PP and endodontic treatment in subjects with type 2 DM in a cross-sectional study. Their investigation had a sample of 30 subjects with type 2 DM and 60 control subjects who were assessed through full-mouth periapical and panoramic radiographs.

These study designs have similar features to the current investigation and all share the DPR as the primary method for detection of PP. Supplementing DPRs with full-mouth periapical radiographs would be beneficial as it increases the sensitivity for detecting PP, but would seldom meet justification under IR(ME)R regulations.

The size of the sample for this current investigation, with 503 DM subjects and 503 control subjects, is larger than the similar studies that have been previously undertaken. Having a larger sample size should increase the level of confidence in the results, reducing the risk of incurring type I (incorrect rejection of the null hypothesis) and type II (incorrect retention of a false null hypothesis) errors.

5.1.2 Inclusion Criteria

When a radiograph was deemed to be of inadequate quality for analysis, that subject was withdrawn. It was not possible to assess whether withdrawn radiographs were from cases or controls until after the radiographic analyses had been completed, as a result of the anonymization, which could have resulted in a difference in size between the two groups. Following exclusion of cases and controls both groups remained the same size,

with 503 subjects in each. The excluded cases were of a similar age, sex and number and so this should have minimal effect on the data overall.

This investigation focused on a subpopulation of the Tayside region in Scotland, United Kingdom, where there is currently good availability to advanced medical and dental care. Similar studies which have looked at prevalence of PP in patients with DM have focused their investigations in specific institutions and various geographic regions, including Estacio de Sa University, Brazil (94); University of Florida, USA (93); University of Barcelona, Spain (87, 92); and University of Seville, Spain (95). Geographic location has the potential to have an influence on the general health of subjects through a variety of factors (96). Living in different regions can affect subjects through variation in the population demographic (e.g. genetic factors, age distribution, sex distribution, prevalence of other diseases), the physical environment (e.g. temperature, altitude, pollution) and or the socio-economic setting (e.g. access to healthcare and services, income and employment status, prevalence of behavioural risk factors, nutrition). Any of these geographic and demographic factors could have some effect on the prevalence of PP in a group of subjects and so results should be interpreted with caution.

Positive relationships have been indicated between PP and a number of systemic factors including coronary artery disease (97, 98), hypertension (98, 99), smoking (100), inherited coagulation disorders (101), chronic liver disease (102), post-menopausal bone density (103), and low-birth-weight preterm births (104). An increased prevalence of related systemic conditions, or other unidentified genetic, environmental and socio-economic confounding factors, could therefore have an effect on the prevalence of PP. Subject data related to these factors was not available in this investigation, largely as a

result of the retrospective design. Construction of linked patient databases for each individual disease process could be beneficial for future research to assess any co-morbidities that may confound results.

5.2 Methodology

This investigation was designed as a retrospective cross-sectional case-controlled study. The advantage of this study design was that there was data available for multiple variables related to the subjects, allowing comparison of many factors. It also allowed for a large number of subjects to be included. The retrospective data collection incurred limitations related to timing of HbA1c measurements.

Assessor 1 displayed a very high level of intra-observer agreement with Cohen's kappa coefficients ranging from 0.939 to 0.986 (Table 23) (105). These kappa coefficient scores are high and it is possible some memory of assessing the DPR previously influenced this.

The DPRs were assessed independently by two assessors. Inter-observer agreement between assessors was calculated based on their analyses of 442 radiographs. The Cohen's kappa coefficient results show a high degree of inter-observer agreement for all variables, ranging from 0.873 to 0.996 (Table 24). For some categories, such as number of teeth and number of teeth with root canal filling, it is understandable that there would be a very high level of agreement between assessors as it is largely a counting exercise and disagreement would not be expected. The agreement for variables such as horizontal alveolar bone loss and number of teeth with periapical periodontitis, there is

slightly more interpretation involved by the assessors. This is reflected in lower kappa coefficients for these variables, with a kappa score of 0.873 for horizontal bone loss. This is still a high kappa coefficient which indicates a very high level of inter-observer agreement. Further reasons for a high level of agreement may include use of a digital measuring tool, a simplified clear criteria for each variable, and thorough calibration of assessors.

A study by Marotta et al also used two reviewers, with a kappa coefficient of 0.84 showing the inter-observer agreement for detection of PP. This study used the Strindberg criteria for assessing the absence/presence of PP. A study by Segura-Egea et al used one observer who used the 'periapical index' (PAI) (74) with calibration and intra-observer kappa coefficients of 0.71 and 0.77 respectively. Although there is not a specific kappa coefficient value that has been agreed to be acceptable, the arbitrary guidelines available consider a score over 0.75 as an excellent level of agreement (106). The kappa coefficient scores for all variables within the current investigation would be considered at an excellent level of agreement.

DPRs provide an image of the jaws that should allow for all teeth which are present to be identified. It is possible that unerupted teeth, supernumeraries, or crowded dentitions could have an effect on the number of teeth identified in a DPR. Anterior teeth may be less clear on some DPR images as this is a region where other anatomical structures may be superimposed. Similarly, all root canal fillings should be radiographically evident as root filling materials are radiopaque. There may be cases where an incomplete root canal treatment was present and the inter-visit medicament may not have been as evident on the radiograph. The kappa coefficient inter-observer scores of

the current investigation were 0.986 for identifying number of teeth and 0.984 for number of teeth with root fillings reflect the near perfect agreement on these variables.

These inter-observer agreement scores are higher than for previous similar studies, showing the study used a repeatable method, although previous studies also have values that are acceptable in research. The higher values in the current investigation when assessing PP were likely most affected by the modification to the PAI scoring system used, which only records presence or absence of PP, rather than grading it on a 5 point scale.

DPRs have been shown to have lower sensitivity at detecting PP than periapical radiographs and cone-beam CT scans. Sensitivity refers to the ability of the test to detect the disease process, in this case PP, when it is present. In a study by Estrela et al (75) the overall sensitivity was found to be 0.28. Use of a DPR therefore will significantly underestimate PP prevalence and is a major limitation of this radiological investigation. Specificity in the same study was found to be 1.00, which was combined with positive predictive values and negative predictive values to give an indication of accuracy. The overall accuracy for DPRs was found to be 0.54, compared to 0.7 when using a periapical radiograph. Periapical radiographs would therefore be preferable when assessing presence of PP from a radiograph.

HbA1c has been used as a measure of glycaemic control in a similar study which focused on type 2 DM and PP (87). It is considered a better indicator than circulating blood glucose because the results indicate the level of control over a longer duration of time. A number of studies investigating an association between periodontal disease and

DM have also used this as their measurement (107-109). Progression of radiographically detectable PP often develops slowly, as does resolution and healing. It has been recommended that annual radiographs are taken for up to four years following endodontic treatment to monitor for signs of radiographic healing (110)(111). Later healing of PP has been identified over 20 years following endodontic treatment in some studies (112, 113), although these were associated with teeth which had overextended root canal fillings.

The slow progression and healing of PP would ideally require data on a subject's glycaemic control over a similar period of time. It is not possible to define a standard period of time for disease progression and healing, but it was considered in this investigation that data collected over a longer time period may be more representative of the variation in healing rates across a population.

HbA1c readings for DM subjects which had been taken between 2007 and 2013 were therefore included in the analysis. The DPRs which were assessed had been taken between 2007 and 2013. It would have been preferable to only include HbA1c readings taken prior to the date of the radiographic investigation as they would have most relevance, but it was not possible to remove HbA1c readings based on date from the database used. The calculation for the mean of the HbA1c readings could therefore include some values which were recorded after a DPR was taken. Similarly, HbA1c readings taken prior to 2007 were not included, which could have further affected the mean HbA1c values.

There is an estimated 5% of the population of Scotland with undiagnosed DM. If the control subjects represent the local population, there is a likelihood that undiagnosed DM subjects with unknown glycaemic control will be present within their group. A prospective study would have been able to eliminate some of these factors, but would have been less feasible as a result of the large sample size and long follow-up period required.

5.3 Findings

The study included 1006 subjects in the final analyses, 503 with a diagnosis of DM and 503 without DM. The prevalence of type 2 DM was higher for males than females and this is consistent with the literature (85).

A number of previous studies have been undertaken with some similar protocols and outcomes. The results of this investigation have been compared with these previous studies and a summary is outlined in Appendix 1. These studies are all reviewed in detail with regards to the various outcomes, in relevant subsections of this thesis. These studies all were either retrospective cohort or case-control studies. Data for these types of studies is more readily available, but it is a lower level of evidence than a prospective design would provide.

5.3.1 Age

The mean age for the investigation was 59.15 years (SD 15.37), which was close to the mean for both the non-diabetic and diabetic group which were 59.07 years and 59.23

years respectively. However, when the diabetic group was separated by type of diabetes, the mean ages were 41.79 years for the type 1 DM group and 62.78 years for the type 2 DM group. The younger age of the type 1 DM group and the older age of the type 2 DM group could be aligned to the common ages for diagnosis and onset of each type of diabetes (13,114). Type 1 and type 2 DM have similarities, but a different pathogenesis and different risk factors, it may therefore have been more appropriate to completely separate each type of diabetes for analysis. In this study all available diabetic subject cases were included and data was analysed both considering DM as a group, and separating it into the sub-types. It is possible that amalgamation of results for the two DM subgroups is not appropriate. In this investigation, analysis between the DM subgroups should provide data on any significant differences.

5.3.2 Number of Teeth

The number of teeth that subjects had was a measurement which could relate to a number of relevant factors. One of the treatment options for patients with PP is for extraction of an infected tooth. It is possible that subjects with a lower number of teeth may have had teeth removed as a result of PP. This could mean that there will be an underestimation of PP prevalence in patients with fewer teeth. Similarly, it has been shown that PD can result in an increased rate of tooth loss (115). A patient with PD could have lost teeth as a result of previous PD, rather than PP. Making an assumption that teeth are largely lost as a result of PP is therefore incorrect. The risk of developing either of these pathological processes is greater with increasing age (116).

All people do not have the same number of permanent teeth with the majority ranging from 28 to 32. This is largely because of the variation in presence or absence of third molars. Hypodontia has been defined as failure of development of one or more permanent teeth, other than the third molar. It has been reported to affect between 2.2-10.1%, depending on the population (117). In this study, the decision was taken to include all teeth. In subjects who have multiple missing teeth, it is not always clear from the morphology whether a retained posterior tooth is a second or third molar. Edentulous subjects were also included in this study, as the absence of teeth could represent a history of PD or PP, as it may have led to their removal. Unerupted teeth were not included because without being exposed to the oral environment, it would not have been possible for them to develop PD or PP.

A statistically significant difference was found between the mean number of teeth in the No DM group and the All DM group, which were 20.51 and 18.87 respectively (p = 0.003). A study by Lopez-Lopez et al found a similar pattern in number of teeth per patient, with a mean of 21.9 teeth for diabetic patients and 24.6 teeth for controls (P = 0.012) (92). This pattern was also found by Segura-Egea et al, where diabetic patients had a mean of 21.6 teeth, compared with 25.4 teeth in controls (95). Both these studies had a greater number of teeth in each group than the current investigation. This could be a result of these studies having a younger patient sample, or geographical factors such as ethnic variation, affordability of treatment, or differences in treatment protocols, such as extractions for orthodontics treatment.

Statistically significant differences were also found between the mean number of teeth in the DM T1 group (23.05) when compared with either the No DM group (20.51, p =

0.015) or the DM T2 group (18.02, $p = 0.000$). The higher number of teeth in the DM T1 group most likely relates to the younger mean age of subjects (23.05), as they have had less time to develop disease processes that could lead to tooth loss.

When comparing the mean number of teeth in the DM T2 and No DM groups, the latter had a statistically significant greater number of teeth (20.51). This is expected as the DM T2 group has a greater risk of developing PD, PP, and caries which can all lead to tooth loss, and PP, which can also lead to tooth loss (118, 119). A study by Lopez-Lopez et al found a similar pattern in number of teeth per patient, with a mean of 21.9 teeth for diabetic patients and 24.6 teeth for controls ($P = 0.012$) (92). This pattern was also found by Segura-Egea et al, where diabetic patients had a mean of 21.6 teeth, compared with 25.4 teeth in controls (95).

The subjects were stratified into groups by ages and this was plotted on a graph against number of teeth (Figure 6). A steady decline in the mean number of teeth is evident as age increases in both the diabetic and non-diabetic group. The mean age for number of teeth remained above 26 for both groups until age 38, but following that age, there is an indication that non-diabetic subjects retained more teeth in each age group. The only age group where a statistically significant difference was found was 69–78 years.

5.3.3 Prevalence of Periapical Periodontitis

The mean prevalence of PP detected in this study was 42.74% when measured by number of patients with at least one tooth affected, and 1.00% when measured as the mean overall number of teeth affected. These results are lower than some studies,

including a study by Segura-Egea et al which looked at the prevalence of PP in a subpopulation in Spain by assessing periapical radiographs. This study found a mean prevalence of PP as 69% per patient, and 5.2% for teeth affected (120). A study by Marotta et al in a Brazilian subpopulation found an overall PP prevalence by teeth of 12.9% (94). Lopez-Lopez et al, in a further Spanish subpopulation, found the prevalence of PP to be 58% per patient (92). A further study has looked at the Tayside region subpopulation and assessed PP prevalence via CBCT scans. This study found the prevalence of PP to be 30.1% by subject and 5.8% by teeth (43). A greater prevalence may have been detected because periapical radiographs were used which are more sensitive at detecting PP. The modified PAI scale used in this investigation had a higher threshold for recording disease, which may underestimate disease prevalence.

When considering PP as a disease process related to DM, it is appropriate to look both at prevalence by patient, but also by tooth as it is possible that subjects in a particular sub-group will have a greater or lesser number of teeth with PP. When considering prevalence of PP by individual subjects no statistical differences were found between groups. Percentage of subjects with at least one tooth with PP were 44% in the DM group, 42% in the No DM group, 44% in the T1 DM group, and 45% in the T2 DM group.

Prevalence by tooth gives an indication of overall presence of PP including all teeth in the sample studied. When PP prevalence by tooth was assessed in the No DM and DM groups, a significant difference was found with a prevalence of 0.87% (95% CI: 0.12), and 1.14% (95% CI: 0.2), respectively. This demonstrates that a greater number of teeth were identified with PP in the DM group. It is also possible that PP prevalence is

affected by an increased risk of pulpal disease developing, an impaired immune response to microbial infection, and impaired healing capability following treatment. When assessed as sub-groups, the mean number of teeth affected by PP in the type 1 DM and type 2 DM groups were 1.59% and 1.03%, although these differences were not found to be statistically significant.

In a study by Segura-Egea et al (95) a higher prevalence of at least one tooth with PP was found in diabetic patients (81%) when compared with controls (58%). It also found diabetics had PP in 7% of their teeth, compared with 4% of teeth with non-diabetics. This study looked at periapical radiographs, which have been shown to have a greater sensitivity for detection of PP than DPRs (75). This study used the original periapical index (74) when assessing the presence of PP, which includes scoring small changes in the bone structure rather than only when well defined radiolucencies are present. These factors may account for the increased detection in prevalence for diabetic patients, when compared with the current investigation.

An increased prevalence of PP was found in a study by Lopez-Lopez et al (92) with 74% of diabetic patients having PP in one or more teeth, compared with 42% in the control group ($P = 0.002$). This study found a higher prevalence of PP in the diabetic group, than the current investigation, although there were similar findings for the control groups. These studies both used DPRs, although the original PAI scoring system was used in the study by Marotta et al, which may account for detection of a greater prevalence of PP.

The study by Marotta et al found that diabetic patients had PP in 15% of their teeth, compared with 12% in non-diabetic patients ($P = 0.05$) (94). This study used periapical radiographs and the original PAI scoring system, which may account for the considerably higher prevalence of PP by teeth. All patients in this study had full mouth periapical radiographs taken as part of an initial dental assessment, but for radiographs to be indicated it is likely pathology was either clinically evident or suspected, which could increase the likelihood of teeth having PP.

The current investigation found differences in prevalence of PP between patients with no diabetes and each different type of diabetes. The mean number of teeth with PP per patient was 1.59 in the group with type 1 DM and 1.03 in the group with type 2 DM, compared with 0.87 for patients with no diabetes. Although the diabetic groups appear to have a greater mean number of teeth with PP, none of these differences were found to be statistically significant.

5.3.4 Prevalence of Root Canal Fillings

The prevalence of teeth with root canal fillings overall in this study was 2.75%. A systematic review of 33 cross-sectional studies with 300,861 teeth found that 10% of teeth had root canal fillings (121), a higher number than found in this study. Other studies which have focused on prevalence in diabetic patients have found root filled teeth in between 2% and 2.8% when measured on a tooth level (94, 95) and 70% when measured by patient (92). The current investigation found an overall prevalence by patient of 37% in the DM, 33% in the type 1 DM group, and 38% in the type 2 DM group. There was no statistical difference between these groups, or when compared

with the control group prevalence by patient, which was 41%. Root canal treatment is most frequently undertaken to manage an inflamed pulp, a necrotic pulp, or in an elective treatment to facilitate restoration of a tooth. In cases of an inflamed or necrotic pulp, a periapical radiolucency can often be detected and indicates the localised inflammatory process occurring in the periradicular tissues (122). The treatment options to allow treatment of PP are largely root canal treatment or extraction of the affected tooth. It is therefore likely that many of the patients with root canal fillings had a history of PP related to these teeth.

5.3.5 Concurrent Endodontic-Periodontal Disease

The prevalence of concurrent endodontic-periodontal disease (CEPD) per tooth was 0.94% in this study. Although 185 teeth with CEPD were identified in the DM group compared with 118 in the control group, no statistical significance was found between these values. A review of the literature did not reveal any studies highlighting the prevalence of these combined disease processes in diabetic patients or populations in general. Concurrent endodontic-periodontal disease with communication can occur in patients who develop both conditions separately, which then communicate, or where one disease process causes the other. Evaluating concurrent endodontic-periodontal disease incurs the challenges of detecting both of these processes on radiographs. Clinical examination with periodontal probing depths and pulp tests could identify these combined disease processes prior to it being evident on a radiograph (123). Future studies assessing CEPD would benefit from clinical examination given the very low prevalence and challenging diagnosis.

5.3.6 Glycosylated Haemoglobin

Glycosylated haemoglobin levels are commonly used as a measure of average plasma glucose concentration, as the lifespan of a red blood cell is around 120 days. Guidelines on the management of DM recommend different medications, interventions and treatment, depending on HbA1c levels (124,125, 126). These guidelines recommend interventions in both types of diabetes at various HbA1c levels, including 6.5%, 7%, 7.5% and 9%. Since there is not a single defined level which represent poorly controlled disease, and severity of control may be significant, stratified analyses were undertaken with HbA1c levels at various measurements and these were compared against radiographic findings.

These stratified analyses split the diabetic group into two further groups to allow comparison of subjects with HbA1c levels below a value and those above that value. When the group were split at the values 8.5% and 9% statistically significant findings were observed for a number of radiographic findings. When the mean number of periapical radiolucencies were assessed it was found to be 1.03 below 8.5% and 1.53 at equal to or above 8/5% ($P = 0.036$). The same parameter was found to have a mean value of 1.00 below 9% and 1.8 at equal to or above 9% ($P = 0.02$). This suggests that patients with poorly controlled DM, where HbA1c levels are equal to or above 8.5%, have more teeth with AP than diabetic patients who have HbA1c levels below 8.5%. When reviewing the data for the presence of alveolar bone loss and for number of teeth statistically significant results were found at the levels of 8.5% and 9% for both parameters. The number of teeth was found to be 18.15 below 8.5% and 20.75 at equal to or above 8.5% ($P = 0.009$), and 18.24 below 9% and 21.19 at equal to or above 9%

(P = 0.05). The presence of alveolar bone loss was found in 52% of patients below 8.5% and 36% at equal to or above 8.5% (P = 0.003) and in 50% of patients below 9% and 36% at equal to or above 9% (P = 0.014). Both these findings may appear contrary to what would be have been expected from the other findings in this study and other studies. The lower mean age of the type 1 DM group was thought to be linked to this, as they will have had a shorter life over which to develop alveolar bone loss or have teeth extracted. However, when the results were stratified for age and diabetes type, almost no statistical differences were found. Only when alveolar bone levels were assess in the type 1 DM group at the HbA1c level of 9% were they found to be statistically significant (P = 0.014) with 25% of patients below HbA1c of 9% having alveolar bone loss, compared with 23% at equal to or greater than HbA1c of 9%. This small difference is unlikely to be clinically significant.

5.4 Multiple Regression Analyses

Multiple linear regression analyses were run to predict number of teeth with PP and prevalence of subjects with PP. The regression model predicting number of teeth with PP did this from the variables of age, presence of horizontal alveolar bone loss, number of teeth, subjects with DM, and number of teeth with root canal fillings. These variables significantly predicted the number of teeth with PP $F(5, 1000) = 17.67$, p, 0.0005, $R2$ = 0.081. The variables of subjects with DM, presence of horizontal alveolar bone loss, and number of teeth with root canal fillings added statistically significantly to the prediction, $p < 0.05$. From this model, these independent variables explain 8.1% of the variability of the number of teeth with PP, and so are weak predictors for this.

The regression model predicting prevalence of subjects with PP did this from the variables of age, presence of horizontal bone loss, number of teeth, subjects with DM, and prevalence of subjects with root canal fillings. These variables significantly predicted the prevalence of subjects with PP $F(5, 1000) = 35.04$, p, 0.0005, $R2 = 0.149$. The variables of subjects with DM, presence of horizontal bone loss, and prevalence of subjects with root canal fillings added statistically significantly to the prediction, $p < 0.05$. From this model, these independent variables explain 14.9% of the variability of the prevalence of subjects with PP, and so are weak predictors for this.

5.5 Strengths and Weaknesses of Study

The main strengths of this study compared with previous similar studies are the size of the sample and analyses of glycosylated haemoglobin. The relatively large sample size should better represent the population being investigated. Analyses of glycosylated haemoglobin is an important parameter to consider when investigating patients with DM, as the control of their disease appears to be significant when considering a range of systemic health factors.

5.6 Implications for Clinical Practice and Future Research

The findings of this study have displayed similar trends to previous research assessing the relationship between DM and PP. Clinicians may encounter fewer teeth, and a greater number of teeth with PP in patients with DM, particularly where their DM is poorly controlled. The findings of this investigation are not strong enough to warrant any change to the dental treatment offered or provided to patients with DM. Further

research into a relationship between DM and PP would be beneficial, particularly studies which were prospective and analysed the presence of PP in conjunction with provision of endodontic treatment.

The use of DPRs as a diagnostic tool has some benefits when considering disease prevalence, but the lower sensitivity for detecting PP makes it a suboptimal tool. Future research would likely wish to consider prevalence of PP as detected by cone-beam CT scans, which have been shown to have greater sensitivity.

This investigation has attempted to assess any association between DM and PP. These diseases processes can both be present for many years and may not always result in symptoms for an individual. There are a number of confounding factors that will always be present which make assessment of the relationship more challenging. The findings of this study of greatest significance are that on a population level, patients with DM have a lower mean number of teeth, higher mean number of teeth with PP. In addition to this, it appears that diabetic patients with very poorly controlled DM also have a higher mean number of teeth with PP.

6. CONCLUSION

6.1 First Aim

The prevalence of PP when assessed by number of teeth was greater in the diabetic group of patients than the non-diabetic group. However, when the prevalence was considered by individual patient, rather than by teeth, no statistically significant difference was found between the groups. The null hypothesis that there is no difference between the prevalence of periapical periodontitis in diabetic patients has therefore been disproved, as a difference was observed when comparing prevalence by teeth.

6.2 Second Aim

Within the diabetic group, statistically significant differences were found for HbA1c values, when the group was split below and above the levels of 8.5% and 9%. At these cut-off points, there were statistically significant differences when assessing the number of teeth with periapical periodontitis, the mean number of teeth present, and the presence of horizontal alveolar bone loss. When considering the mean number of teeth with periapical periodontitis, this was 1.00 at HbA1c < 9% and 1.8 => 9% ($p = 0.002$). This therefore disproves the null hypothesis that there is no relationship in diabetic subjects, between the prevalence of periapical periodontitis and increased levels of circulating glycosylated haemoglobin.

6.3 Third Aim

Statistically significant differences were found in the mean number of teeth between the diabetic and non-diabetic groups, with diabetic patients having a lower mean number of teeth (18.87) than non-diabetics (20.51). There was not a statistically significant difference found when comparing the horizontal alveolar bone loss of the two groups, but statistically significant differences were found when the diabetic subgroups were compared. There was a considerable age difference between the diabetic subgroups, so it is not possible to ascertain if this is a true reflection of the wider diabetic population.

6.4 Fourth Aim

No differences were found between the two groups when comparing the number of teeth with root canal fillings or the periapical status of root canal filled teeth.

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8. APPENDICES

Study	DM Type	Study Design	Outcome Measure	Radiograph Type	Sample Size (Case/Control)	Mean Number of Teeth	Prevalence PP by Subject	Prevalence PP by Tooth	Prevalence of RFT by Subject	Prevalence of RFT by Tooth	Significant Predictors from Regression
Britto et al, 2003 (93)	1, 2	Retrospective cohort	1. Non-RFT with PP 2. RFT with PP 3. RFT without PP	DPR and full-mouth periapicals	53 (30 DM/ 23 No DM)	-	-	-	-	-	M>F T2>T1 DM
Fouad and Burleson, 2003 (127)	1, 2	Retrospective cohort	1. Cases with symptomatic PP 2. Cases with PP 3. Cases with PD 4. Cases with flare-ups	Not specified	5244 (58 T1 DM/184 T2 DM/5002 No DM)	-	DM 65% No DM 25% *p* = 0.058	-	-	-	-
Segura-Egea et al, 2005 (95)	2	Retrospective cohort	PAI	Full mouth periapicals	70 (38 DM/32 No DM)	DM 21.6 No DM 24.5 *p* = 0.025	DM 81% No DM 58% *p* = 0.04	DM 7% No DM 4% *p* = 0.007	DM 31% No DM 42% *p* = 0.25	DM 2% No DM 2% *p* = 0.62	Presence of PP
Lopez-Lopez et al, 2011 (92)	2	Cross-sectional case-control	PAI	DPR	100 (50 DM/ 50 No DM)	DM 21.9 No DM 24.6 *p* = 0.012	DM 74% No DM 42% *p* = 0.002	DM 0.9% No DM 0.7% *p* = >0.05	DM 70% No DM 50% *p* = 0.043	-	No. of teeth, Presence of PP, No. teeth with PP, Presence of RFT, No. of RFT, RFT with PP, No. RFT with PP
Marotta et al, 2012 (94)	2	Cross-sectional case-control	Strindberg's criteria	DPR and full-mouth periapicals	90 (30 DM/ 60 No DM)	DM 21.7 No DM 22.8 *p* = >0.05	DM 80% No DM 87% *p* = >0.05	DM 15% No DM 12% *p* = 0.05	DM 77% No DM 87% *p* = >0.05	DM 13% No DM 15% *p* = 0.25	-
Sanchez-Dominguez et al, 2015 (87)	2	Cross-sectional case-control	PAI	DPR	83 (24 HbA1c≥6.5%/ 59 HbA1c<6.5%)	HbA1c≥6.5% 21.5 HbA1c<6.5% 19.9 *p* = >0.05	-	HbA1c≥6.5% 1.7 HbA1c<6.5% 1.5 *p* = >0.05	-	HbA1c≥6.5% 0.7 HbA1c<6.5% 0.5 *p* = >0.05	Periapical status HbA1c≥6.5%
Higgins et al	1, 2	Cross-sectional case-control	PAI	DPR	1006 (503 DM / 503 No DM)	DM 18.9 No DM 20.5 *p* = 0.003	DM 44% No DM 42% *p* = 0.445	DM 1.1% No DM 0.9% *p* = 0.021	DM 37% No DM 41% *p* = 0.245	DM 0.8% No DM 0.9% *p* = 0.072	No. teeth with PP, Age, Hor. bone loss, Presence of DM

Appendix 1: Summary of studies which have assessed prevalence of periapical periodontitis and diabetes mellitus

Appendix 2

FGDP (UK) Selection Criteria for Dental Radiography 2013

Selection criteria for panoramic radiography include:

1. Where a bony lesion of an unerupted tooth is of a size or position that precludes its complete demonstration on intraoral radiographs.
2. In patients with a grossly neglected dentition, for whom there is a clinically determined likelihood of multiple extractions being required.
3. For the assessment of third molars prior to planned surgical intervention.
4. As part of an orthodontic assessment where there is a clinical need to know the state of the dentition and the presence/absence of teeth
5. Panoramic radiographs should only be taken in the presence of specific clinical signs and symptoms. There is no justification for review panoramic radiographs at arbitrary time intervals.

Appendix 3

List of Abbreviations

All DM	full group of subjects with diabetes mellitus
CP	chronic periodontitis
CEPD	combined endodontic-periodontal disease
DM	diabetes mellitus
HABL	horizontal alveolar bone level
MODY	maturity onset diabetes of the young
No DM	full group of subjects without a diagnosis of diabetes mellitus
PP	periapical periodontitis
RCT	root canal treatment
RFT	root filled teeth
SFR	salivary flow rate
T1 DM	full group of subjects with type 1 diabetes mellitus
T2 DM	full group of subjects with type 2 diabetes mellitus