

**The use of MRFA as an adjunct to conventional clinical
examination following peri-implantitis treatment.**

A 12 month follow-up.

**A thesis submitted to the University of Dublin in partial fulfillment of the
degree of Doctorate in Dental Surgery D.Ch.Dent. (Periodontology)**

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Declaration

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Summary

Aim:

The aims of the present study were to investigate the impact of peri-implantitis treatment upon periodontal clinical parameters and implant stability quotient values.

To ascertain if magnetic resonance frequency analysis (MRFA) can be used as a diagnostic tool to demonstrate post operative healing following treatment of peri-implantitis; and to identify the most appropriate time for re-evaluation of implant stability.

Materials and Methods:

Patients were sampled from a cohort of patients with peri-implantitis, referred or presenting to Dublin Dental University Hospital.

Prostheses of diseased implants were dismantled at baseline and periodontal diagnostic parameters were taken (PPD, CAL, BoP, Plaque score). Baseline MRFA levels were taken with an Osstell™ device, in addition to baseline radiographs prior to any treatment.

Patients were treated in accordance with the severity of their disease. All patients received non-surgical therapy following baseline examination; surgical and regenerative therapy was provided where suitable.

Post baseline therapy, patients were reassessed at 3, 6 and 12 months and all clinical parameters repeated in addition to MRFA measurements; with the exception of 3 months probing where regenerative surgery was carried out. Radiographs were repeated at 12 months.

Results:

18 patients were enrolled in the study with 57 implants treated for peri-implantitis. All mean tested clinical periodontal diagnostic parameters showed a statistically significant improvement in the 12 months post-initial therapy without exception. There was a trend for increasing mean implant stability quotient (ISQ) levels over 12 months which was not significant. There was a statistically significant correlation between changes in all tested mean periodontal parameters and changes in ISQ levels over 12 months with the exception of plaque and bleeding on probing scores which showed no significant correlation.

Conclusions:

Overall, in the medium to short term, all treatments were successful in the management of peri-implantitis.

When sub-analysis was carried out based on treatment provided, implants treated surgically with GTR or GBR achieved better clinical results (as evidenced by PD reduction and bone gain) and showed more frequent correlations with MRFA readings.

MRFA technology, in the form of the Osstell™ device, can be used as a complement to the commonly used periodontal tools for the evaluation of post operative implant stability following treatment of peri-implant disease.

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Introduction

The provision of dental implant therapy has revolutionized modern periodontal practice, providing prosthodontic options for missing or failing teeth; that had not previously existed for both patient and clinician.

The concept of osseointegration was first described in the 1950s, and later received widespread acceptance as a concept in the 1980s (Albrektsson et al, 1981).

Implant therapy provides long-term solutions where teeth have been lost, with meta-analysis suggesting survival rates of fixed restorations of up to 95.4% and 92.8% for five and ten years respectively (Pjetursson et al, 2004).

However, implant success cannot be determined on survival rates alone; crestal bone and associated tissue loss may lead to functional and aesthetic issues. As time progresses and dental implants continue to endure the oral environment, the burden of peri-implant disease has become evident.

1.1 Definitions - Peri-implant diseases

1.1.1 Peri-implant mucositis (PIM)

Following the initial definition of peri-implantitis by Mombelli in 1987, further definitions for peri-implant disease, including PIM, were suggested at the 1st European workshop on periodontology (Albrektsson & Isidor, 1994).

PIM was defined as “a reversible inflammatory reaction of the tissues surrounding an implant, much akin to gingivitis”. It was deemed to differ from peri-implantitis as a reversible

condition with no loss of surrounding bone tissue.

This definition was further amended at the 6th European workshop of Periodontology, where PIM was defined as “the presence of inflammation in the mucosa at an implant with no signs of loss of supporting bone” (Zitzmann & Berglundh, 2008).

At a later European workshop of Periodontology it was suggested PIM could be diagnosed by bleeding on gentle probing (Lang & Berglundh, 2011). An alternate definition was provided in a 2013 systematic review, where PIM was defined as “inflamed mucosa with a bleeding index of 2 or more and/or suppuration, without bone loss” (Atieh et al, 2013).

In 2018 a new classification system for periodontal diseases and conditions was introduced by the World Workshop on the Classification of Periodontal and Peri-implant Disease and Conditions, in order to replace the Armitage 1999 classification introduced nearly 20 years prior. Under this new classification PIM was defined as “presence of bleeding and/or suppuration on gentle probing with or without increased probing depth compared to previous examinations; with absence of bone loss beyond crestal bone level changes resulting from initial bone remodeling” (Berglundh et al, 2018).

1.1.2 Peri-implantitis (PI)

First described by Mombelli in 1987, PI was deemed to be an infectious disease similar to chronic periodontitis.

Definitions for peri-implant disease, as previously mentioned, were first suggested at the 1st European workshop on periodontology (Albrektsson & Isidor, 1994). PI was described as “an inflammatory reaction of the tissues surrounding an implant”, and was deemed to differ from PIM with the additional presence of associated bone loss around the implant and its

irreversible presentation.

The 2008 consensus report from the European workshop of periodontology reviewed the literature to provide diagnostic criteria for peri-implant disease (Linde & Meyle, 2008).

Accordingly, it stated that whilst PIM presents as redness and swelling of the soft tissues surrounding an implant with bleeding on probing; PI was often associated with suppuration, and always accompanied by loss of surrounding bone.

At the 7th European workshop on Periodontology, PI was further defined as a change in crestal bone height with time and bleeding on probing, with or without deepening of probing pocket depth (Lang & Berglundh, 2011).

PI has also been defined as presence of inflamed mucosa with bleeding on probing, pocket depth of 5mm or more and cumulative bone loss of 2mm or more or bone loss at 3 threads of the implant (Atieh et al, 2013).

The heterogeneity of diagnostic criteria for both PIM and PI present in the literature somewhat complicates both clinical and scientific evaluation of peri-implant disease. Indeed, one 2012 review found 9 different thresholds for bone loss around implants had been suggested in definitions for PI in the literature to that point (Sanz & Chapple, 2012). Hence, at the 8th European workshop on Periodontology, it was suggested that agreed definitions for future research on peri-implant disease should be used. The report suggested that in the absence of baseline radiographs, 2mm estimated bone loss and the presence of inflammation could be defined as PI; if baseline radiographs were available 1-1.5mm bone loss and the presence of inflammation could be defined as PI (Sanz & Chapple, 2012).

Under the new 2018 classification PI is defined as ‘a plaque-associated pathologic condition occurring in the tissue around dental implants, characterised by inflammation in the peri-

implant mucosa and subsequent progressive loss of supporting bone’.

In the absence of previous examination data PI can be diagnosed on the basis of:

- Presence of bleeding on probing and/or suppuration on gentle probing.
- Probing depths of $\geq 6\text{mm}$.
- Bone levels $\geq 3\text{mm}$ apical to the most coronal portion of the intraosseous part of the implant (Berglundh et al, 2018).

1.2 Prevalence of peri-implant disease

Multiple systematic reviews have attempted to outline the prevalence of peri-implant disease.

Table 1: Prevalence of peri-implant disease.				
Study	Study Characteristics	Follow-up	Prevalence of PIM	Prevalence of PI
Zitzmann & Berglundh 2008	• Systematic Review • Cross-sectional and Longitudinal studies • Studies with ≥ 5 years follow-up • ≥ 50 subjects per study • 2 studies met inclusion criteria • 298 patients, 1399 implants	9.4-10.8 years	79% of subjects 50-90% of implants	28-56% of subjects 12-43% of implants
Atieh et al 2013	• Systematic Review • Prospective, retrospective, cross-sectional and observational cohort studies • ≥ 5 years follow-up • 9 studies met inclusion criteria • 1,497 patients; 6283 implants	≥ 5 years	63.4% of subjects 30.7% of implants	18.8% of subjects 9.6% of implants
Derks and Tomasi 2015	• Systematic Review • Prospective, retrospective, cross-sectional and observational cohort studies • No minimum follow-up period • ≥ 100 subjects per study • 11 studies met inclusion criteria • 2,136 patients, number of implants not reported	3.4-11 years	42.9% of subjects	21.7% of subjects

As previously discussed, it is apparent there is a lack of consensus regarding terminology, aetiology, diagnosis and indeed management of peri-implant disease. The wide range in levels of peri-implant disease reported in the research is could be the result of differing definitions of disease when measuring and reporting on peri-implant disease (Derks & Tomasi, 2015, Mombelli et al, 2012, Tomasi & Derks, 2012).

1.3 Progression of peri-implant disease:

Albrektsson et al (1986) suggested criteria for acceptable bone loss over time, based on early data on machined surface implants placed in a two-stage implant placement protocol. This paper suggested an acceptable level of crestal bone loss of 1.5mm in the first year of loading, followed by a maximum of 0.2mm loss each year thereafter.

Derks & Tomasi (2015) demonstrated using meta-regression, that there was a statistically significant positive relationship between the prevalence of PI and mean implant function time.

Derks et al (2016) carried out a 9-year retrospective radiographic study of 596 patients who received implant therapy in 2003; of whom 62 presented with moderate to severe PI effecting 105 implants. Mean bone loss at 9 years was 3.5mm equating to an annual estimated bone loss of 0.38mm. However, analysis of the radiographs demonstrated that the progression of bone loss was not linear and in fact accelerated over time, suggesting that annual bone loss figures may be misleading. The onset of peri-implantitis occurred early, with 81% of subjects showing at least one implant with over 0.5mm of bone loss at 3 years. This is contrary to periodontal disease, which is generally a gradual disease of late onset (Kassebaum et al, 2014).

1.4 Aetiology of Peri-implant disease

1.4.1 Bacterial biofilm

It has been demonstrated in human studies that once implants are exposed to the transmucosal environment in partially edentulous patients, they are exposed to oral bacteria resulting in the formation of a bacterial biofilm within 30 minutes (Furst et al, 2007). The composition of these initial biofilms on the implant surface has been shown to be similar to those found on

teeth in a patient with healthy periodontal tissues (Agaerbaek et al, 2006).

This initial biofilm consists of predominantly of gram-positive bacteria, mainly facultative cocci and rods; however small numbers of gram-negative bacteria can be found. (Leonardt et, al 1999, Agerbaek et al, 2006, Furst et al, 2007)

Implants diagnosed with PI show a change in the nature of the biofilm, to a colony with a higher proportion of gram-negative anaerobic bacteria. This includes a high prevalence of periodontal pathogens such as *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, members of the Red Complex; and *Fusobacterium* & *Prevotella intermedia*, members of the Orange Complex, as described by Socransky et al. in 1998 (Heitz-Mayfield & Lang, 2010).

Conversely, many studies are starting to show there are subtle differences in the microbial biofilm associated with peri-implant disease and that of periodontitis, with a study identifying elevated levels of *S. aureus* in PI samples; a pathogen not commonly associated with periodontitis (Renvert et al, 2008). It has been proposed that the surface topography of the implants themselves may have an influence on the type and prevalence of bacterial species present, which may differ from that of a root surface (Teughels et al, 2006).

1.4.2 Host response

Although bacterial pathogens and the formation of a microbial biofilm initiate the disease process; the ensuing inflammatory response and interplay between the host and pathogens is key in the pathogenesis of tissue destruction (Figuero et al 2014).

The literature has shown many similarities regarding the host response to biofilm formation on dental implants and natural teeth. The majority of the research studying the histological

response of the tissues to biofilm formation comes from animal studies. This may be in part due to the ethical issue of allowing unhindered disease progression in the human model, coupled with the need for block excision of the site for histological analysis.

Animal studies have demonstrated an initial host response to the formation of the implant biofilm resulting in mucositis, much akin to gingivitis formation around teeth, demonstrating a cause-and-effect relationship (Berglundh et al, 2007).

As peri-implant disease progresses from PIM to PI the tissues demonstrate higher levels of inflammatory cell infiltrate within the apical extension of the junctional epithelium, with a similar composition as seen in periodontal lesions around teeth (Ericsson et al, 1996). This study demonstrated that in PI lesions, the apical extension of this inflammatory cell infiltrate extends further apically at a much earlier stage, suggesting the progression of PI lesions occurs more rapidly than in periodontal disease.

1.5 Risk indicators for peri-implantitis

In a 2008 systematic review, Heitz-Mayfield et al analyzed 138 articles, with a minimum of 5 years of follow-up, to assess potential risk factors for peri-implant disease. They found substantial evidence to support poor oral hygiene, a history of periodontal disease and smoking as risk factors for progression of peri-implant disease. They found limited evidence to support diabetes and alcohol consumption as risk factors for peri-implant disease. There was limited or conflicting evidence when considering the macro- & micro-topography of the implant surface and genetic traits of patients as risk factors for progression of disease.

Conversely, in a mean 23.3 year follow up of 86 patients with dental implants, Renvert et al (2018) found the only strong predictor of developing PI when analyzed at a subject level was

having ≥ 3 dental implants. Smoking, gender, and history of periodontal disease were not found to be strong predictors of disease progression, nor a previous diagnosis of PIM.

1.5.1 Oral hygiene

The literature demonstrates a strong correlation between poor oral hygiene and development of peri-implant disease.

One study demonstrated the relationship between poor oral hygiene and development of peri-implantitis, with an odds ratio of 14.3 for development of PI in patients with very poor oral hygiene compared to patients with good plaque control (Ferreira et al, 2006). Another study further highlighted the importance of plaque and suitable oral hygiene regimes by analyzing disease progression in implants based on the accessibility of the implants and prostheses for cleaning and maintenance. In this study inaccessible implants had peri-implantitis 48% of the time, in comparison to only 4% in implants accessible for cleaning (Serino & Ström, 2008).

In an average 6-year follow-up of 134 patients with implants there was a statistically significant correlation between patients who complied with supportive periodontal therapy (SPT) and those patients who did not regularly attended for SPT and the incidence of peri-implantitis. Non-compliant patients had a 11-fold higher chance of developing peri-implantitis. (Rinke et al, 2011)

1.5.2 Smoking

Smoking has been widely referenced in the literature as a risk factor for peri-implant disease. A study was conducted assessing implant failure in maintained partially edentulous patients who had implant therapy 2 to 11 years prior. 10 of 89 patients enrolled in the study suffered

implant failure, of which 80% were smokers who were non-compliant with the suggested maintenance program. Logistic regression analysis demonstrated a significant association between peri-implantitis and smoking with an odds ratio of 31.58 (Rinke et al, 2011).

Amri et al (2017) conducted a 5-year follow-up study on 61 patients with immediately placed or delayed implant protocols, and found that patients who smoked had statistically significantly higher levels of plaque, bleeding on probing and crestal bone loss around their implants compared to non-smokers.

A further observational, cross-sectional study found smoking increased the probability of developing PI by approximately 3 times when compared to non-smokers (Pimental et al, 2018).

Conversely, one study failed to validate smoking as a reliable predictive factor for development of PI over a mean 23.3 years of implants in situ (Renvert et al, 2018).

1.5.3 History of periodontal disease

Given the similar nature of periodontal and peri-implant disease with regard to the formation of a microbial biofilm and the host response, it has been suggested that a history of periodontal disease may be a risk factor for development of PI.

A 2006 literature review found high implant survival rates of over 90% in patients, regardless of their periodontal history over a 10-year period. However, patients with a history of periodontitis had a statistically significant increase in peri-implant marginal bone loss after 5 years, in addition to a higher incidence of PI after 10 years compared to patients with no history of periodontal disease (Schou et al, 2006).

Another study carried out a meta-analysis demonstrating implant failure rates in patients with

a history of periodontal disease 3 times that of those in patients with no history of periodontal disease. In addition they found a statistically significant difference in marginal bone loss between the two groups, with patients with a history of periodontal disease exhibiting greater peri-implant bone loss (Safii et al, 2010).

In a 10 year follow-up study of 112 patients treated for periodontal disease who subsequently received implant therapy, patients who initially had moderate to severe periodontal disease initially demonstrated higher residual probing depth and bleeding on probing scores compared to patients who initially did not suffer from periodontal disease. At 10 years 47.2% of patients with initial severe periodontal disease exhibited PI compared to only 10.7% in patients with no history of periodontal disease (Roccuzzo et al, 2012).

These findings complement those of the aforementioned Heitz-Mayfield 2008 systematic review, presenting a history of periodontal disease as a risk-factor for PI progression.

1.5.4 Excess Cement

In a systematic review including 945 patients and 1010 cement-retained implant restorations, it was documented that there is an association with a tendency towards higher disease prevalence with cemented- compared to screw-retained implant restorations. This was particularly the case when fixed partial dentures or splinted crowns were used. In addition it demonstrated that undetected excess cement occurs irrespective of type of abutment or cement used. The prevalence of disease was higher where shorter soft tissue healing times were applied. Early follow-ups of post-prosthetic loading allowed for early detection of disease early in the inflammatory process (Staubli et al, 2017).

1.5.5 Presence or Absence of Keratinised Mucosa.

The presence or absence of keratinized mucosa surrounding osseointegrated implants and the role this may play in prevention of PI is inconsistently reported in the literature. Whilst it can be surmised that the absence of an adequate band of keratinized mucosa around implants can lead to increased local plaque levels and higher gingival index scores; a causative relationship between absence of keratinized tissue and subsequent bone loss is hard to demonstrate (Brito et al 2014). An earlier review found similar results, whereby increased plaque scores around implants and gingival inflammation was evident in implants with inadequate keratinized mucosa (<2mm) (Wennström & Derks, 2012). Again, no conclusions could be drawn as to the effect on marginal bone levels around implants with inadequate keratinized mucosa. Statistical analysis was not possible due to the heterogeneity of the studies in this area of research.

Roccuzzo and colleagues completed a 10-year follow-up of 98 patients who received implants in private practice. The finding of increased plaque accumulation around implants with inadequate keratinized tissue was once again evident; even in patients with good oral hygiene and compliance with supportive peri-implant therapy recalls (Roccuzzo et al, 2016).

Schwarz et al allowed PIM to develop in a human randomized controlled trial analyzing the effect of both keratinized tissue height and differing healing abutment designs. Where PIM was allowed to develop through temporarily refraining from oral hygiene measures followed by a period of disease resolution, it was concluded that areas with <2mm keratinized tissue were more susceptible to PIM. As PIM is a known pre-cursor to PI in the absence of patient or operator intervention this may suggest the role of inadequate keratinized tissue as a risk indicator for PI (Schwarz et al, 2018).

There is evidently a large body of evidence linking inadequate levels of keratinized tissue around implants to increased plaque accumulation and increased inflammation; but little evidence directly linking it to peri-implant bone loss, and therefore endorsing it as a risk factor for disease progression.

One study has indicated that suitable levels of keratinized tissue around implants may conversely be a risk factor for development of peri-implantitis, wherein implants with at least 12 months in situ had higher prevalence of PI where ≥ 3 mm of keratinized tissue was present compared to sites with less keratinized tissue (Pimental et al, 2018).

1.6 Implant surface effect on initiation and progression of peri-implant disease

As implant therapy and technology improves, multiple implant surfaces and coatings have been manufactured, with the aim of accelerating or improving osseointegration. However, the implant surface may also affect the rate of disease initiation and progression.

A 2011 systematic review including 13 studies on the effect of implant surfaces on the progression of peri-implant disease; found contrasting and limited evidence available in the literature on the effect of implant surface on the progression of peri-implant disease; hence preventing the ability to make established clinical protocols (Renvert et al, 2011).

Rougher surface implants were deemed to potentially collect more plaque and be clinically harder to decontaminate leading to increased risk of disease progression. Conversely, the rougher surface may lead to a more positive response to regenerative surface of diseased implants due to micro- and macro-surface area and energy.

Polizzi and his co-workers compared survival rates of minimally rough machined surface original Brånemark implants and moderately rough TiUnite implants over 10 years. At 10

years there was a 90.3% and 96.6% survival rate in the Brånemark group and TiUnite group respectively; suggesting implant survival is higher where moderately rough surfaces are used. When considering peri-implantitis as opposed to implant survival they concluded only 2% of the implants had PI at 10 years; however the ratio of diseased implants was 9/1 for TiUnite/Brånemark suggesting the rougher surface may be more susceptible to disease (Polizzi et al, 2013).

Laboratory studies have shown the implant surface has an effect on biofilm formation. One study evaluated the formation of intra-oral biofilms on titanium discs with different surface coatings showing machined surface discs were slower at developing bacterial biofilms and also had a higher affinity for fibroblast growth compared to roughened or acid blasted surfaces. It was postulated these findings could be applied to implants in situ inferring rougher implants may be more susceptible to PI progression (John et al, 2015).

Van Assche and colleagues carried out microbiological analysis of submucosal flora on TiOblast (Astra Tech) and Brånemark implants after 12 years in function. They discovered that the systems, despite their differences in micro- and macro-structure had no significant differences in subgingival microbiome composition. Additionally, the presence of subgingival periodontal pathogens did not always result in bone loss (Van Assche et al, 2011).

The effect of implant macro- and micro-topography of implants on bony healing, osseointegration and implant survival is well known; however, systematic literature focusing on the effect of implant design on peri-implant bone loss and disease is scarce (De Bruyn et al, 2017).

1.7 Peri-Implant Defect Configuration

The bony configuration of peri-implantitis induced defects, and the implications for successful treatment of disease have been studied.

In 2007, Schwarz et al provided a classification system for peri-implant bony defects based on 40 implants with peri-implantitis, which were assessed during open surgery, and the defect configuration noted. Defects were classified into both horizontal and vertical defects with subcategories for vertical defects. 79% of naturally occurring peri-implantitis defects had a horizontal component, with the most common vertical defect presenting as a circumferential defect in 55.3% of cases.

Much of the research on the progression and treatment of peri-implant disease utilizes ligature-induced peri-implantitis defects in the dog or monkey model. A second component of the Schwarz et al 2007 study was to analyze the bony defects formed around 30 implants in 5 beagle dogs using the ligature-induced disease method; and compare these to the naturally occurring defects found in situ in human patients. Much like in the human model the circumferential defect was the most commonly found defect (86.6%) with 53.3% of defects having a horizontal component. These results would indicate the ligature-induced model in animals is appropriate for research on the treatment of peri-implantitis defects.

In 2019 this classification was revisited and adjusted. A CBCT study was carried out assessing defect configuration and severity on 158 diseased implants. Defects were classified as infraosseous, horizontal or a combination of both; before being subclassified as dehiscid, 2/3-wall or circumferential. In addition defects were characterized as 'slight', 'moderate' and 'advanced' based on the severity of bone loss. The most prevalent morphology type was

infraosseous 2/3-wall defects (55% of defects analysed) followed by infraosseous dehiscenced defects (16.5%) and combination dehiscenced defects (13.9%). The majority of defects exhibited a 'moderate' severity of bone loss (Monje et al, 2019).

The configuration of a PI defect is of critical importance when deciding upon which treatment modalities may be suitable for the treatment of each individual implant, indeed the type of defect present will affect the outcome of any therapy.

A human clinical trial evaluated the effect of pre-operative defect configuration on treatment outcomes on 27 patients. Defects were treated with open flap debridement, mechanical decontamination, grafted with Xenograft a collagen membranes were to secure the graft. This study found the greatest positive changes in probing depths and clinical attachment level were found in cases with circumferential pre-operative defects; 1-wall defects or defects with buccal dehiscences did not respond as well to treatment by comparison (Schwarz et al, 2010).

1.8 Current methods of assessing the presence of and degree of peri-implant disease

1.8.1 Clinical examination

1.8.1.1 Probing

The use of periodontal probing to assess periodontal probing depths and relevant clinical attachment levels has long been an essential tool in detecting and diagnosing periodontal disease around teeth (Fowler et al, 1994). However, histologically the connection between teeth to the periodontium, and implants to the surrounding tissues differs. Taking this into consideration, the response of the tissues surrounding a tooth may differ from those

surrounding an implant (Coli et al, 2017).

In clinical health the probing depth demonstrates the apical extension of the epithelium around both teeth and implants. In the presence of inflammation the periodontal tissues become more permeable and more readily penetrated by probing, extending up to 1.2mm apical to the initial histological attachment level (Fowler et al, 1994). This penetrability of inflamed tissues has been documented in periodontal tissues around implants (Schou et al, 2002).

Peri-implant tissues have also been shown to be more sensitive to differences in probing forces than periodontal tissue surrounding teeth, as well as potentially more penetrable than the periodontium (Mombelli et al, 1997).

Much like in the periodontium, a probing force of no more than 0.25N is recommended when probing peri-implant tissues; allowing clinical sufficiency to assess the peri-implant tissues, whilst refraining from causing permanent damage to the tissues (Etter et al, 2002).

Studies have demonstrated an increase in probing depth over time correlates to attachment loss around implants in conjunction with associated bone loss, making it an appropriate diagnostic tool for assessing progression of peri-implant disease. A 1991 prospective human clinical study by Quirynen et al found a correlation between changes in radiographic bone levels and loss relative to changes in probing depths, therefore validating this method of assessment.

(Quirynen et al, 1991) Another prospective human clinical trial also demonstrated a correlation between increased clinical probing depths in implants with marginal bone loss and signs of PI when compared to 'healthy' implants (Hultin et al, 2002). It has been suggested that a probing depth of 3mm could be considered 'healthy' when considering dental implants, (Mombelli & Lang, 1994) however it should be considered that these values can vary based on implant supra-structure and design.

Conversely, Lekholm et al (1986) demonstrated, in a human clinical trial, that deep pockets

around implants with bleeding on probing may not necessarily be related to bone loss, histological changes or microflora associated with peri-implant disease; and hence probing depths could not be relied on for diagnosing disease, particularly as a sole method of diagnosis.

Notwithstanding, probing depths around implants are still used routinely as a diagnostic tool and are included in the most recent definitions of PIM & PI.

1.8.1.2 Bleeding on probing

Bleeding on probing (BOP) has been suggested as a method of assessing inflammation and potential for progression of disease around teeth with much research conducted in this field in the late 1980s and early 1990s. A study by Lang et al followed 41 periodontal patients (3807 sites) in a maintenance program for over 2 years; they found lack of BOP was an accurate predictor of sites that would not undergo further attachment loss (88% accuracy) (Lang et al, 1990).

Bleeding on probing is routinely included in the various definitions of peri-implant disease suggested in the European consensus reports (Linde & Meyle, 2008, Lang & Bergundh, 2011, Sanz & Chapple, 2012, Berglundh et al, 2018). However, it should be noted that much of the research included in the consensus reports on BOP around implants may be underpowered statistically lacking sufficient numbers; and hence is not outright proof that bleeding around implants is indicative of disease or indeed risk for disease progression (Coli et al, 2017).

As previously mentioned, Lekholm et al (1986) demonstrated that deep pockets around implants with bleeding on probing may not necessarily be related to bone loss, histological changes or microflora associated with peri-implant disease. Another study used to demonstrate

prevalence of peri-implant disease found BOP in 93.9% of implants with ‘progressive’ bone loss, but also 90.9% in implants with stable bone (Fransson et al, 2008).

Another long-term study found very low prevalence of peri-implantitis, and a survival rate of 95.1%, on sandblasted & acid-etched implants despite high levels of BOP (87%) on the implants after 10 years (Fischer et al, 2012).

Consequently, the use of BOP as an indicator of peri-implant disease should be utilized with caution, and certainly not as a sole deciding diagnostic factor for disease.

1.8.2 Radiographic Examination

Intra-oral periapical radiography, orthopantomography and cone-beam computerized tomography, have all been used in the surgical planning for implant placement and subsequent assessment of implant health.

Periapical radiography and orthopantomography in particular, represent quick and low cost methods of assessing peri-implant health through assessment of peri-implant bone levels.

In the Albrektsson et al 1986 study, levels of acceptable or expected crestal bone loss around osseointegrated machined surface implants were published. This amounted to 1.5mm of bone loss or remodeling in the first year followed by 0.2mm every year thereafter, with implants exhibiting 85% survival after 5 years in function and 80% after 10 years. Where baseline radiographs are unavailable, these figures may be useful in assessing the presence or progression of disease, in combination with other clinical investigations.

Zechner et al (2003) carried out a 5-year follow-up study comparing the accuracy of periapical radiographs and orthopantomographs when assessing crestal bone levels around diseased implants. They found the mean difference in measurements equated to 0.2mm suggesting the

two methods were comparable when measuring marginal bone levels.

However, in a surgically-based study of 46 treated implants, it was demonstrated that there was a statistically significant discrepancy between radiographic bone levels and surgically confirmed bone levels around disease implants. This study found peri-apical radiography underestimated peri-implant bone loss by an average of 1.3mm. Moreover periapical radiographs were of little diagnostic benefit when attempting to ascertain defect configuration (Garcia-Garcia et al, 2016).

One study used radiographs to assess the stability of 412 turned surface Brånemark implants. Experienced radiologists had an 83% success rate in identifying implants with questionable integration and mobility with only 11% of prosthesis being unnecessarily deconstructed for treatment based on radiographic assessment (Gröndal & Lekholm, 1997).

The definitions suggested in the consensus reports by Linde & Meyle, 2008, Sanz & Chapple, 2012 & Berglundh et al, 2018 include bone loss as a defining factor in peri-implantitis and hence radiography is an integral part of diagnosis. Indeed, one study suggested, compared to other clinical indices, radiographic analysis of implants may be one of the only viable methods in assessing implant health and disease based on marginal bone levels (Verhoeven et al, 2000).

1.8.3 Limitations of current methods of diagnosis

As previously mentioned, the histological relationship between the tooth and periodontium and the implant with its surrounding peri-implant tissue are subtly different. The dento-gingival junction is a highly ordered and specialized tissue junction, whilst the implant-tissue interface is the result of a foreign body reaction to biomaterials with high levels of biocompatibility, resulting in a fibrous scar tissue of epithelium and connective tissue. Hence

proven periodontal indices when it comes to periodontal disease such as the use of a periodontal probe, bleeding on probing and assessment of radiographic bone level may not be applicable to or entirely appropriate for long-term diagnosis of peri-implant disease or disease resolution (Coli et al, 2017, De Bruyn et al, 2013).

For example a zero tolerance rule to BOP and increased pocket depths may lead to unnecessary treatment of otherwise healthy implants.

Koldsland et al (2010) evaluated different diagnostic parameters and severities of peri-implant disease on their 8 year follow up study. They showed that 60% of implants exhibited bleeding on probing at 8 years, with 23% having probing depths equal or above 4mm. Despite this only 15% and 8% of implants exhibited bone loss of 2-3mm and 3-4mm respectively, indicating there is a disproportionate level of bleeding on probing and increase in probing depths compared to bone loss and hence this may lead to over-diagnosis of disease in the absence of good radiographs.

Pain, swelling, loss of function, redness and purulent discharge may be indicative of need for treatment in the absence of further diagnostic aids (Coli et al, 2017).

Verhoeven et al (2000) concluded that, in their study of 16 patients and 32 implants, that the use of plaque index, gingival index, probing depth and the Periotest™ device showed poor sensitivity to changes in implant health. They specified only radiographs showed specificity when diagnosing changes in implant health and therefore, of all the aforementioned tests, these may be the most useful and fitting for clinical practice.

In terms of the use of radiology as an assessment of implant health, radiographic evidence of stable bone does not necessarily correlate with histologic osseointegration. (Sewerin et al, 1997) And as previously mentioned, peri-apical radiography may underestimate the true severity of peri-implant disease (Garcia-Garcia et al, 2016).

Few papers have provided valuable diagnostic measures of predicting true peri-implant disease resolution or provided evidence regarding the evaluation of surgical treatment of peri-implant disease (Figuro et al, 2014).

1.9 Treatment of peri-implant mucositis.

The available literature suggests that, much akin to gingivitis, PIM is a reversible condition brought on by bacterial biofilm formation, which can be effectively managed with non-surgical therapy (Renvert & Polyzois, 2015, Figuro et al, 2014).

This non-surgical therapy encompasses mechanical debridement, with or without antimicrobial therapy. Mechanical debridement including the use of currettes, ultrasonic scalers, titanium brushes and air-abrasion.

Titanium currettes have been suggested around dental implants as opposed to standard stainless steel currettes to prevent alterations to implant surfaces, which may in turn further contribute to bacterial aggregation (Hallstrom et al, 2012, Ronay et al, 2017). Similarly, specialized ultrasonic scaler tips, such as polyether-etherketone-coated tips, have been designed for use around implants preventing alterations to the implant surface.

Many methods for surface decontamination have been suggested as a therapy or adjunct therapy to non-surgical mechanical therapy for PIM including antimicrobial therapy, either as a mouthwash or local delivery, or the use of Er:YAG laser technology (Renvert et al, 2011, Sahm et al, 2011, Renvert & Polyzois, 2015, Figuro et al, 2014).

However the use of locally delivered antimicrobials, either as a sole therapy or as an adjunct to

mechanical debridement, have failed to demonstrate additional clinical benefits compared to mechanical therapy alone; which has been shown to be successful in the treatment of PIM (Figuero et al, 2014).

When diagnosed early, PIM is a condition that can be easily managed as long as the patient is motivated and maintains good levels of oral hygiene; irrespective of the modality of clinical treatment provided in the treatment of PIM (Renvert & Polyzois, 2015, Polyzois, 2019).

1.10 Treatment of Peri-implantitis

When considering the roughened surfaces and thread patterns, implants quite clearly pose a difficult quandary when it comes to removal of the bacterial biofilm and subsequent maintenance; technically more challenging to decontaminate than root surfaces commonly treated during periodontal disease.

Indeed, PI has been shown to be more refractory to treatment when compared to similar procedures carried out on natural teeth, often requiring a more invasive surgical approach (Khoshkam et al, 2013, Jepsen et al, 2016, Renvert & Polyzois, 2015, Figuero et al, 2014).

In cases where implants are mobile or deemed non-suitable for resective or regenerative treatments due to the severity of the disease, the clinician may feel implant removal is the most suitable treatment option for the patient. Many methods have been suggested for implant removal including counter-torqueing of the implant, removal with piezo-surgery, surgical burs or indeed trephine burs (Bowkett et al, 2016).

1.10.1 Non-surgical treatment of peri-implantitis / mechanical decontamination

Many studies have assessed the role of non-surgical therapy in the treatment of PI. These studies include the use of currettes, ultrasonics, local and systemic antimicrobials and the use of glycine air-abrasion.

Glycine air-abrasion was suggested for treatment of periodontal defects by Petersilka et al (2003), as opposed to traditional air-abrasion techniques such as sodium-bicarbonate used for stain removal, which could be too abrasive and cause tissue damage around periodontal defects.

A bench study was completed comparing the use of air-abrasion, ultrasonics and currettes in the non-surgical treatment of fabricated PI defects of differing depths and angles. (Ronay et al, 2017) Using implants soaked in a dye to simulate the bacterial biofilm, it was concluded that air-abrasion with glycine powder was the most efficient method of removal of the biofilm, removing on average 66% of the dye. This was far superior to the results achieved with ultrasonics and currettes, which achieved only 33% and 26% dye removal, respectively. When comparing treatment by qualified periodontists versus dental students, air-abrasion was also found to be the least technique-sensitive method, and the most efficient technique for biofilm removal. Unlike the use of ultrasonics and steel currettes, air-abrasion also had no macroscopic effects on the implant surface in the form of scratching or gauging.

A similar study published in 2019 tested the same 3 mechanical decontamination methods finding, like Ronay et al (2017), that air abrasion with glycine powder was statistically more efficient at removing dye simulating a biofilm when compared to the use of hand currettes or sonic scalers in closed defects (Keim et al, 2019).

Air-abrasion as a method of biofilm removal was compared to the use of an Er:YAG laser in a

randomized clinical trial (Renvert et al, 2011), when used in a non-surgical approach. Improvements were seen using both techniques in approximately half of patients showing improved probing depths, bleeding on probing and frequency of suppuration in pockets $\geq 3\text{mm}$. Air-abrasion was also compared with mechanical debridements and irrigation with chlorhexidine in a non-surgical approach; and although both techniques were moderately successful, air-abrasion was found to be the more effective method of decontamination (Sahm et al, 2011). One study of 21 patients treated with non-surgical therapy including mechanical debridement, glycine air abrasion and metronidazole use, followed by 12 months of supportive maintenance, achieved significant clinical and radiological improvements around implants; with none of the implants presenting with progressive bone loss (Nart et al, 2019). However, the existing literature suggests that non-surgical mechanical therapy alone shows only limited improvements in clinical parameters currently used to assess peri-implant disease. (Renvert 2008, Renvert & Polyzois, 2015) The addition of localized antimicrobials such as chlorhexidine, minocycline and doxycycline has been shown to demonstrate limited further clinical improvements in treatment PI; nevertheless, the clinical relevance of these small improvements in the literature was limited (Figuro et al, 2014).

1.10.2 Surface decontamination

As with periodontal disease, it is widely accepted that peri-implant disease is caused, in part, by the formation of a microbial biofilm on the implant or implant component surfaces. Therefore it is logical that treatment of peri-implant disease focuses primarily on removal of this biofilm (Renvert et al, 2008). The choice of surface decontaminant or treatment protocol for decontamination of the implant is thought to have an influence on the outcome of PI

treatment (Claffey et al, 2008).

Many decontamination modalities have been suggested including mechanical debridement with currettes, air-abrasive devices, chemical decontamination, implantoplasty and the use of Er:YAG laser technology. All have been found to have varying degrees of success when it comes to achieving positive treatment outcomes when combined with surgery (Roccuzzo et al, 2011, Schwarz et al, 2011, Pommer et al, 2016, Ramanauskaite et al, 2016). One study demonstrated 3% hydrogen peroxide (H₂O₂) was effective when combined with mechanical debridement as a chemical decontaminant for implant surfaces, where access to the implant surface was achievable (Alotaibi et al, 2019). No single protocol for implant surface decontamination nor choice of grafting material has been shown to be superior. A further complicating factor in the literature is the fact that, understandably, regenerative studies routinely include both a decontaminating technique in combination with regenerative techniques, hence providing cofounders to treatment success that often prevents comparison of single variables alone.

1.10.3 Surgical treatment of Peri-implantitis

Despite its success in the treatment of peri-implant mucositis, non-surgical periodontal therapy is deemed to be of limited efficiency in the treatment of peri-implantitis (Renvert et al, 2008, Mahato et al, 2016, Ramnauskaite et al, 2016). This is understandable given the complex macro-and micro-structure of implants compared to root surface, and to the challenges involved in accessing and decontaminating implant surfaces. The rationale behind surgery as a treatment of PI is improved access and therefore enhanced ability to clean implant surfaces, in conjunction with removal of diseased or infected surrounding tissue.

Suggested surgical modalities have included resective and regenerative approaches, most often combined with an attempt to remove the biofilm mechanically, chemically or a combination of both.

A systematic review by Mahato et al (2016) including 10 surgical and 10 non-surgical studies for the treatment of PI concluded that surgical treatment with a regenerative approach attained more positive outcomes than a non-surgical approach. However, no single surgical treatment modality was suggested as being superior.

Open flap debridement surgery has been shown to be more successful in treating peri-implantitis than non-surgical therapy; and adjunctive surface decontamination can potentially resolve peri-implantitis and promote bony infill of peri-implantitis defects. However, clinical research on the human model continues to be scarce (Claffey et al, 2008).

The use of systemic antibiotics in conjunction with surgery is a common finding across the literature but as this stage there is limited research available advocating their use (Huynh-Ba et al, 2012).

1.10.3.1 Access/Resective surgical approaches

The decision as to whether to implement a resective or regenerative approach around diseased implants depends largely on the type of defect present (Renvert & Polyzois, 2015).

In a 5-year follow-up study assessing results of access surgery alone, resolution of disease was evident in 58% of implants; however, despite treatment, 4 of 26 implants were lost over the 5-year period (Leonhardt et al, 2003).

Serino & Turri (2011) studied diseased implants that had undergone a resective surgery, and subsequently received supportive peri-implant therapy over a 5-year study. Their method

entailed apically repositioned flap surgery in conjunction with mechanical therapy and use of saline and chlorhexidine for decontamination on 71 diseased implants. The findings demonstrated just over half of PI lesions had been effectively treated at 2-year follow-up (58%). Implants with deeper initial probing depths did not exhibit the same level of healing as implants with the shallower initial defects; with 74% of implants with initial probing depths of 2-4mm exhibiting health after 2 years compared to only 50% of implants with initial probing depths of 5-6mm.

Carcuac et al (2017) evaluated the effect of differing methods of decontamination including saline, mechanical contamination and both local and systemic antibiotics on diseased implants, when applying a pocket elimination surgical approach on 100 implants. They demonstrated a mean pocket depth reduction of 2.7mm at 3-years post-intial therapy when employing this surgical approach, with a 40% reduction in implants presenting with bleeding on probing. After 3 years 35% of implants still presented with PPD ≥ 5 mm; the effects of systemic antibiotics were not maintained over 3 years, and there was a tendancy for smooth surface implants to respond more effectively to treatment over the follow-up period.

1.10.3.2 Implantoplasty

A clinical trial by Schwarz et al (2011) utilized implantoplasty, by removing supracrestal threads with a bur, as a method of surface decontamination and to ease future maintenance. Implants were then further decontaminated using mechanical debridement and saline or with an Er:YAG laser; and subsequently grafted with xenograft particles and collagen. Both groups underwent comparable levels of reduction of bleeding on probing and increase in radiographic bone fill. The technique of implantoplasty was in therefore deemed successful, however no

control group without implantoplasty was used.

One potential complication of implantoplasty is the potential for release of titanium particles into the surrounding hard and soft tissues. Titanium particles are present at increased levels in peri-implant tissues surrounding diseased implants when compared to healthy implants; implantoplasty has been shown to further increase levels of titanium particles in the surrounding tissues post-surgically (Suárez-López del Amo et al, 2018). This may be a problem as titanium particles have been shown to interfere with cell function and promote inflammation in in-vitro experimentation, with reported cases of hypersensitivity; however titanium particles are detected in healthy and non-healthy implant sites alike (Mombelli et al, 2018).

1.10.3.3 Regenerative surgical approaches

Regenerative approaches to PI treatment have been suggested with the objectives being to increase tissue support surrounding the implant, preventing tissue recession post-surgery, and to attempt to achieve some degree of re-osseointegration (Figuero et al, 2014).

Various grafting materials have been suggested for the regenerative therapy of PI defects. A 4-year clinical trial following implants that underwent surgical regenerative therapy demonstrated reductions in PPD, as well as clinical attachment level gain and radiographic bone fill present 4 years post-treatment (Schwarz et al, 2009). This study found clinically superior results were evident when bovine xenograft and collagen membranes were used in combination compared to when hydroxyapatite crystals alone were used as the regenerative material. In 2017 Rocuzzo et al conducted a 7-year follow up on patients with diseased titanium-plasma-sprayed (TPS) or sand-blasted and acid etched (SLA) surface implants treated

with deproteinized bovine bone mineral and 10% collagen, following mechanical and chemical decontamination. At 7 years the survival rate for the SLA implants was 83% and 71% for the TPS implants. Where a successful outcome for therapy was defined as probing depths of ≤ 5 mm with absence of bleeding or suppuration on probing and no further bone loss, the success rates were only 14% for TPS implants and 58% for SLA implants. Mercado et al (2018) suggested a protocol of decontamination with Ethyl-diamine tetra-acetic acid (EDTA), regeneration with bovine xenograft and 10% collagen in combination with the antimicrobial doxycycline and enamel matrix derivative (EMD). Where appropriate, connective tissue grafting was used as an adjunct. This study found 56.6% of implants were deemed 'successfully treated' after 3 years, demonstrating maintainable probing depths and lack of progression of disease. An initial mean probing depth of 8.9mm at baseline on the diseased implants was reduced and maintained at a mean probing depth of 3.5mm. It has been reported that bone grafting around implants can be successful over a 3-year period with or without the use of resorbable membranes (Roos-Jansaker et al, 2011).

To date no 'gold standard' treatment approach has been identified for surgical regenerative treatment of PI and no single method of surface decontamination or regenerative material has been found to be clinically superior (Claffey et al, 2008). Through amalgamation of numerous studies, one review paper suggested a 'novel' protocol for treatment of peri-implantitis. This entailed open flap debridement with currettes, mechanical and chemical implant surface debridement via air-abrasion with glycine and EDTA application, followed by chlorhexidine irrigation. The defects were then grafted with freeze-dried bone allograft and Leucocyte platelet-rich fibrin (L-PRF) membranes with a gentamicin antibiotic mix (Ramansauskaite et al, 2016).

Much akin to periodontal surgery one important factor dictating the success and suitability of regenerative treatment may be the existing defect configuration. Schwarz et al (2010) demonstrated improved peri-implant clinical outcomes in grafted circumferential infrabony defects when compared to defects with varying degrees of buccal dehiscence. This suggests that circumferential bony defects around implants may be the most suitable for regenerative treatment.

1.10.3.3.1 Xenograft

Xenograft materials are among the proposed options for grafting materials for periodontal and implant related surgeries, including surgery to treat PI. By definition, a xenograft is a graft material taken from a donor of another species. Much research has been conducted on the use of xenograft in the treatment of periodontal infra-bony defects. One of the larger studies by Tonetti et al (2004) included 124 patients; in which bovine xenograft was used in the treatment of infra-bony defects, resulting in clinically significant probing attachment level gain compared to open flap debridement alone. However the literature varies in the perceived benefit of Xenograft in conjunction with GTR in periodontal defects compared to GTR alone, which may be just as effective (Murphy & Gunsolley, 2003).

Also of interest when considering the use of xenograft, particularly around implants, is the role of defect configuration. Polyzois et al (2007) demonstrated in their dog model study that wider defects around implants may benefit from the use of bovine xenograft; whereas narrower circumferential bony defects - in this study <1mm in diameter - may not obtain any additional healing benefits with the use of xenograft when compared to conventional healing via the

formation of a blood clot in the defect. Renvert and his colleagues treated 3- and 4-wall peri-implantitis defects surgically, grafting the defects with Endobon®, a bovine xenograft product; and compared one year outcomes against open flap debridement alone. The use of xenograft improved the treatment outcome when considering defect fill, reduction in probing depths, and the absence of bleeding on probing with no suppuration. A number needed to treat analysis identified an absolute risk reduction of 32.8% in favour of the test procedure using xenograft (Renvert et al, 2018).

1.10.3.3.2 Leucocyte-Platelet-Rich Fibrin (L-PRF)

Since the concept of periodontal regeneration was introduced, many different grafting materials have been suggested for this purpose including the use of autograft, allograft, xenograft and autoplast materials. Whilst these materials may potentially stimulate periodontal regeneration, they all rely on having adequate blood supply to provide cells and nutrients essential for formation. Over the past 20 years platelet concentrates, previously used in the medical field, have been suggested to have potential for periodontal regeneration. Platelets play a key role in wound healing and regeneration and have been shown to secrete a multitude of growth factors, cytokines and chemokines such as Platelet Derived Growth Factor (PDGF) and Vascular Endothelial Growth Factor (VEGF), which are known to be instrumental in periodontal wound healing. These growth factors are released in greater volume in platelet concentrates compared to normal blood samples (El-Sharkawy et al, 2007). Due to the level of interest in this material myriad publications on platelet concentrates have been published over the past two decades, utilising different technologies resulting in differing biological materials.

This stimulated then publication of a classification system for these materials in 2009 (Dohan Ehrenfest, 2009).

Table 2: Simplified table of commonly used platelet concentrates in Periodontology

Biological Product	Acronym
Pure platelet-rich plasma	P-PRP
Leucocyte and platelet-rich plasma	L-PRP
Pure platelet-rich fibrin	P-PRF
Leucocyte and platelet-rich fibrin	L-PRF

First introduced in 2001, L-PRF is an optimized blood clot in terms of wound healing, as it contains cells, growth factors and a fibrin matrix scaffold - all natural ingredients for wound healing (Choukroun et al, 2001). It has been hypothesized that the fibrin matrix allows for gradual release of growth factors over time (Dohan Ehrenfest, 2009), and indeed L-PRF has been shown to release a greater volume of growth factors over a longer time span compared to PRP (Schär et al, 2015). One study demonstrated L-PRF formulated using an Intralock Intraspin™ centrifuge contained 97% of available platelets and 50% of leucocytes within the blood sample taken (Dohan Ehrenfest, 2010a).

L-PRF has been shown to increase the proliferation rate of gingival fibroblasts by 3x and osteoblasts by 5.5x compared to cells exposed to normal blood samples (Dohan Ehrenfest, 2009). A later study by the same author demonstrated L-PRF had the ability to promote differentiation of human bone mesenchymal cells further questioning its role as a regenerative material (Dohan Ehrenfest, 2010b). Whilst the evidence for the use of L-PRF in periodontal regeneration is limited, a systematic review conducted in 2017 showed that the use of L-PRF

in conjunction with periodontal surgery resulted in an additional clinical attachment gain of 1.2mm in infrabony defects, and 1.3mm in furcation defects when compared to open flap debridement alone (Castro et al, 2017a). There were less comprehensive results in a systematic review assessing the use of L-PRF for bone augmentation and around implants, although generally positive outcomes were reported (Castro et al, 2017b). Despite the positive results presented in these two systematic reviews, the same protocols were not adhered to in all of the included studies and there was a moderate-to-high risk of bias in the majority of the studies.

1.11 The concept of re-osseointegration

Even with surgical intervention and regenerative treatment, it is unclear if true osseointegration can be achieved on previously contaminated implant surfaces.

Using a dog model Kolondis et al (2003) placed 12 previously contaminated implants into the mandible and demonstrated that all of the implants managed to successfully re-osseointegrate histologically regardless of the method of surface decontamination utilized. However implants were placed into fresh, native bone and the previously contaminated implants were not therefore, surrounded by any form of bony defect or diseased tissue. In a 2009 systematic review by Renvert et al, 25 studies were analyzed with regard to re-osseointegration on previously contaminated implant surfaces. Contrasting and conflicting evidence was found; however, the authors were able to conclude that in the majority of studies re-osseointegration of previously contaminated implants was not complete and was somewhere in the range of 1-84%.

Early animal studies using histological analysis have shown that, in the majority of cases,

following regeneration there is a connective tissue connection to the implant, rather than bone-to-implant contact, (Persson et al, 1999, Sennerby et al, 2005, Schwarz et al, 2006).

Conversely, a recent study in the dog model comparing re-osseointegration between moderately-rough and smooth surfaces utilizing differing grafting techniques demonstrated signs of re-osseointegration on implants treated following ligature induced PI. In this study, implants with a smooth surface responded comparatively better to treatment in terms of radiographic bone gain, re-osseointegration and resolution of disease than implants with a moderately rough surface (Almohandes et al, 2019).

Histological evidence of re-osseointegration not been comprehensively researched in humans due to ethical constraints about obtaining samples, but should be a consideration when evaluating the long-term prognosis and outcome of regenerative treatment around previously contaminated implants (Grunder et al, 1993, Ericsson et al, 1996, Persson et al, 1999, Wetzel et al, 1999, Shibli et al, 2003, Schwarz et al, 2006). Although re-osseointegration may be one of the goals of successful regenerative procedures, it may be the case that surgery may not resolve PI and result in re-osseointegration of the previously contaminated implant; but may merely fill the defect created by the disease process (Renvert & Polyzois, 2015).

1.12 Supportive Peri-Implant Therapy & Long-Term Follow-up

The role of supportive periodontal therapy (SPT) in the long-term success of periodontal treatment has been well established (Hirschfield and Wasserman, 1978, Axelsson et al, 2004).

Supportive peri-implant therapy should therefore be a fundamental component in the maintenance of improved clinical outcomes following peri-implant therapy.

Serino & Turri (2011) successfully treated patients with PI with open flap debridement, implant decontamination and often soft tissue resection. Over 5 years of subsequent professional maintenance only 13% of implants surgically treated for peri-implantitis went on to suffer further attachment loss (Serino et al, 2015). These studies highlighted the importance of maintenance of patients treated for PI.

Heitz-Mayfield et al (2018) conducted a similar prospective 5-year clinical trial of implants treated with open flap surgery with implant debridement. In this study of 24 patients with 36 implants statistically significant reductions in probing depths achieved through surgery were largely maintained following 5 years of sustained supportive peri-implant therapy. Where success was defined as absence of probing depths ≥ 5 mm with concomitant bleeding on probing/suppuration, and absence of progressive bone loss, these outcomes were seen in 63% of patients and 53% of implants at 5 years. Even in motivated and well maintained patients such as in this study, only 42% of implants demonstrated no sites with bleeding on probing at 5 years post-treatment.

1.13 Outcome measures for treatment for peri-implant disease.

Currently used methods of evaluating the success of treatment for peri-implant disease include measuring probing pocket depths and bleeding on probing; as well as lack of symptoms, swelling, redness, loss of function, lack of mobility and stabilization of radiographic bone levels. Unfortunately, traditional periodontal indices and measurements may not be truly applicable to the peri-implant model (Coli et al, 2017), and hence additional diagnostic tests or indices may be of use when determining the success of therapy for peri-implant disease.

Furthermore, there is currently a lack of consensus in the literature as to a true, detectable, clinical end-point for treatment of peri-implant disease, leading to heterogeneity in research outcomes and difficulty in comparing results of different studies.

1.14 Implant stability

Implant stability is a critical factor in the success of implant treatment, and prosthodontic treatment thereafter. Implant stability can be defined as the absence of clinical mobility, which could also be suggested as a definition of osseointegration. However, even a clinically stable osseointegrated implant will show signs of mobility on a micro-scale when loaded. Factors influencing the amount of micro movement in loading include bone-implant contact and implant design. The amount and quality of the bone tissue surrounding an implant will have a large effect on the stability of the implant, and the micro- and macro-design of the implant will affect the bone-implant interface, hence influencing stability (Sennerby & Meredith, 2008).

In situ, an implant undergoes clinical loading many directions and degrees of force; including intrusive and extrusive forces, rotational forces and bending forces. Consequently the outcome of an implant stability analysis is highly dependent on the direction and type of force applied during the testing (Sennerby & Meredith, 2008).

1.14.1 Methods of measuring implant stability

Many methods of assessing implant stability have been suggested. Clinically stability is often judged on the cutting resistance of the implant during its insertion into the osteotomy. At the

time of implant placement, a torque wrench may also be used to assess implant stability by the amount of torque required to seat the implant (Aparicio et al, 2006). Alternatively, percussion testing may be used to assess implant stability by tapping a mirror handle or blunt instrument against the implant or abutment. A high pitched or ringing sound from the implant may be a good indicator of the implant stability. However this method of testing is crude at best, and may provide more information about the instrument than the implant itself (Sennerby & Meredith, 2008).

Applying reverse torque to the implant at the abutment phase prior to restoration has also been suggested as a method of gauging implant stability (Sullivan et al, 1996). The risks of performing this test on the bone-implant interface at potentially osseointegrating implants are obvious, and hence alternative methods of assessing implant stability are preferable. Surgical re-entry to visually inspect implants and the surrounding bone has also been suggested. However, along with counter-torqueing, this could result in adverse effects on the implant stability and surrounding tissues (Valderrama et al, 1997).

Due to the rudimentary nature of these tests, alternate methods have been suggested to assess implant stability; these include assessment of damping capacity and resonance frequency analysis, the latter in both in electrical and magnetic forms. These techniques potentially present minimally invasive methods for testing implant stability and, theoretically, osseointegration.

1.14.2 Resonance Frequency Analysis (RFA)

Resonance frequency analysis is a minimally invasive technique that can be used to assess implant stability. By utilising a transducer attached to the implant, a lateral bending force can

be applied to the implant, albeit on a small-scale, producing an implant stability reading. As force is applied, the implant undergoes a lateral bending force, in which the implant is displaced, returning to its original position once the force is removed. This type of system is largely dependent upon three factors: First, the design of the transducer; second, the stiffness of the implant fixture and the implant-bone interface; and third, the proportion of the implant that sits supracrestal (Sennerby & Meredith, 2008).

In the mid-90s it was suggested that resonance frequency analysis could be applied to implants to test the stability and potentially osseointegration of implants (Meredith et al, 1996).

These authors suggested the use of electronic resonance frequency analysis (ERFA) to assess implant stability. Their initial clinical trial was 3-fold in its design: Firstly the EFRA technology was tested on implants of different lengths mounted at different heights in aluminum blocks. Secondly this technology was placed on implants in slowly setting resin to see if changes in density could be identified over time. Thirdly, the technology was applied to implants in situ to test its suitability. This study indicated that resonance frequency analysis could differentiate between implants mounted at different levels in aluminum blocks, suggesting that the proportion of exposed implant may influence implant stability readings.

The study also demonstrated that RFA could be used to detect changes in stability of implants encased in setting resin, suggesting it may be able to detect subtle changes in bone quality that take place during osseointegration. Once it was established that ERFA could be applied to implant in situ, the authors hypothesized that resonance frequency analysis may be suitable to test healing, osseointegration and changes in bone height around implants.

Since Meredith first suggested the use of resonance frequency analysis as a method to test implant stability in the 1990s many generations of RFA machines have entered clinical use.

The initial ERFA devices used by Meredith et al (1996) included a lot of cabling and

computerized equipment making them cumbersome and not practical for everyday clinical use. These machines were also comparatively slow at analyzing frequencies compared to more modern devices (Sennerby and Meredith 2008). For ease of use and to create a minimally invasive technique, transducers were introduced as simple responders that could be clipped or screwed into the implant well. However the initial transducers manufactured all had their own resonance frequencies and hence had to be calibrated before they could be used clinically for comparable measurements (Sennerby & Meredith, 2008).

Subsequently, magnetic resonance frequency analysis (MRFA) machines have become more popular due to their relative ease of clinical use. As technology progresses new MRFA devices such as the Osstell™ have been introduced. These use precalibrated transducers in the form of the SmartPeg™, and smaller hand-held devices that make MRFA practical for everyday clinical use.

1.14.2.1 Osstell™

The Osstell™ device uses a sensor (SmartPeg™), which is screwed into the platform of an implant. Magnetic pulses are gently applied to the peg, eliciting a bending force. Various SmartPegs™ are available to fit many of the commonly used commercially available implants. The peg contains a small magnet, which is excited by magnetic pulses applied by an applicator attached to a hand-held computer. The smart peg will vibrate for a short while in two perpendicular directions and then stop. The higher the stability of the implant, the higher the vibration frequency of the smart peg (Hz). These frequencies are then converted into a simple 1-100 scale called ISQ (Implant Stability Quotient). ISQ 1 corresponds approximately to 1,000Hz and ISQ 100 to approximately 10,000Hz; although the scale is not necessarily linear.

According to the manufacturer, and reportedly based on over 700 references, ISQ values of 70 and above represent high implant stability, values of 60-69 medium implant stability and less than 60 indicate low implant stability. (Baltayan et al 2016)

1.15 Factors influencing resonance frequency analysis

1.15.1 The implant-bone interface

Many studies have assessed the relationship between bone quality and RFA data.

Early studies compared cutting resistance at time of osteotomy preparation and implant placement. Friberg et al (1999) carried out a study on maxillary implants comparing cutting resistance and RFA, coupled with a 20-month follow up of RFA values. The two considerable findings of this study were that firstly there was a relationship between increased cutting resistance, which could indicate high bone density, and increased RFA values. Secondly, after 1 year in function all implants tended to reach similar RFA values, despite initial variation in stability values. Similar findings were demonstrated by Andersson et al (2008) in their study of 102 implants. An inverse relationship between bone-density demonstrated by cutting torque, and changes in implant stability were found over a one-year follow-up. In addition there was a correlation between bone quality and initial implant stability, where implants placed in soft bone with a low primary stability showed a marked increase in stability over 12 months in comparison to more subtle changes in RFA values of implants placed in dense bone with initial high stability. The findings regarding the relationship between bone quality and density and initial RFA values indicate that the stiffness of the implant-bone interface is higher in dense bone than in soft bone. These findings are mirrored throughout the literature and are

validated by the Turkeyilmaz et al (2009) cadaver study, in which a positive correlation was found between cutting insertion torque and RFA values, in addition to RFA values and Hounsfield Units analyzed by computed tomography scans.

In conjunction with many other authors, Ostman et al (2006) established that RFA values are routinely found to be higher in the mandible than the maxilla, these differences are thought to be caused by relative differences in the density of maxillary and mandibular bone. Other findings from this study of 905 consecutively placed implants showed that stability could also be dependent on gender, implant diameter and the anterior / posterior position of the implant; and that implants of increasing length often showed lower RFA values.

Conversely, a study by Huwiler et al (2007) found there was no correlation between ISQ values and bone density and/or bone trabecular connectivity based on use of micro-CT analysis of osteotomy cores taken with a trephine prior to placement of 23 Straumann™ implants. The authors speculated that ISQ levels do not in fact give an accurate representation of the bone-implant interface at the time of implant placement; but more likely reflect the density and thickness of the cortical layer of the alveolar crest.

Studies have suggested an increased amount and thickness of the cortical bone surrounding an implant at time of placement has a positive effect on RFA values. In a study of 225 implants placed in both the maxilla and mandible and analyzed via computed topography, Myiamoto et al (2005) was able to demonstrate a correlation between available cortical bone and RFA values. Similarly, Nkenke et al (2003) was able to demonstrate a positive correlation between crestal cortical bone height and RFA values in their study on cadavers.

1.15.2 Marginal bone loss

In the initial Meredith et al (1996) study on the use of RFA as a method to test implant stability, it was shown that RFA could be used to differentiate between implants mounted at differing levels in aluminum blocks. This early study suggested that RFA may be suitable for the assessment of marginal bone levels or loss around implants. Sennerby et al (2005) were able to demonstrate that even small changes in marginal bone levels could be detected by changes in RFA. This study evaluated experimentally made marginal bone defects in the dog model and evaluated changes in RFA values with radiographic and histological analysis; results demonstrated that even a minor loss in marginal bone levels resulted in a decrease in electronic RFA values.

In their 5 year study of 52 maxillary implants, Meredith et al (1997) found a positive correlation between bone loss and decreased resonance frequency values by measuring the number of radiographically exposed threads after 5 years and the comparative electronic resonance frequency values. Turkyilmaz et al (2006) found a similar correlation between marginal bone loss and decreasing RFA values in mandibular implants in the first 6 months following implant placement. However no such correlation was seen after the 6 month mark in this 1 year follow-up study; the authors suggested that the increase in stability after 6 months may be due to a compensatory effect of new bone formation and remodeling around the remaining covered implant surface. Conversely, Fischer et al (2008) found no correlation in the relationship between marginal bone loss and RFA values in the first year post implant placement. However, following 3 to 5 years of follow up the same authors found a strong correlation between marginal bone loss and decreasing RFA values.

In 2018 a study was conducted in the beagle dog model assessing if there was a correlation between marginal bone loss caused by ligature induced PI and changes in ISQ values over time. 36 implants were subjected to ligature-induced PI, with marginal bone loss increasing and ISQ levels decreasing with time resulting a strong negative correlation ($r=-0.58$, $p < 0.001$) at all 4 tested timepoints. A decrease of 1 ISQ point equated to approximately 1mm of marginal bone loss, despite ISQ values failing to show correlations with any other clinical parameters recorded (Monje et al, 2018).

1.15.3 Orientation of transducer

In an ideal situation an implant should be surrounded by ample bone in all planes, however this is not necessarily always the case. Bone may often be thinner in the bucco-lingual than the mesio-distal dimension and this may result in discrepancies between relative RFA values. Early generation RFA machines often produced differing readings dependent upon the direction the magnetic or electronic force was applied. Veltri et al (2007) discovered in their study that ISQ levels may differ by up to 10 points dependent on whether the transducer was placed in a mesio-distal or bucco-lingual direction.

Some newer generations of RFA machines such as the Osstell Mentor™ take averages of such measurements to ensure continuity in readings taken from different directions, however this suggests caution should be taken when comparing readings from machines of different generations. Valderamma et al (2007) completed a randomized controlled trial comparing 777 RFA measurements on original electronic RFA (ERFA) machines and 711 measurements with newer magnetic RFA machines (MFRA). They found a mean difference of 8-12 points with higher measurements being found on newer MFRA machines compared to the older ERFA.

This again reiterates caution should be taken when comparing results from different generations of or different forms of resonance frequency analysis.

1.16 Trends in implant stability at implants post-placement.

Many studies have assessed changes in RFA values of newly placed implants.

Valderamma et al (2007) carried out a randomized controlled trial in which 34 implants were placed in 17 patients; the patients were followed up with RFA measurements every week post-surgery for 6 weeks and again one last time at 12 weeks. The findings demonstrated that mean implant stability decreased in the first 1-2 weeks by approximately an ISQ of 1.5 and increased again by an ISQ of 1.5 from weeks 3-6. Huwieler et al (2007) took MRFA values on 23 Straumann™ implants at regular intervals in the first 12 weeks post placement. They found an initial rise in the levels of stability in the first week post placement before a drop in ISQ values, with the lowest values evident 3 weeks post-placement. Following the third week the ISQ levels rose again to levels either at or above those detected at the time of implant placement.

Andersson et al (2008) evaluated 1-year follow-up RFA values on 102 newly placed Neoss™ implants. In this study, implants placed in type 1 and 2 bone underwent a slight decrease in stability before all implants reached a comparable level of stability after 12 months.

This initial loss in stability seen in the aforementioned studies may be attributed to the healing and remodeling process of bone, including the initial resorptive phase, which may result in a temporary weakening of the implant-bone interface. These findings are mirrored in the Glauser et al (2004) study; however a study by Fischer et al (2008) using tapered form

implants demonstrated ever increasing RFA values in a 12-month follow up until terminal RFA values were reached. Turkyilmaz et al (2006) demonstrated implant stability decreased in the first 6 months following implant placement in correlation with bony remodeling, however no such correlation was seen after the 6-month mark in this 1 year follow-up study. As previously mentioned, Fischer et al (2008) found no relationship between marginal bone loss and decreased RFA values in the first year post implant placement, only for a strong correlation to be found after 3-5 years follow-up.

In the Becker et al (2005) study, 73 immediate implants were assessed at time of placement and pre-prosthetically during the healing abutment phase. The average time between measurements was 5.6 months and the authors reported on average 2-point increase in ISQ over that time. Interestingly, they also found that implants with an initially low ISQ reading - indicating lower initial stability - increased in stability over time; whereas implants with an initially high stability either remained the same or decreased over the pre-prosthetic time period. Therefore, these authors suggested that all implants reach a similar level of stability, irrespective of the level of primary stability. However, it is important to note that this was limited to immediate implants with only two measurements taken. In their one-year follow-up study, Nedir et al (2004) placed implants in 36 patients. RFA measurements were taken 7 times during the first 3 months of healing. Implants with a higher initial stability (ISQ 60-69) showed an initial decrease in stability over the first 8 weeks before returning to the initial ISQ levels; whereas implants with an initially lower ISQ (<60) showed a gradual increase in stability. Implants with a very high initial stability (ISQ >69) underwent an initial decrease in stability in the first 4 weeks subsequently remaining stable.

A study analyzing 64 implants with 4 weeks follow-up by Oncu et al (2015) demonstrated that sites where L-PRF was placed in the osteotomy site prior to implant placement demonstrated

increased primary implant stability average 7 ISQ points by the end of the study. Interestingly, implants placed in sockets with L-PRF did not seem to undergo the initial early loss in stability like control implants; which underwent a 2.6 ISQ loss in the first week post placement before rebounding by the fourth week.

1.17 Use of RFA as a predictor of implant failure.

Rodrigo et al (2010) looked at the diagnostic value of MRFA, specifically Osstell™, as a predictive tool for early implant survival. MRFA measurements were taken at the time of implant placement and pre-prosthetically at an average of 2.8 months after placement. A threshold of ISQ 60 was set for analysis. Their results suggested that MRFA readings taken at the time of implant placement are not significant in terms of predicting implant failure, but readings taken at the pre-prosthetic phase may serve as significant predictors of failure. Of implants with a pre-prosthetic ISQ of ≤ 60 , 19% of implants were considered failures; whereas no implants with an ISQ of >60 were considered failures. Huwiler et al (2007) speculated that MRFA is not a reliable predictor of implant failure. In their study of 23 implants, 1 implant failed 3 weeks post-placement. This implant had a high primary stability and continued to show high stability before undergoing an ISQ drop of 23 points in 1 week to an ISQ of 45. Clinical mobility was detected on attachment of the transducer and the implant removed; hence in this case MRFA was not necessarily an indicator of implant failure until after the fact. Nedir et al (2004) suggested a minimum safety threshold of ISQ 47 required to torque a prosthetic abutment to 35nm, stating that values less than that would be deemed a risk. However it should be noted that the Osstell™ device used in this study was a prior

generation to the latest Osstell™ machines, which provide IS values approximately 10 ISQ units higher on average than their predecessors (Valderamma et al, 2007). Consequently the above studies suggest that a pre-prosthetic MRFA value may be of more use in predicting implant failure than values taken at time of implant placement.

MRFA has been suggested as a valid diagnostic tool in monitoring PI progression. Monje et al (2018) conducted a study of 36 implants subjected to ligature induced PI in a dog-model. They demonstrated a strong negative correlation ($r = -.58$, $p = <0.001$) between MRFA measurements (Osstell Mentor™) and changes in marginal bone level assessed by computerized tomography. A prediction of marginal bone loss showed a decrease in marginal bone levels of 1mm equated to an approximate drop of 1 ISQ point. Through histological analysis, these authors also demonstrated that there was also significant correlation between ISQ levels and bone-to-implant contact, although they failed to show any correlation between periodontal probing depths or signs of inflammation and ISQ levels. This paper complements the previously cited evidence that MRFA may be able to predict changes in marginal bone loss and hence disease progression.

1.18 Limitations of Resonance Frequency Analysis.

In 2017, Andreotti et al carried out a comprehensive systematic review on MRFA and Dampening Capacity Analysis (DCA) devices comparing and contrasting their efficacy regarding implant stability analysis. MRFA was deduced to be the more reliable and reproducible technology, however the results of different forms of resonance frequency analysis were not comparable. The authors summarized that MRFA is a useful diagnostic aid

but should be used in conjunction with clinical and radiographic analysis to confirm diagnosis before making clinical decisions with regard to treatment.

As previously mentioned, Valderrama et al (2007) conducted a randomized controlled trial to test, among other variables, if the results of the older ERFA device could be compared and contrasted to the newer MRFA devices. Over 1400 measurements were taken on 34 newly placed implants over a 12-week period using both ERFA and MRFA devices. It was concluded both devices gave repeatable ISQ values, although the MRFA device routinely gave ISQ readings 8-12 points higher, and that MRFA technology should not be compared to older ERFA values for clinical diagnostics. One substantial limitation of the technology is that, to achieve reproducible and comparable readings, similar generations of devices with identical technology are required.

Additionally implants produced by different manufacturers may give differing ISQ levels regardless of bone density and implant stability. Consequently RFA values between different implant forms or manufacturers are not necessarily comparable. Implants of different systems may eventually reach a maximum level of stability with time. For example a Straumann™ implant may eventually reach a stability of ISQ 55-65 whereas a Brånemark™ implant may reach a final stability of ISQ 65-75 (Sennerby & Meredith, 2008). This has obvious ramifications when evaluating implant stability at time of placement, loading or in identifying early or late implant failures.

Nedir et al (2004) surmised that MRFA was not a reliable diagnostic tool when identifying mobile implants, and found implant stability can only be reliably determined for implants with an $ISQ \geq 47$. It may be the case that there is a minimum threshold beyond which MRFA can be used to detect implant stability through the bending forces applied to detect stiffness. Once a

certain level of implant mobility, as opposed to stability, is achieved the technology may be rendered ineffective.

Some studies have suggested that it is only the most coronal third of the implant that determines the degree of rigidity measured by RFA (Nkenke et al, 2003, Gedrange et al, 2005, Miyamoto et al, 2005) and therefore RFA is not a true measurement of implant stability. Indeed some authors postulate that RFA is not an accurate measurement of bone-to-implant contact at microscopic level, and is merely an indication of the bone-to-implant complex stiffness (Turkyilmaz et al, 2009) or cortical bone thickness (Huwiler et al, 2007).

1.19 RFA as an indicator of successful peri-implant treatment.

There is very little available literature on the use of resonance frequency analysis as an indicator of successful peri-implant treatment, or studies showing correlations between commonly utilized improved periodontal indices and improved RFA values.

Sennerby et al (2005) demonstrated healing of experimentally induced peri-implantitis in the dog model resulted in improved RFA values when tested with ERFA. They stated new bone was formed around both machined and SLA surface implants following open flap surgery. RFA values increased in correlation with improved radiographic and histological findings. Interestingly RFA values improved comparatively better on SLA implants in comparison to machined implants; the authors suggested this may be due to the fact that a thin connected tissue capsule formed around the machined surface implants compared to direct implant-bone contact on the SLA implants on histological analysis.

2. Materials and Methods

Aims & Objectives

The aim of the present study was to investigate the impact of peri-implantitis treatment upon clinical parameters and implant stability quotient values, and to ascertain if MRFA can be used as a diagnostic tool to demonstrate post operative healing following treatment of peri-implantitis.

The secondary objective was to identify the most appropriate time for re-evaluation of implant stability following treatment with using MRFA technology.

2.1 Study Design

This study was a prospective clinical study on a cohort of patients attending Dublin Dental University Hospital who were referred for peri-implant disease or in whom peri-implant disease was diagnosed.

2.2 Ethical Approval

An application for ethical approval was submitted to St James' Hospital research ethics committee (JREC). The study protocol was approved in March 2017. Reference (2017-05 list19(2)) (*Appendix 1*)

2.3 Study sample

Subjects were recruited from a population of patients who were referred to the Dublin Dental University Hospital for the treatment of peri-implant disease; or in patients whom peri-implant disease was diagnosed during their treatment in the Dental Hospital.

2.3.1 Inclusion Criteria

- 1) The implants included in the study were Brånemark (Nobel Biocare™, USA), Zimmer Biomet innovations™ (Palm beach gardens, Florida, USA); Straumann™ (Waldenburg, Switzerland) or Ankylos™ (Dentsply™, USA).
- 2) Implants supporting removable or fixed implant prostheses, both cemented and screw-retained; provided prostheses could be removed without risk of permanent damage.

Figure 1: Single Implant Crown Prior- and Post-Deconstruction.



Figure 2: Denture Bar Prior- and Post-Deconstruction

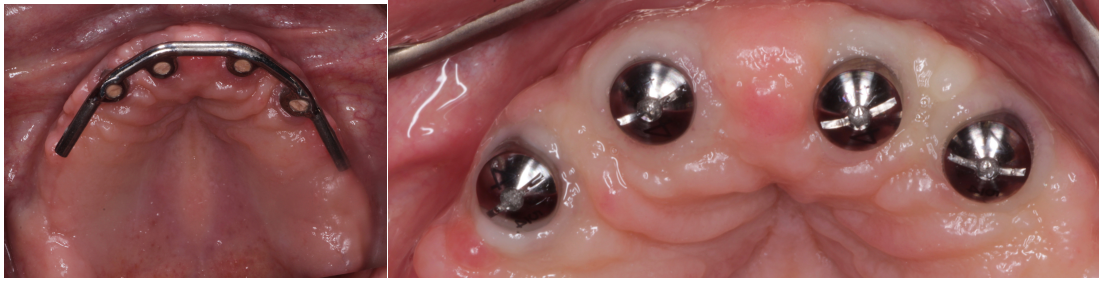


Figure 3: Full-arch Hybrid Prior- and Post-Deconstruction



2.3.2 Exclusion Criteria

- 1) Dental implants other than the 4 manufacturing companies listed above.
- 2) Treatment of peri-implant disease in the past 3 months.
- 3) Pregnancy or lactation.
- 4) Mental disability or psychiatric illness that would contradict surgical intervention.
- 5) Medical history that precludes the patient from oral surgery.

2.3.3 Consent

Patients deemed suitable for the study were provided with a consent form and attached information leaflet (*Appendix 2*) and contacted seven days later to ascertain if they were willing to participate. The main authors email address was provided should patients have further questions or queries that could be answered pre-commencement of the trial.

2.4 Study Outline

Patients were initially diagnosed with peri-implantitis as a result of examination by EM (Ed Madeley), IP (Ioannis Polyzois) or PH (Peter Harrison).

At the initial appointment full periodontal charting around implants and implant stability measurements MRFA were recorded. Additionally baseline radiographs were taken, either intra-oral periapical radiographs using the paralleling technique; or an orthopantomogram.

Patients and implants were treated according to individual patient and site needs. All patients received oral hygiene instruction and non-surgical debridement of the implants. In cases of peri-implantitis where implants required open flap debridement or surgical regeneration this was carried out based on the individual characteristics of the patient and implant site.

Whatever was deemed clinically as the best treatment option for the implant was carried out in an evidence-based approach.

Treatment was carried out by one of 3 operators; EM (Ed Madeley), IP (Ioannis Polyzois) & PH (Peter Harrison).

Medical history and smoking status was confirmed at each appointment.

Further MRFA measurements and probing depth clinical measurements were recorded at 3 months, 6 months and 1 year post-treatment as outlined in the table below.

Table 3: Timeframe of research.

	Baseline	3 Months	6 Months	12 Months
Clinical Measurements	✓	✓*	✓	✓
MRFA (Osstell™)	✓	✓	✓	✓
Treatment	✓			
Radiographs	✓			✓
Oral Hygiene Instructions	✓	✓	✓	✓

* Clinical measurements not taken at 3 months where regenerative surgery completed

2.5 Clinical Parameters

All clinical and implant stability measurements were carried out by one examiner (I.P).

With regard to probing depths, six sites were recorded to the nearest millimetre on each implant with a Hu-Friedy™ UNC periodontal probe (Hu-Friedy™, Chicago, IL, USA).

Recession defects on the implants were recorded where present to the nearest millimetre.

Bleeding and/or suppuration were recorded at six sites as either present or absent.

Levels of keratinized tissue attachment on the effected implants was measured mid-buccally using the the same UNC probe.

Plaque levels on the implants were recorded at six sites as present or absent and expressed as a percentage of implant sites effected as per the O'Leary plaque index (O'Leary et al 1972).

2.6 Radiographic Measurements

Intra-oral periapical radiographs or an orthopantomagram were taken at baseline and at one year examination to aid in diagnosis. Radiographs were taken using long-cone paralleling technique and phosphor plates which were developed using a digital scanner. The radiographs were assessed by one examiner (E.M) using Planmeca Romexis Pro™ software. Radiographs were pre-calibrated to a known dimension (implant length), and mesial and distal measurements were taken at each implant from the platform to the first bone contact.

2.7 Diagnosis

Only implants that were diagnosed according to the 2018 classification were included in the study (Berglundh et al 2018).

Peri-implantitis: “A plaque associated pathological condition occurring in the tissues around dental implants, characterised by inflammation in the peri-implant mucosa and subsequent progressive loss of supporting bone.”

Criteria for diagnosis according to the 2018 classification of periodontal diseases:

- Presence of BoP and or/suppuration.
- Increased probing depth compared to previous examinations.
- Presence of bone loss beyond crestal bone level changes resulting from initial bone remodelling.

Where no previous radiographs or records were available, implants were diagnosed with peri-implantitis where:

- Presence of bleeding on probing and/or suppuration on gentle probing.
- Probing depths of $\geq 6\text{mm}$.
- Bone levels $\geq 3\text{mm}$ apical to the most coronal portion of the intraosseous part of the implant. (Berglundh et al 2018)

2.8 Implant Stability Measurements

Implant stability was assessed by magnetic resonance frequency analysis (MRFA) using the Osstell Mentor ISQ™ (Osstell AB, Gothenburg, Sweden).

Osstell™ measurements were taken at baseline, 3, 6 and 12 months. At each of these visits the restorations were removed from the implants and a Smart Peg was mounted to the platform of the implant using the screw channel, using hand-tightening only as per the manufacturers instructions. (Fig 4) Each Smart Peg was single use and specific to the particular brand of implant and implant connection.

A magnetic force was then applied to the peg via the sensor on the Osstell™ machine and the

resonance frequency analysed. Mesio-distal and bucco-lingual measurements were recorded on each implant and each measurement was taken 3 times to assure accuracy. (Fig 5) A mean recording was taken on each implant based on the mesio-distal and bucco-lingual ISQ values.

Figure 4: The application of a smart-peg to the implant platform and use of the Osstell Mentor™. Image courtesy of Osstell™ promotional material.

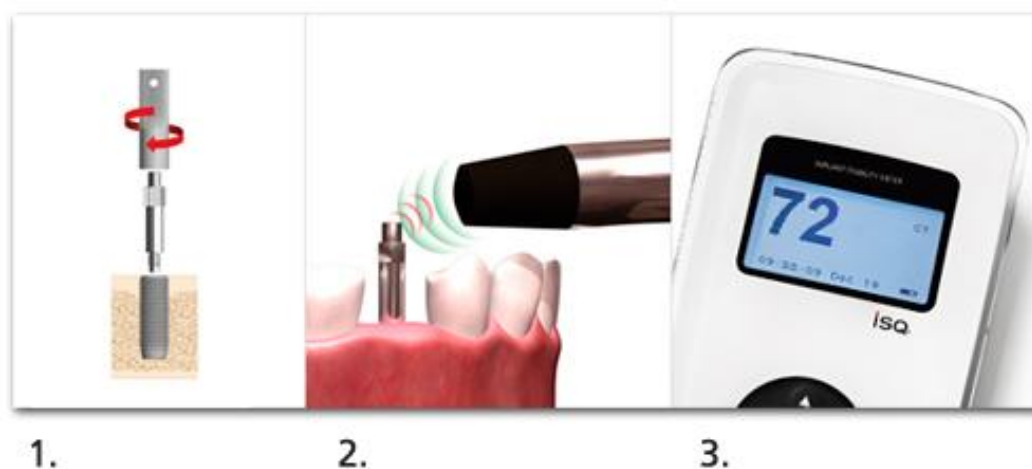


Figure 5: Application of the Osstell Mentor™ sensor to the smart-peg.



Once the ISQ values had been obtained the smart peg was removed and the restoration or healing abutment immediately replaced.

2.9 Treatment

Patients were treated according to their specific peri-implantitis defects and wishes.

All prostheses were dismantled so implants could be accessed from platform level.

All patients received non-surgical therapy prior to any surgical therapy or as a monotherapy.

Non-surgical therapy consisted of oral hygiene instructions, mechanical debridement of the implant surfaces with titanium currettes and local application of 1% chlorhexidine gel to the affected implants.

Where deemed appropriate implants received surgical intervention. Implants were treated by open flap debridement with chemical decontamination of the implant surface using 3% hydrogen peroxide, in addition to mechanical debridement with titanium currettes. Implants were further treated with the use of regenerative materials where the bony defects were suitable for grafting, alternately a resective surgical approach was applied.

Regenerative materials used included bovine Xenograft (Endobon™, Zimmer Biomet™), resorbable collagen barrier membranes (Osseoguard™, Zimmer Biomet™), Leucocyte platelet-rich fibrin (L-PRF) membranes, and L-PRF mixed with bovine xenograft and fibrinogen (L-PRF block).

Oral hygiene instructions were provided during the initial treatment phase and reinforced at each follow-up procedure.

Where prostheses were deemed to be prohibitive for access for cleaning by the patient at home, prosthesis recontouring was carried out where appropriate.

2.10 Data Analysis

Data was collected on a single tabulated data collection sheet. (Appendix 3) At the end of data collection all data was inputted into Microsoft Excel™ and subsequently transferred into SPSS™ statistical software (IBM™, USA) for statistical analysis.

2.11 Statistical Analysis

All data was analysed at implant level.

Data was initially checked for normal and non-normal distribution.

Changes in periodontal parameters and ISQ changes over time as well as baseline and 12 month bone levels were initially assessed. Where data was normally distributed One-Way ANOVA analysis was carried out to test statistical significance and means are reported; by contrast where data was non-normally distributed Kruskal-Wallis analysis was completed and both means and median values are reported.

Due to the nature of the differing treatment modalities employed in the study sub-group analysis was undertaken. The four treatment groups analysed were:

- 1) Non-surgical therapy only. (Treatment Modality I, TMI)
- 2) Non-surgical therapy followed by open flap debridement +/- resective surgery.
(Treatment Modality II, TMII)
- 3) Non-surgical therapy followed by open flap debridement with guided tissue regeneration (resorbable collagen membrane only) or resorbable Leukocyte Platelet-Rich Fibrin plugs and/or membranes. (Treatment Modality III, TMIII)
- 4) Non-surgical therapy followed by open flap debridement with regenerative therapy using guided bone regeneration (collagen membrane with bovine xenograft) or

Leukocyte Platelet-Rich Fibrin +/- hard tissue grafting with bovine xenograft. Also known as the L-PRF block. (Treatment Modality IV, TMIV)

Where data was normally distributed a One-Way ANOVA analysis was carried out to test statistical significance and means were reported; by contrast where data was non-normally distributed a Kruskal-Wallis analysis was completed and both means and median values were reported.

Changes in periodontal measures taken at each time point were tested for correlation with changes in ISQ readings taken at the same time points. Where data was normally distributed Pearson correlation coefficient testing was undertaken and by contrast where data was non-normally distributed Spearman correlation testing was utilised. As with the periodontal outcome analysis, the data was initially analysed as a whole including all implants regardless of treatment received. Subsequently, the data was analysed by subgroup based on the treatment provided.

3. Results

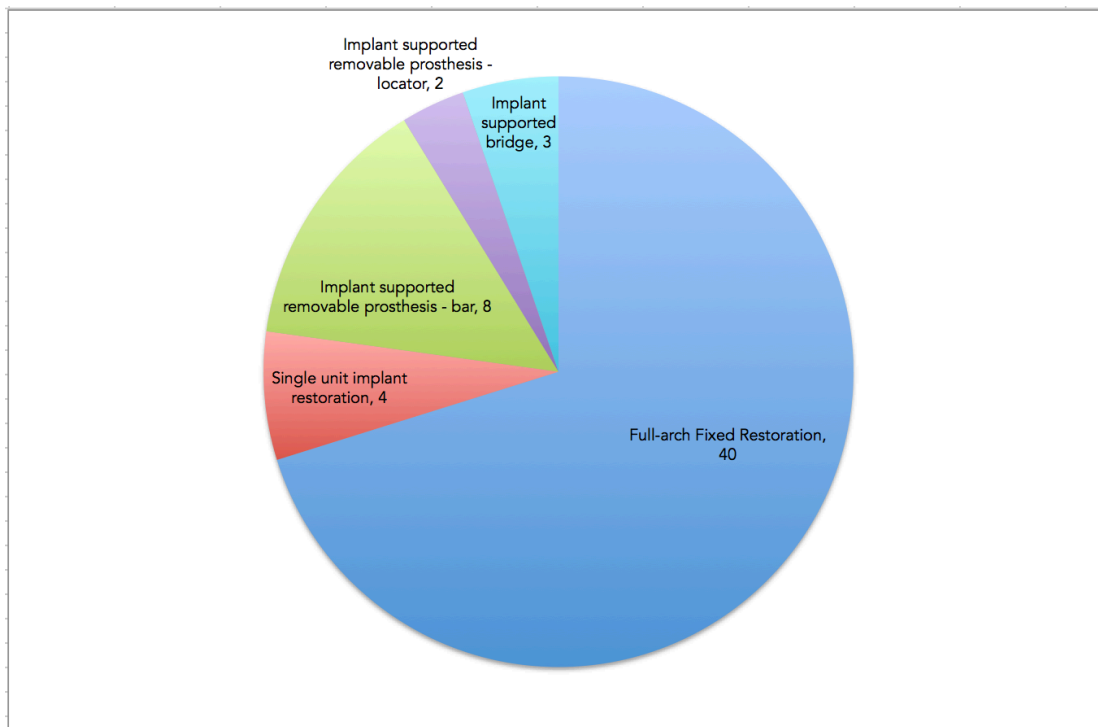
3.1 Demographics

18 patients (5 Male and 13 Female) with 57 implants were included in the study. The mean age of the patients was 67.10 years of age with a range between 57 and 79 years of age.

Of the 57 treated implants; 1 implant was Straumann™ (Straumann Group, Basel, Switzerland), 3 were Ankylos™ (Dentsply™, Sirona) and the remainder of the implants were either Zimmer Biomet™ (Biomet, USA) or Brånemark™ (Nobel Biocare™, USA).

Figure 6 shows the various types of resoration supported by the treated implants, with the majority of implants included in the study supporting full-arch fixed restorations.

Figure 6: Types of implant supported restorations included in the study cohort.



3.2 Periodontal Clinical Outcomes

Table 4 outlines the overall periodontal clinical outcomes at each time point of all the implants included in the study. Where data was normally distributed One-Way ANOVA analysis was carried out to test statistical significance and means are reported; by contrast where data was non-normally distributed Kruskal-Wallis analysis was completed and both means and median values are reported.

Two implants were extracted at baseline following detection of clinical mobility.

Following peri-implant therapy, over the subsequent 12 months there was an overall average reduction in bone loss of 0.27mm which was non-statistically significant. By contrast over 12 months all other recorded periodontal parameters showed statistically significant improvements compared to baseline. There was a 1.88mm reduction in deepest probing depth ($p<0.0001$), a 1.57mm reduction in average probing depth ($p<0.0001$), a 1.46mm gain in clinical attachment level ($p<0.0001$), and reductions in plaque score and bleeding score of 50% ($p<0.0001$) and 66% ($p<0.0001$) respectively.

The following figures demonstrate trends in periodontal parameters over 12 months including post-hoc statistical analysis showing relative periods of significance using Tukey post-hoc ANOVA for normally distributed data and Kruskal-Wallis for non-normally distributed data.

Table 4: Clinical Periodontal Outcomes

Variable	Baseline	3 Months	6 Months	12 months	
Marginal Bone Level (mm)	54			50	N
	- 4.30 (2.13)			- 4.03 (1.74)	Mean (SD)
	0.00mm			0.00	Min bone loss
	11.90mm			8.60	Max bone loss
		.534			
Deepest Probing Depth (mm)	57	25	53	55	N
	5.86 (2.63)	3.33 (1.05)	3.89 (1.45)	3.98 (1.56)	Mean (SD)
	6.00	3.00	4.00	4.00	Median
	2.00	2.00	2.00	2.00	Min
	17.00	5.00	7.00	10.00	Max
	<0.0001*				Sig.
Average Probing Depth (mm)	57	25	53	55	N
	4.92 (2.49)	2.49 (0.97)	3.23 (1.24)	3.35 (1.48)	Mean (SD)
	1.50	1.17	1.50	1.17	Min
	16.83	4.67	6.33	9.33	Max
	<0.0001**				Sig.
Average Clinical Attachment Loss (mm)	57	25	53	55	N
	5.48 (2.56)	2.76 (1.29)	3.74 (1.38)	4.02 (1.63)	Mean (SD)
	1.50	1.17	1.50	1.83	Min
	16.83	6.17	6.33	9.33	Max
	<0.0001**				Sig.
Bleeding on Probing (%)	57	25	53	55	N
	62.00% (43.66)	21.33% (28.27)	36.85% (34.81)	35.15% (37.08)	Mean (SD)
	83.00%	17.00%	33.00%	17.00%	Median
	0.00%	0.00%	0.00%	0.00%	Min
	100%	100%	100%	100%	Max
	<0.0001*				Sig.
Plaque Score (%)	57	25	53	55	N
	76.32% (42.13)	23.33% (37.37)	36.48% (40.17)	53.33% (47.40)	Mean (SD)
	100%	0.00%	33.00%	50.00%	Median
	0.00%	0.00%	0.00%	0.00%	Min
	100%	100.00%	100%	100%	Max
	<0.0001*				Sig.

**, Significant at the 0.01 level (one-way ANOVA for normally distributed data)

* Significant at the 0.01 level (Kruskal-Wallis for non-normally distributed data)

Figure 7: Deepest Probing Depth

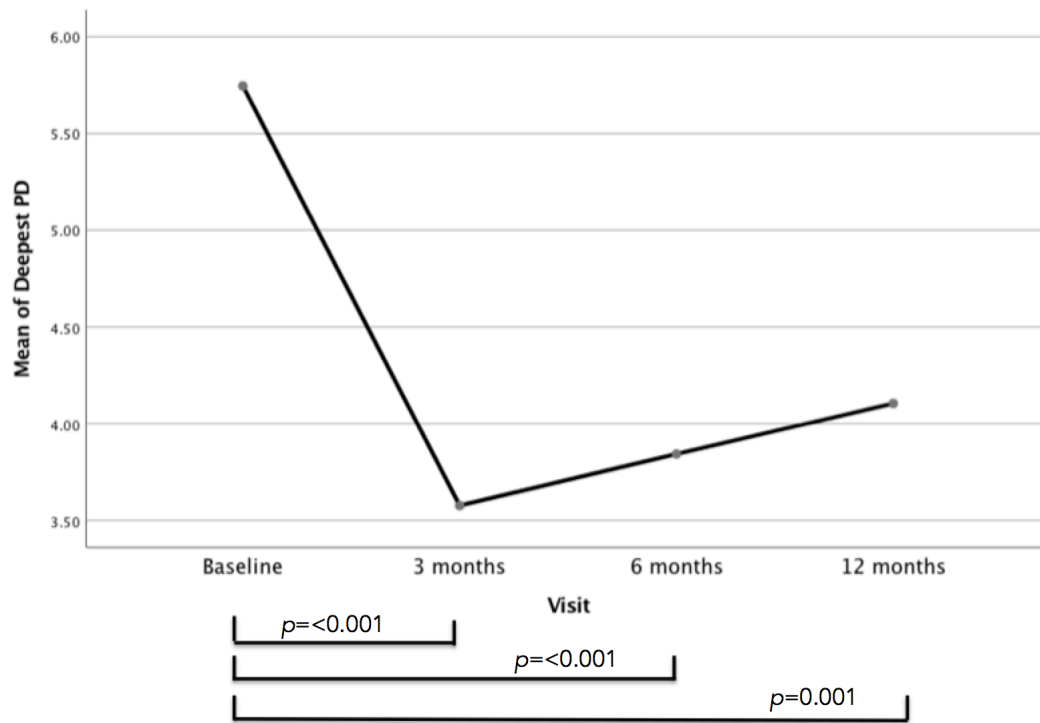


Figure 8: Mean Probing Depth

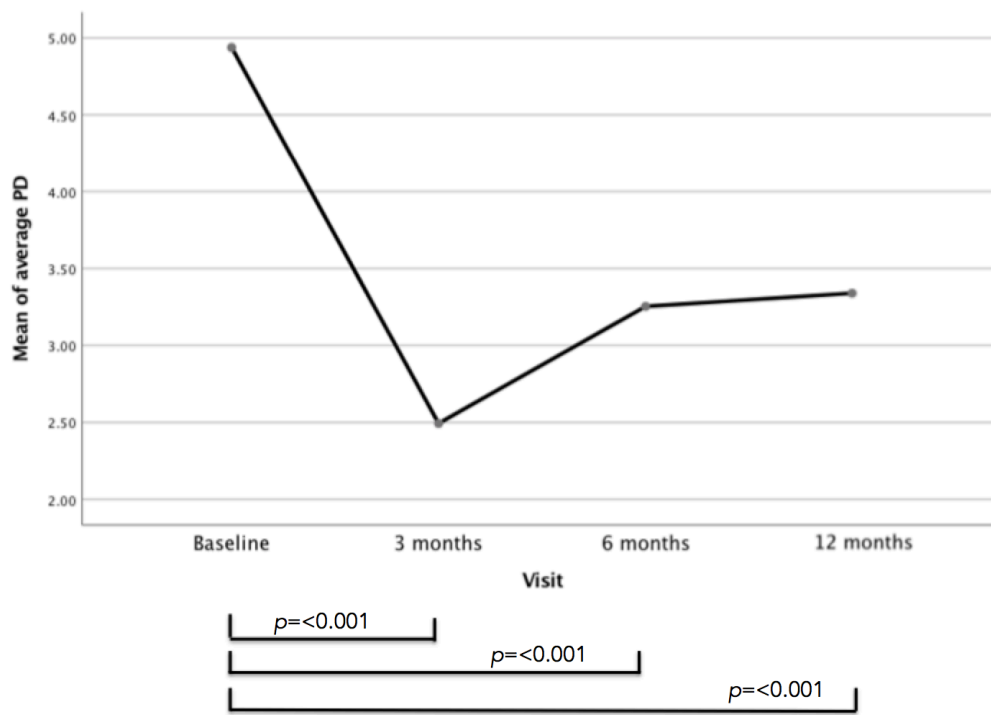


Figure 9: Mean Attachment Loss

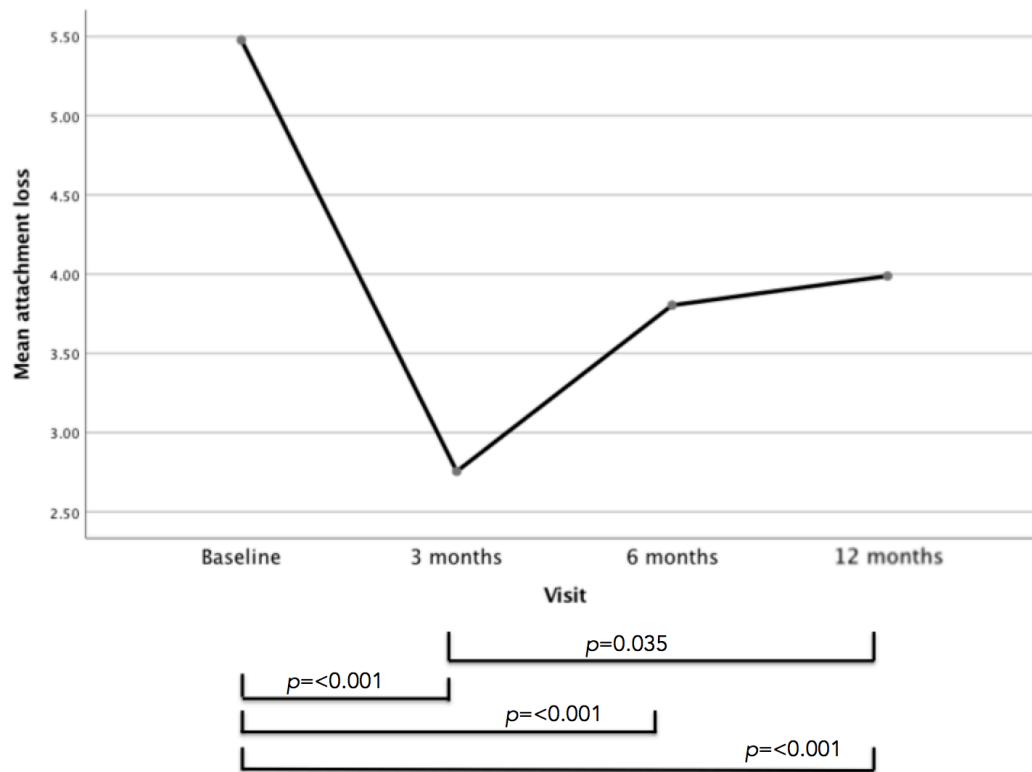


Figure 10: Mean Plaque Scores

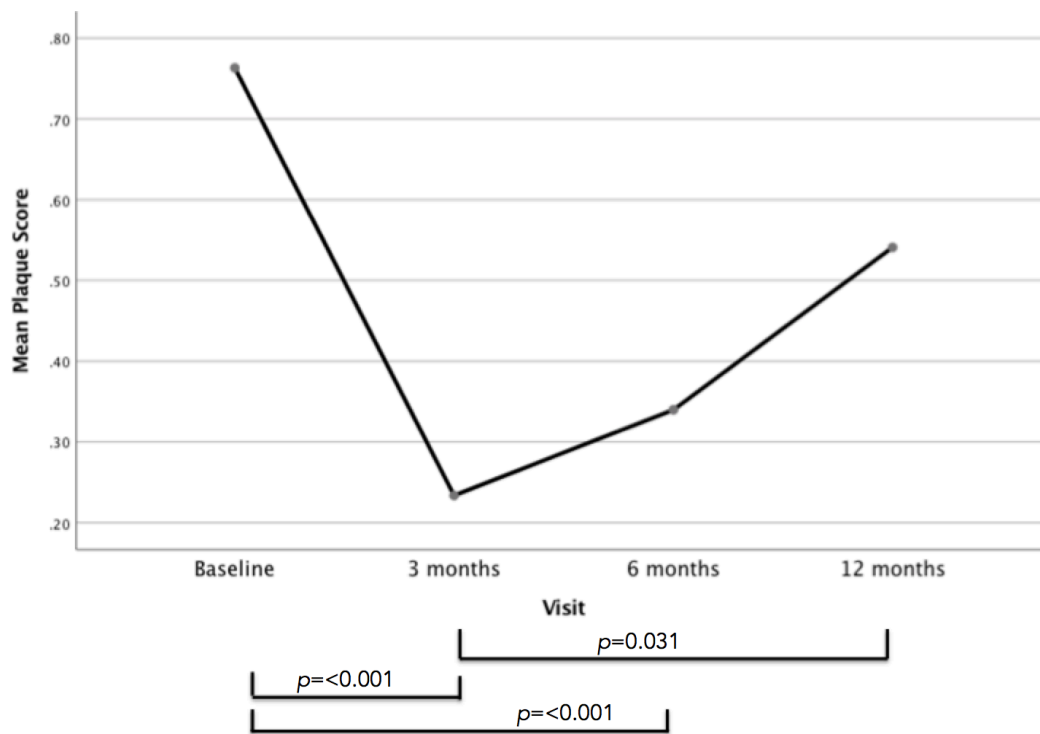
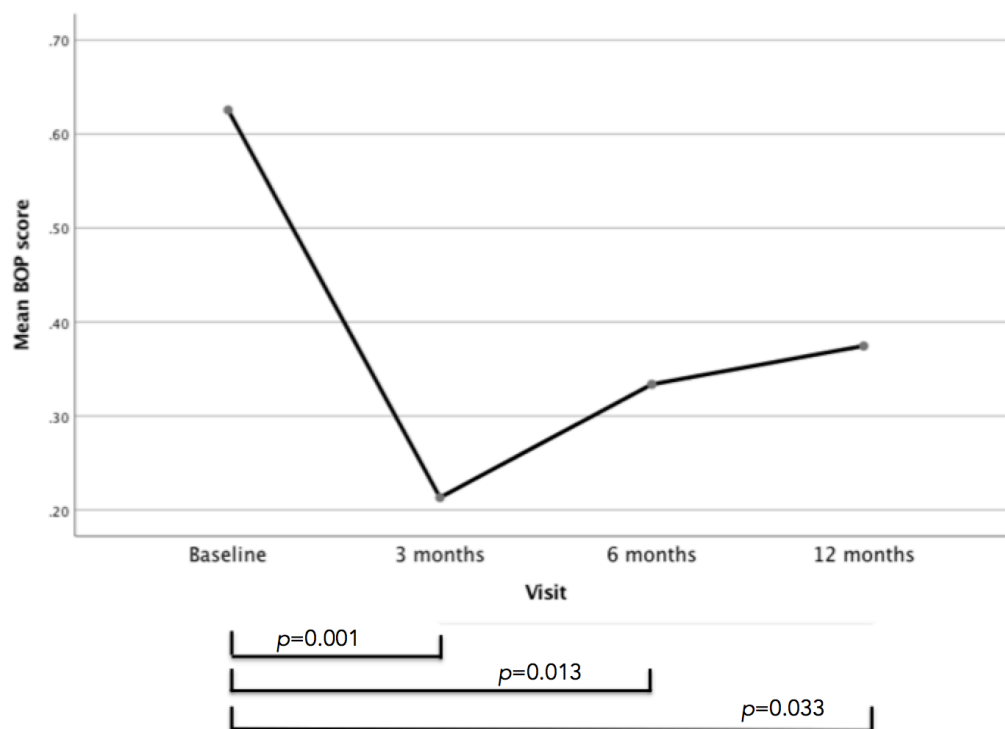


Figure 11: Mean Bleeding on Probing Scores



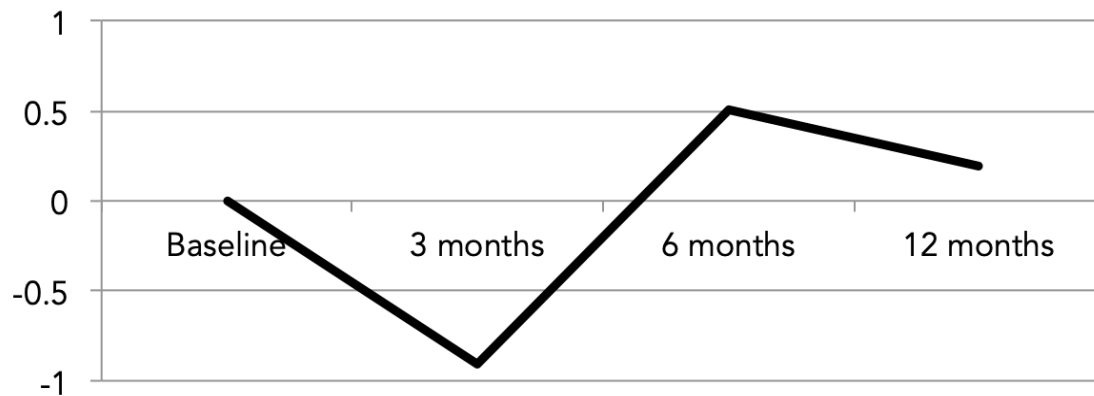
3.3 Magnetic Resonance Frequency Analysis Outcomes

Implant Stability Quotient (ISQ) Values taken at the four timepoints are listed in the table below. Despite a trend for increasing values over the 12 months post-therapy the results failed to reach statistical significance.

Table 5: ISQ Values

	Baseline	3 Months	6 Months	12 Months	
Change in ISQ from baseline		55	52	54	N
		-0.91 (4.66)	0.51 (4.58)	0.18 (5.60)	Mean (SD)
		9.00	10.50	15.00	Max
		-17.00	-8.50	-15.00	Min
		.797			Sig.

Figure 12: Trend in ISQ levels over 12 months



3.4 Sub-Group Analysis

Due to the nature of the differing treatment modalities employed in the study sub-group analysis was undertaken. The four treatment groups analysed were:

- 1) Non-surgical therapy only. (Treatment Modality I, TMI)
- 2) Non-surgical therapy followed by open flap debridement +/- resective surgery.
(Treatment Modality II, TMII)
- 3) Non-surgical therapy followed by open flap debridement with guided tissue regeneration (resorbable collagen membrane only) or resorbable Leukocyte Platelet-Rich Fibrin plugs and/or membranes. (Treatment Modality III, TMIII)
- 4) Non-surgical therapy followed by open flap debridement with regenerative therapy using guided bone regeneration (collagen membrane with bovine xenograft) or Leukocyte Platelet-Rich Fibrin +/- hard tissue grafting with bovine xenograft. Also known as the L-PRF block (Treatment Modality IV, TMIV)

Where data was normally distributed a One-Way ANOVA analysis was carried out to test statistical significance and means are reported; by contrast where data was non-normally distributed a Kruskal-Wallis analysis was completed and both means and median values are reported.

With regard to bone level changes, sub analysis revealed no additional statistical significant changes as with the overall results. Full tabulated data for this subanalysis is available in Appendix 4.

When changes in deepest probing depths were sub-analysed based on treatment modality all treatment groups maintained statistically significant differences in deepest probing depths over the study period. In addition post-hoc time point analysis on any treatment modality subanalysis which achieved statistical significance was carried out, and full tabulated data is available in Appendix 5.

Table 6: Subanalysis of changes in deepest probing depth based on treatment modality.

Deepest Probing Depth (mm)	Baseline	3 Month Change	6 Month Change	12 month Change	
Treatment Modality I	16	16	16	16	N
	4.86 (1.25)	-1.81 (2.00)	-1.06 (1.18)	-1.12 (0.88)	Mean (SD)
	3.00	0	0	0	Min
	8.00	-8.00	-5.00	-3.00	Max
	.01				Sig.
Treatment Modality II	9	9	9	9	N
	4.44 (1.59)	-1.00 (1.12)	-1.67 (1.32)	-1.44 (1.13)	Mean (SD)
	2.00	0.00	0.00	0.00	Min
	6.00	-3.00	-3.00	-3.00	Max
	.011				Sig.
Treatment Modality III	18		17	18	N
	6.17 (2.64)		-2.44 (2.74)	-1.89 (2.82)	Mean (SD)
	6.00		-2.00	-1.50	Median
	3.00		1.00	3.00	Min
	13.00		-10.00	-10.0	Max
	.004				Sig.
Treatment Modality IV	12		11	12	N
	7.42 (3.60)		-1.91 (3.24)	-2.58 (3.63)	Mean (SD)
	3.00		1.00	1.00	Min
	17.00		-10.00	-11.00	Max
	.031				Sig.

In terms of average probing depth changes over 12 months subanalysis showed significant changes in all time points for non-surgical therapy and at 6 and 9 months where a membrane or L-PRF was used in conjunction with open flap debridement. (Full tabulated data with post-hoc analysis in Appendix 6)

Table 7: Subanalysis of changes in average probing depth based on treatment modality.

Average PPD (mm)	Baseline	3 Month Change	6 Month Change	12 month Change	
Treatment Modality I	16	16	16	16	N
	4.03 (1.21)	-1.72 (1.29)	-0.94 (1.09)	-0.90 (0.86)	Mean (SD)
	2.83	-0.33	0.67	1.00	Min
	11.90	-5.50	-4.5	-3.00	Max
	<.001				Sig.
Treatment Modality II	9	9	9	9	N
	3.56 (1.38)	-0.74 (0.89)	-1.15 (1.11)	-1.07 (1.13)	Mean (SD)
	1.50	1.00	0.50	0.33	Min
	5.83	-2.00	-3.00	-2.67	Max
	.062				Sig.
Treatment Modality III	18		17	18	N
	5.19 (2.29)		-2.19 (2.26)	-1.77 (2.42)	Mean (SD)
	1.50		0.59	2.83	Min
	10.83		-8.00	-8.17	Max
	.001				Sig.
Treatment Modality IV	12		11	12	N
	6.43 (3.61)		-1.95 (3.41)	-2.25 (3.85)	Mean (SD)
	3.00		0.83	1.67	Min
	16.83		-11.17	-12.50	Max
	.056				Sig.

When subjected to treatment modality subanalysis all treatments resulted in statistically significant changes in attachment level over 12 months with the exception of the open flap debridement only group. (Full tabulated data with post-hoc analysis in Appendix 7)

Table 8: Subanalysis of changes in average attachment loss based on treatment modality.

Attachment (mm)	Baseline	3 Month Change	6 Month Change	12 month Change	
Treatment Modality I	16	16	16	16	N
	4.21 (1.12)	-1.81 (1.25)	-1.05 (1.12)	-0.95 (0.87)	Mean (SD)
	2.83	-0.33	0.67	1.00	Min
	7.00	-5.50	-4.5	-3.00	Max
	<.001				Sig.
Treatment Modality II	9	9	9	9	N
	4.11 (1.66)	-0.07 (0.59)	-0.98 (0.85)	-0.52 (1.08)	Mean (SD)
	1.50	0.00	0.00	0.67	Min
	6.17	-1.50	-2.50	-2.57	Max
	.608				Sig.
Treatment Modality III	18		17	18	N
	5.82 (2.24)		-1.89 (2.12)	-1.25 (2.37)	Mean
	2.50		1.00	2.83	Min
	10.833		-7.50	-7.50	Max
	.010				Sig.
Treatment Modality IV	12		11	12	N
	6.99 (3.49)		-2.31 (3.06)	-2.48 (3.46)	Mean
	3.00		-0.33	-0.17	Min
	16.83		-11.00	-12.00	Max
	.030				Sig.

Only the implants that received open flap debridement and implant decontamination without any use of a membrane or grafting material showed a statistically significant decrease in bleeding on probing when subjected to treatment modality subgroup analysis. (Full tabulated post-hoc analysis in Appendix 8)

Table 9: Subanalysis of changes in Bleeding on Probing based on treatment modality.

Bleeding on Probing (%)	Baseline	3 Month	6 Month	12 month	
Treatment Modality I	16	16	16	16	N
	53.00% (46)	20.00% (29)	24.00% (29)	28.00% (36)	Mean (SD)
	50.00%	8.00%	17.00%	17.00%	Median
	0.00	0.00	0.00	0.00	Min
	100.00	100.00	100.00	100.00	Max
	.173				Sig.
Treatment Modality II	9	9	9	9	N
	85.00% (18)	24.00% (29)	26.00% (22)	46.00% (41)	Mean
	50.00	0.00	0.00	0.00	Min
	100.00	83.00	67.00	100.00	Max
	<.0001				Sig.
Treatment Modality III	18		17	18	N
	49.00% (51)		37.00% (39)	32.00% (35)	Mean
	42.00%		33.00%	17.00%	Median
	0.00		0.00	0.00	Min
	100		100	100	Max
	.807				Sig.
Treatment Modality IV	12		11	12	N
	81.00% (31)		59.00% (37)	40.00% (40)	Mean
	100.00%		50.00%	42.00%	Median
	0.00		17.00	0.00	Min
	100.00		100.00	100.00	Max
	.084				Sig.

By contrast, all treatment modalities demonstrated statistically significant reductions in plaque scores over the 12 month study period. (Full tabulated post-hoc analysis in Appendix 9)

Table 10: Subanalysis of changes in Plaque Scores based on treatment modality.

Plaque score (%)	Baseline	3 Month	6 Month	12 month	
Treatment Modality I	16	16	16	16	N
	45% (50)	7% (25)	18% (22)	56% (51)	Mean (SD)
	8%	0%	0%	100%	Median
	0	0	0	0	Min
	100	100	50	100	Max
	.018				Sig.
Treatment Modality II	9	9	9	9	N
	100% (0)	52% (39)	41% (46)	76% (38)	Mean (SD)
	100	0	0	0	Min
	100	100	100	100	Max
	.008				Sig.
Treatment Modality III	18		17	18	N
	80% (40)		43% (40)	43% (45)	Mean (SD)
	100		33%	33%	Median
	0		0	0	Min
	100		100	100	Max
	.016				Sig.
Treatment Modailty IV	12		11	12	N
	92% (29)		47% (50)	43% (51)	Mean (SD)
	100%		50%	42%	Median
	0		0	0	Min
	100		100	100	Max
	.020				Sig.

When subjected to treatment modality subgroup analysis the ISQ changes over time showed no significant changes over time.

With the exception of implants that received open flap debridement only, all groups underwent an initial decrease in ISQ values at the 3 month visit.

There was a trend for more substantial increases in ISQ levels where hard tissue grafting materials were used. An increase in ISQ values was only seen with regenerative and non-surgical therapies. In implants treated with open flap debridement only the ISQ levels remained largely stable; whereas the ISQ values decreased in implants treated with GTR or collagen membranes only.

Table 11: Subanalysis of changes in ISQ levels based on treatment modality.

Osstell (ISQ)	Baseline	3 Month Change	6 Month Change	12 month Change	
Treatment Modality I	16	16	15	15	N
	67.47 (4.65)	-0.09 (3.48)	1.23 (2.45)	0.17 (3.72)	Mean (SD)
	59.00	-6.00	-2.50	-6.00	Min
	76.00	8.00	5.00	7.00	Max
	.811				Sig.
Treatment Modality II	9	9	9	9	N
	64.28 (6.57)	0.28 (6.25)	1.61 (5.95)	0.06 (5.73)	Mean (SD)
	51.00	-9.00	-8.50	-11.00	Min
	73.00	9.00	10.50	9.50	Max
	.967				Sig.
Treatment Modality III	18	18	17	18	N
	65.17 (6.61)	-2.47 (5.05)	-1.41 (4.92)	-1.50 (5.58)	Mean (SD)
	50.00	-17.00	-8.50	-15.00	Min
	77.00	6.00	10.00	8.00	Max
	.756				Sig.
Treatment Modality IV	12	12	11	12	N
	57.54 (10.96)	-0.54 (4.01)	1.59 (4.71)	2.83 (7.03)	Mean (SD)
	31.00	-6.00	-6.50	-7.50	Min
	71.00	6.50	8.00	15.00	Max
	.617				Sig.

3.5 Analysis of correlations between periodontal treatment outcomes and implant stability quotient readings.

An analysis was carried out to assess correlations between changes in periodontal outcomes and respective changes in ISQ levels at the various tested timepoints in the study. Where data was normally distributed, Pearson correlation coefficient testing was undertaken; and by contrast where data was non-normally distributed, Spearman correlation testing was utilised. As with the periodontal outcome analysis, the data was initially analysed as a whole including all implants. Subsequently, the data was analysed by subgroup based on the treatment provided.

When the data set was analysed as a whole, there was moderate negative correlation ($r = -.580, p = <.0001$) between the average change in deepest probing depth (1.8mm reduction, SD 2.43) and the average change in ISQ (0.18 increase, SD 5.60) from baseline to 12 months; changes at 3 and 6 months readings failed to reach significance.

When evaluating average implant probing depth recordings, there was again a moderate negative correlation ($r = -.493, p = <.0001$) between average probing depth change (1.51mm reduction, SD 2.35) and change in ISQ levels (0.18 increase, SD 5.60) from baseline to 12 months; changes at 3 and 6 months readings failed to reach significance.

Changes in average attachment level over 12 months showed a similar pattern with a moderate negative correlation ($r = -.496, p = <.001$) between changes in average attachment level (1.31mm reduction in attachment loss, SD 2.24) and change in ISQ levels (0.18 increase, SD 5.60) from baseline to 12 months; changes at 3 and 6 months readings failed to reach significance.

In addition, there was moderate negative correlation ($r = -.413, p = .003$) between changes at bone level between baseline and 12 months (0.08mm reduction in bone loss, SD 1.44) and change in ISQ value over the same time period (0.18 increase, SD 5.60).

Figure 13: Scatterplot demonstrating a moderate correlation between change in deepest probing depth and change in ISQ levels at 12 months.

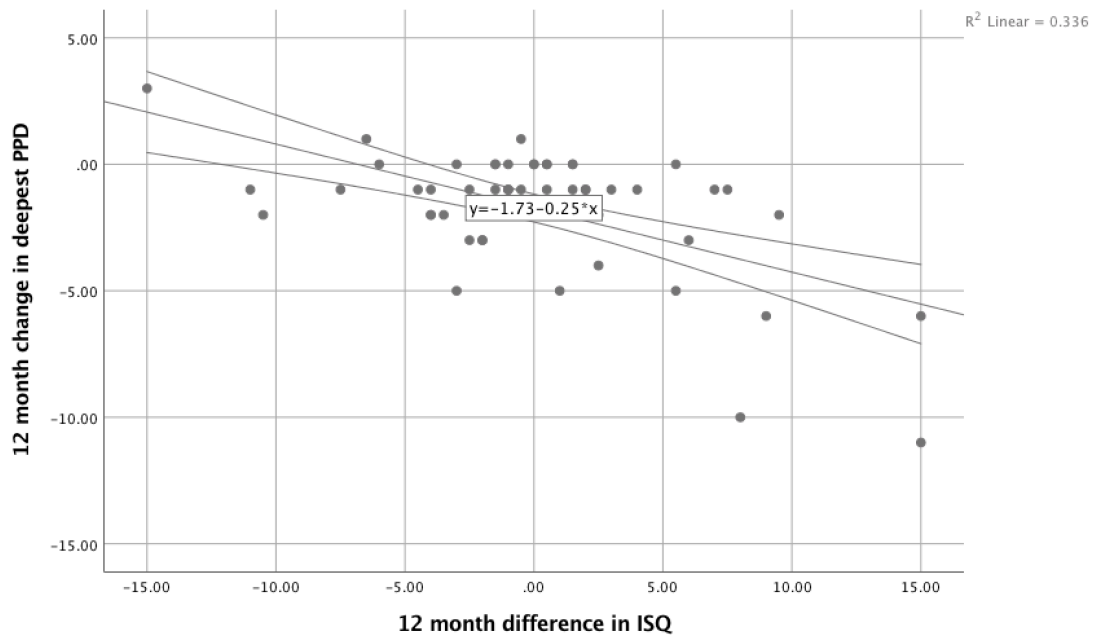


Figure 14: Scatterplot demonstrating a moderate correlation between change in average probing depth and change in ISQ levels at 12 months.

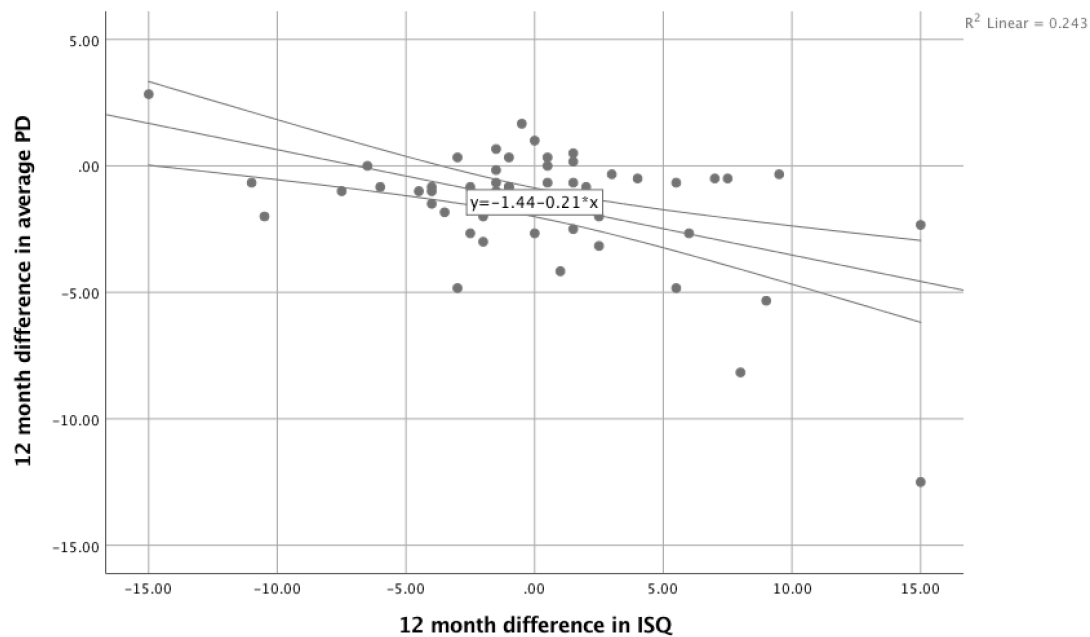


Figure 15: Scatterplot demonstrating a moderate correlation between change in average attachment level and change in ISQ levels at 12 months

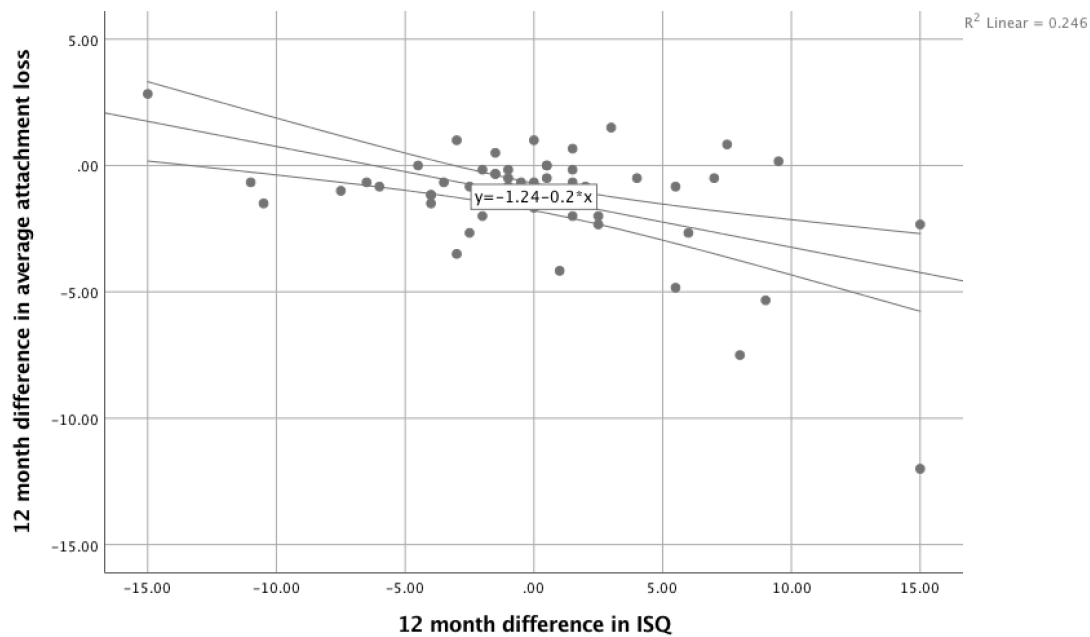
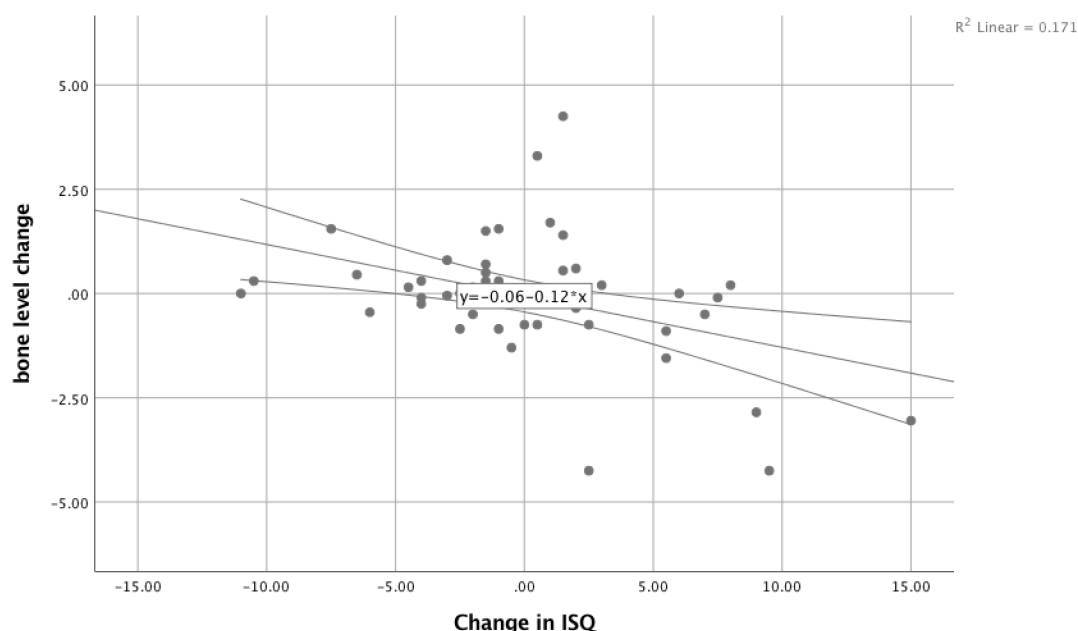


Figure 16: Scatterplot demonstrating a moderate correlation between bone level change and change in ISQ levels at 12 months



No significant correlations were detected where changes in bleeding on probing values and plaque scores were compared to changes in ISQ values at any timepoint.

3.6 Sub-Group Analysis

Correlation testing of normally and non-normally distributed data was applied to the treatment subgroups.

A strong negative correlation between changes in ISQ levels and changes in deepest probing depth were found at the 6 month timepoint for implants in TMII ($r = -.704, p = .034$; 1.67mm reduction in PD vs 1.61 ISQ increase); a moderate negative correlation at 12 months for implants in TMIII ($r = -.591, p = .01$; 2.06mm reduction in PD vs 1.50 ISQ increase), and a strong negative correlation for implants in TMIV ($r = -.844, p = .001$; 2.58mm reduction in PD vs 2.83 ISQ increase.) (Scatterplots of significant correlations in Appendix 10)

Table 12: Subanalysis correlations between changes in ISQ levels and changes in deepest probing depths.

Pearson Correlation: ISQ vs Deepest Probing Depth	3 Month	6 Month	12 month	
All	-1.52mm (1.75)	-1.81mm (2.31)	-1.8mm (2.43)	Mean PPD difference (Standard Deviation)
	-0.91 (4.66)	0.51 (4.58)	0.18 (5.60)	Mean ISQ difference (Standard Deviation)
	-0.99	-.223	-.580**	Pearson Correlation
	.638	.111	0.000004	Sig. (2-tailed)
Treatment Modality I	-1.81mm (2.01)	-1.06mm (1.18)	-1.13mm (.88)	Mean PPD difference (Standard Deviation)
	-0.09 (3.48)	1.23 (2.44)	0.17 (3.72)	Mean ISQ difference (Standard Deviation)
	.117	.250	.165	Pearson Correlation
	.665	.369	.557	Sig. (2-tailed)
Treatment Modality II	-1.00mm (1.11)	-1.67mm (1.32)	-1.44mm (1.13)	Mean PPD difference (Standard Deviation)
	0.28 (6.25)	1.61 (5.95)	0.06 (5.73)	Mean ISQ difference (Standard Deviation)
	-.591	-.704*	-.295	Pearson Correlation
	.094	.034		Sig. (2-tailed)
Treatment Modality III		-2.53mm (2.74)	-2.06mm (2.82)	Mean PPD difference (Standard Deviation)
		-1.41 (4.92)	-1.50 (5.58)	Mean ISQ difference (Standard Deviation)
		-.288	-.591**	Pearson Correlation
		.379	.010	Sig. (2-tailed)
Treatment Modality IV		-1.91mm (3.24)	-2.58mm (3.63)	Mean PPD difference (Standard Deviation)
		1.59 (4.71)	2.83 (7.02)	Mean ISQ difference (Standard Deviation)
		-.430	-.844**	Pearson Correlation
		.187	.001	Sig. (2-tailed)

*. Correlation is significant at the 0.05 level (2-tailed)

**.. Correlation is significant at the 0.01 level (2-tailed)

A strong negative correlations between changes in ISQ level and average implant probing depth were found at the 12 month timepoint for implants in TMIII ($r = -.534, p = .023$; 1.77mm reduction in average PD vs 1.50 ISQ decrease), and TMIV ($r = -.706, p = .01$; 2.25mm reduction in average PPD vs 2.83 increase in ISQ) compared to baseline measurements. (Full tabulated data and scatterplots of significant correlations in Appendix 11)

When subgroup correlation analysis of changes in attachment levels changes vs changes in ISQ values compared to baseline were carried out, only implants treated with hard tissue grafting showed a strong correlation ($r = -.736, p = .006$; 2.48mm mean gain in attachment vs 2.83 mean increase in ISQ). (Full tabulated data and scatterplot in Appendix 12)

When considering the relationship between changes in plaque score and bleeding on probing over time compared to changes in ISQ only one significant correlation was found. There was a strong correlation for implants which were treated with either a barrier membrane or L-PRF when considering changes in plaque scores and changes in ISQ values at the 12 month timepoint ($r = .563, p = .015$; 50% reduction in plaque scores, 1.50 reduction in ISQ). (Tables and scatterplots in appendix 13)

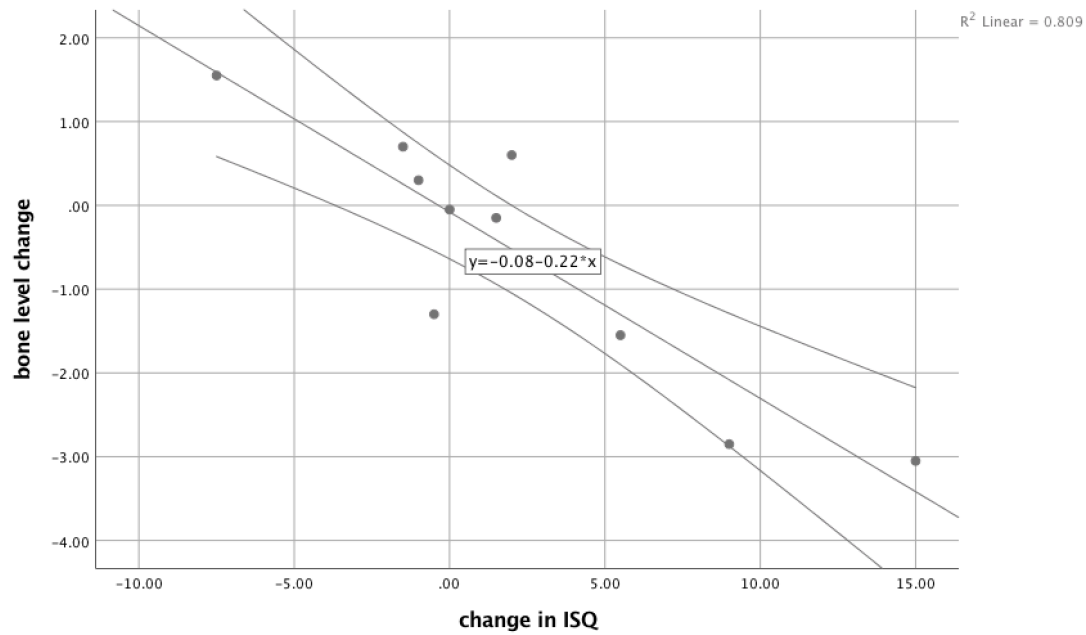
Subgroup analysis showed only implants treated with hard tissue grafting showed a highly significant negative correlation between bone level changes and changes in ISQ values over 12 months ($r = -.899, p = <0.001$; 0.58mm bone gain vs 2.83mm increase in ISQ values).

Table 13: Subanalysis correlations between changes in ISQ levels and changes in bone level.

Pearson Correlation: ISQ vs degree of bone loss (mm)	12 months	
All	-.08mm (1.44)	Mean bone loss level change (SD)
	0.18 (5.60)	Mean ISQ difference (SD)
	-.413**	Pearson Correlation
	.003	Sig. (2-tailed)
Treatment Modality I	-.09mm (0.72)	Mean bone loss level change (SD)
	0.17 (3.72)	Mean ISQ difference (SD)
	-.192	Pearson Correlation
	.512	Sig. (2-tailed)
Treatment Modality II	-.06mm (2.22)	Mean bone loss level change (SD)
	0.06 (5.72)	Mean ISQ difference (SD)
	-.349	Pearson Correlation
	.358	Sig. (2-tailed)
Treatment Modality III	0.21mm (1.45)	Mean bone loss level change (SD)
	-1.50 (5.58)	Mean ISQ difference (SD)
	-.104	Pearson Correlation
	.691	Sig. (2-tailed)
Treatment Modality IV	-0.58mm (1.54)	Mean bone loss level change (SD)
	2.83 (7.03)	Mean ISQ difference (SD)
	-.899**	Pearson Correlation
	0.000399	Sig. (2-tailed)

**. Correlation is significant at the 0.01 level (2-tailed)

Figure 17: Scatterplot demonstrating negative correlation between bone level change and change in ISQ levels at 12 months in implants treated with hard tissue grafting.



3.7 Analysis of keratinised tissue levels at baseline and periodontal parameters

Correlations between baseline levels of keratinised tissue and all tested periodontal parameters failed to reach statistical significance. (Appendix 14)

4. Discussion

The aim of the present study was to investigate the impact of peri-implantitis therapy upon periodontal clinical parameters and implant stability quotient values, to ascertain whether MRFA could be used as a diagnostic tool to demonstrate post operative healing following treatment of peri-implantitis.

The secondary objective was to identify the most appropriate time for re-evaluation of implant stability following treatment when using MRFA technology.

Despite the heterogeneity in treatment provided, as a whole periodontal outcomes improved during the follow up period. When considering the whole sample at the completion of the study, implants showed an average 0.27mm bone gain, a 1.88mm reduction in deepest probing depth, a 1.57mm reduction in average probing depth and a 1.46mm average gain in attachment.

Plaque and bleeding scores also showed significant decreases with a median 50% reduction in plaque scores and 66% reduction in bleeding on probing at 12 months post-therapy.

Improvements in clinical outcomes in this study as a result of intervention are comparable with clinical outcomes in the literature.

In the study herein, probing depth reductions were greater where surgical interventions were carried out, and even greater where regenerative materials were used. A systematic review by Chan et al (2014) reported that surgically treated pathologic peri-implant pockets using open flap debridement or resective approaches achieved a weighted mean average pocket reduction

of 2.04-2.38mm equating to 33.4-37.9% of the original pocket depth; implants treated this way in our study resulted in a mean pocket reduction of 1.07mm or 30% of original pocket depth. In the same systematic review, peri-implant sites treated with regenerative materials saw a pocket reduction of 2.32-3.16mm or 37.1-48.2% of the original pocket depth. In the study herein, similarly treated implants achieved a pocket reduction of 1.77-2.25mm or 33-35% of the original pocket depth.

When considering reductions in percentage of sites with bleeding on probing in the Chan et al systematic review, there was an average of 21.2-50.2% reduction in bleeding on probing across treatment modalities. For the entire sample of implants we recorded a median reduction in percentage of sites with bleeding on probing of 66% at 12 months.

When considering the sample as a whole, there was an average baseline bone loss of 4.30mm from the implant platform, and at 12 months a modest bone gain of 0.27mm. This overall bone gain was the only periodontal parameter assessed that did not show statistical significance when the implants were analysed as a complete group. Cassetta et al (2018) showed that intra-oral periapical radiographs underestimate the amount of marginal bone loss around implants by an average of 0.45mm compared to surgically verified bone loss, with another study showing an underestimation of 1.30mm (Garcia-Garcia et al, 2016). Whilst these studies both show an underestimation, they demonstrate there is a discrepancy between radiographically determined and surgically determined bone levels. The overall changes in bone levels seen in this study are minimal compared to known margins of error in the literature when considering interpretation of radiographs and hence the clinical significance of a perceived 0.27mm bone gain could be questioned.

Despite digital calibration of the radiographs based on known implant lengths and diameters; one limitation of the study herein is the lack of standardization of radiographs. Radiographs were taken using the paralleling technique using stock film holders. No acrylic stents or similar techniques were employed which may have improved the accuracy of radiographic comparison of implants between baseline and 12 months.

The inaccuracy of bone level interpretation may be further questioned when considering the treatment group subanalysis. Whilst the greatest bone gain (0.58mm) was seen in implants treated with regenerative surgery and hard tissue grafting, implants treated non-surgically achieved a bone gain of 0.29mm whilst implants treated with open flap debridement showed an average 0.48mm bone loss. The finding of 0.48mm bone loss in non-grafted surgically treated implants is not unexpected. There is a substantial body of evidence in the literature which shows bone loss following periodontal surgery. Wood et al showed a mean bone loss of 0.62mm following full mucoperiosteal flap periodontal surgery, in a human re-entry study with Fickl et al later showing a mean bone loss of 0.28mm for the same procedure in the dog model. It would be reasonable to assume this phenomenon of bone loss post- periodontal surgery could be applied to peri-implant surgeries with full thickness flaps (Wood et al, 1972, Fickl et al, 2011).

When considering probing measurements, plaque scores and bleeding on probing scores, the most encouraging clinical outcomes were seen at 3 months post initial therapy without exception. Following the 3 month timepoint in the study there was a tendency for slight relapse in all tested parameters. Deepest probing depth reduced by 2.53mm at 3 months, whereas at 12 months this initial reduction had decreased to a final 1.88mm probing depth reduction. The same pattern was seen for average probing depth which saw an initial reduction

of 2.43mm, decreasing to 1.63mm at 12 months. Average attachment loss showed a reduction of 2.72mm at 3 months, decreasing to 1.46mm at 12 months.

Similarly, plaque scores reduced by a mean 52.99% at 3 months and 22.99% at 12 months; with percentage of sites showing bleeding reducing by a mean 40.67% at 3 months and 26.85% at 12 months.

This initial greater reduction is suggestive of the initial success in the treatment of the diseased implants; the tendency for relapse demonstrates the difficulty in maintaining these results over longer time periods. This is a theme that is mirrored in the literature.

Serino et al (2011) showed that 42% of initially successfully treated implants, treated with a resective surgical approach, had probing depths ≥ 6 mm with bleeding on probing and/or suppuration at 2 year follow-up; with only 50% of implants with initial probing depths of ≥ 5 mm being disease-free 2 years post-surgical intervention. In another study, 42% of initially successfully surgically treated implants showed signs of disease at 5 years, defined as bone loss ≥ 3 threads with concurrent bleeding on probing and/or suppuration, with 15% of initially successfully treated implants lost over the follow-up period (Leonhardt et al, 2003).

Decreasing reductions in probing depths and attachment levels over time in our study could be attributed to relapses in improved oral hygiene practices or long-term difficulties maintaining oral hygiene around implants; resulting in increasing plaque scores and subsequent inflammation, demonstrated by rising bleeding on probing scores.

The relationship between poor oral hygiene and progression of disease is extensively reported in the peri-implant literature. Ferreira et al (2006) showed an odds ratio of 14.3 for development of PI in patients with poor oral hygiene compared to those with adequate plaque control. It should also be taken into consideration that 40 of 57 implants in our study were

supporting full arch prostheses; which, particularly in an ageing population with potentially deteriorating manual dexterity, may pose a challenge in achieving adequate maintenance at home. It has been shown that implants with inaccessibility for cleaning have a much higher incidence of PI (48%) compared to implants accessible for cleaning (4%) (Serino & Ström, 2008).

Implants that received regenerative therapy in this study did not undergo clinical measurements at 3 months, therefore 3 month periodontal data in this study includes only non-surgically or surgically treated implants without regenerative therapy. In implants that received regenerative therapy significant further reductions in deepest probing depth and attachment loss were seen between 6 and 12 months, with 0.67mm subsequent pocket reduction and 0.17mm additional attachment gain in the later 6 months of the study. Interestingly, plaque and bleeding scores in this group did not show the relapse in bleeding on probing and plaque scores seen across the implant cohort as a whole.

The post-treatment follow-up period in this study is comparatively short compared to equivalent recently published literature. Dalago et al (2019) carried out a 3 year follow up of surgically and non-surgically treated diseased implants, with clinical examination at 1, 2- and 3-years post-initial therapy. Initial reductions in probing depths seen at 1-year post therapy were largely maintained, with a slight tendency for relapse by the third year post therapy. The same trend applied to bleeding scores and there was continued loss of crestal bone loss with time.

Unlike overall results in periodontal parameters at 3 months which saw positive changes in response to clinical intervention, there was a trend for reduction in MRFA measurements with an average ISQ change of -0.91 between baseline and 3 months.

This may suggest that the MRFA technology is not sensitive to early improved soft tissue outcomes following therapy for peri-implant disease.

There is a wealth of evidence establishing a pattern of initial decline in ISQ levels immediately post implant placement (Huwiler et al 2007, Andersson et al 2008, Glauser et al 2004, Turkyilmaz et al 2006, Nedir et al 2004). In these studies initial decreases in ISQ levels were generally seen in the first 2-3 weeks post-placement and were deemed to occur in conjunction with initially bony remodelling following implant placement; coinciding with an initial temporary weakening of the implant-bone interface.

It may be the case that a similar process occurs following treatment of peri-implantitis with initial bony remodelling resulting in a temporary weakening of the bone-implant interface.

When treatment group subanalysis was carried out it showed a negligible change in ISQ levels at 3 months of -0.09 was observed where non-surgical therapy was carried out compared to a -2.47 change in ISQ levels where implants were treated surgically in conjunction with L-PRF membranes. This could potentially be explained by the initial bony remodelling that occurs post surgery as seen in the implant placement studies mentioned above. However, none of the changes in ISQ levels over 12 months reached statistical significance when analysed as a whole or in treatment modality subanalysis; and the small sample size of each group when considering treatment modality subanalysis could have a negative effect on the validity of the findings.

Despite not reaching statistical significance, there was a trend for ISQ levels to increase from 3-6 months and somewhat stabilise from there. Implants treated with regenerative surgical

therapy and hard tissue grafting showed increasing ISQ levels from 3 months to 12 months with an eventual average 2.83 ISQ increase from baseline, compared to an average 0.19 increase when considering the whole sample of implants.

Changes in periodontal measures taken at each time point were tested for correlation with changes in ISQ readings taken at the same time points, and subsequently subjected to treatment subgroup analysis. When all the implants were assessed regardless of treatment provided there were several significant correlations between periodontal parameters and changes in ISQ.

There was significant negative correlations between deepest probing depth, average probing depth, attachment levels and changes in bone levels at 12 months from baseline with changes in ISQ from baseline. Where probing depths, attachment and bone loss reduced with time, ISQ levels increased. When analysed as a complete sample, no other timepoint in the study showed statistically significant correlations between changes in periodontal parameters and changes in ISQ levels. This may indicate that if this technology is intended to be used as a diagnostic tool in monitoring outcomes post peri-implant therapy within the first year post-therapy, 12 months may be the most suitable time to utilise this technology.

Subgroup analysis based on treatment provided showed implants treated by regenerative surgical therapy using either xenograft, or xenograft in combination with L-PRF and fibrinogen, maintained significant correlation with changes in ISQ levels at 12 months and changes to probing depths, attachment levels and bone changes. This is unsurprising given this treatment group consistently exhibited the greatest changes in periodontal parameters as a result of treatment as well as the greatest average changes in ISQ levels.

The results of correlation testing indicate that in addition to 12 months being the most suitable timepoint to utilise this technology in the first year post peri-implant therapy, it may be most appropriate for use in cases treated with surgical regenerative therapy.

When used in cases treated non-surgically or with surgical therapy without the use of regenerative materials, MRFA may be of limited diagnostic use in the clinical setting.

It should also be noted that although there were statistically significant correlations, the clinical significance of changes in ISQ could be questioned.

When a mean change in all the implants is considered, the average change in ISQ levels was an increase of 0.19 over 12 months, which is a modest improvement. If this was the case, clinically changes like this would likely go undetected as the Osstell Mentor™ technology generates ISQ levels as round figures without decimal places.

Like the results suggest, the technology may be of more diagnostic use in cases with more substantial clinical or bony changes, or cases treated with regenerative therapy.

The average change in ISQ at 12 months in implants treated with hard tissue regenerative surgical therapy showed an average ISQ increase of 2.83 at 12 months with an average probing depth reduction of 2.25mm; compared to an ISQ increase of 0.06 and an average probing depth reduction of 1.07mm in implants treated with open flap surgery alone.

Perhaps more compelling evidence for the use of MRFA regarding cases with greater clinical changes can be found by examining the cases with the most extreme positive and negative clinical outcomes in the treated implant cohort.

Implants 49 and 50 in this study were treated with non-surgical therapy, followed by open flap-debridement, chemical decontamination with 3% hydrogen peroxide, and were

subsequently grafted with bovine xenograft, L-PRF and Fibrinogen. L-PRF membranes were placed over the grafting material prior to closure. Implant 49 had a baseline deepest probing depth of 9mm which reduced to 4mm at 12 months, and an average radiographic bone gain of 1.55mm; which correlated to a 12 month increase in ISQ of 5.5. Implant 50 had a baseline deepest probing depth of 9mm which reduced to 3mm at 12 months, and an average radiographic bone gain of 2.85mm; which correlated to a 12 month increase in ISQ of 9 points.

Conversely implant 51 in the study was treated with non-surgical therapy, and open flap debridement with chemical disinfection using 3% hydrogen peroxide. Clinically this implant deteriorated over the 12 months of the study starting with an initial baseline deepest probing depth of 7mm which increased to 10mm over the 12 month period in conjunction with a decrease in ISQ of 15 points.

Data from these cases at the extremities of both positive and negative clinical outcomes within our study suggest again MRFA could potentially be more sensitive to more profound changes in clinical outcomes.

Bony defect configuration of diseased implants was not formally recorded in the study data sheets, and therefore not statistically analysed for any relationships to ISQ values in this study. Defect configuration was however assessed during surgery, and dictated which treatment modality could be applied in the majority of cases.

In certain cases where Leucocyte Platelet-Rich Fibrin was used in conjunction with bovine xenograft and fibrinogen, such as implants 49 and 50, grafting materials were applied beyond the confines of the bony defects; not in the manner traditionally suggested for regenerative therapy in an attempt to maintain soft tissue architecture around implants. Interestingly, it is

implants treated in this manner that showed the greatest positive changes in ISQ levels over 12 months.

The Osstell Mentor™ technology used in this study was routinely straightforward for clinical use and produced repeatable and reproducible measurements at each timepoint.

On occasional data collection appointments there was difficulty in using the Osstell Mentor™ device to generate ISQ readings; this was exclusively limited to implants in the anterior maxilla. One implant in the maxillary left central incisor position in this study was eliminated from 6 -and 12-month analysis, as the device was unable to generate ISQ readings for this implant after the first two data collection appointments. To the best of the authors knowledge, this potential shortcoming of the technology has not been discussed in the literature.

In this study no significant correlation between baseline levels of keratinised tissue and severity of baseline peri-implant disease was shown; keratinised mucosa (KM) measured as the apico-coronal width of keratinised mucosa from the gingival margin to the mucogingival junction.

This is contradictory to a large body of evidence linking inadequate levels of keratinized tissue around implants to increased plaque accumulation and increased inflammation, albeit with little evidence directly linking it to peri-implant bone loss (Wennström & Derks, 2012, Brito et al, 2014, Roccuzzo et al, 2016, Schwarz et al, 2018). In a recently published study with a larger sample size, Giske et al (2019) assessed the presence of peri-implant disease on 231 implants in 52 patients, where a width of <2mm defined as reduced KM. They showed a positive association between reduced KM and peri-implant mucositis as well as severity of disease.

When assessing the clinical significance of results in this study one must consider the limitations of this study. Most likely the most profound limitation is the small sample size of only 57 implants, which when combined with the multiple treatment modalities provided for the implants adds many variables and decreases treatment subgroup sample sizes. For a true intergroup treatment modality analysis substantially larger sample sizes would be required and hence clinical significance of the subgroup analysis could be questioned.

Conversely, the varying treatment modalities provided may mimic peri-implant therapy in hospital, general or specialised practice setting; where implants are treated according to disease severity, peri-implant defect present as well as operator and patient preference.

Therefore when assessing if MRFA is a valid diagnostic tool in the follow-up of peri-implantitis therapy irrespective of treatment employed, a study design like this with multiple treatment options provided may be appropriate. Evidently further research with larger sample sizes on the diagnostic use of MRFA in peri-implant therapy follow-up would be beneficial.

As alluded to previously, the partial relapse of plaque and bleeding scores as a whole between 3 months and 12 months is a potential limitation of this study. Had the patients been reviewed more regularly and oral hygiene practices further reinforced, it is hard to know as to whether the encouraging periodontal outcomes seen at 3 months may have been maintained up to 12 months.

Conclusions:

Overall, in the medium to short term, all treatments were successful in the management of peri-implantitis.

When sub-analysis was carried out based on treatment provided, implants treated surgically with GTR or GBR achieved better clinical results (as evidenced by PD reduction and bone gain) and showed more frequent correlations with MFRA readings.

MRFA technology, in the form of the Osstell™ device, can be used as an adjunct to the commonly used periodontal tools for the evaluation of post-operative healing following treatment of peri-implant disease.

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Appendix

Appendix 1 - Ethical Approval

Appendix 2 - Participant Information Sheet and Consent form

Appendix 3 - Data collection sheet

Appendix 4 - Bone level changes based on subgroup analysis.

Appendix 5 - Subanalysis of periodontal outcomes based on treatment modalities with post-hoc analysis where appropriate based on statistical significance. – Deepest PPD

Appendix 6 - Subanalysis of periodontal outcomes based on treatment modalities with post-hoc analysis where appropriate based on statistical significance. – Average PPD

Appendix 7 - Subanalysis of periodontal outcomes based on treatment modalities with post-hoc analysis where appropriate based on statistical significance. – Average Attachment level

Appendix 8 - Subanalysis of periodontal outcomes based on treatment modalities with post-hoc analysis where appropriate based on statistical significance. – Bleeding on Probing Scores

Appendix 9 - Subanalysis of periodontal outcomes based on treatment modalities with post-hoc analysis where appropriate based on statistical significance. – Bleeding on Probing Scores

Appendix 10 - Scatterplots of significant relationships in subanalysis of changes in deepest probing depth vs changes in ISQ based on treatment modality.

Appendix 11 - Scatterplots of significant relationships in subanalysis of changes in deepest probing depth vs changes in ISQ based on treatment modality.

Appendix 12 - Table and scatterplots of significant relationships in subanalysis of changes in average attachment level vs changes in ISQ based on treatment modality.

Appendix 13 - Table and scatterplots of significant relationships in subanalysis of changes in plaque scores and bleeding on probing vs changes in ISQ based on treatment modality.

Appendix 14 - Correlation between baseline keratinised tissue and periodontal parameters.

Appendix 1: Ethical Approval

THIS NOTEPAPER MUST NOT BE USED FOR
PRESCRIPTIONS OR INVOICING PURPOSES

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie



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Dr. Ed Madeley
Dublin Dental University Hospital
Trinity College Dublin
Lincoln Place
Dublin 2

18th May 2017

Re: Longitudinal analysis of treatment of peri-implant disease utilising magnetic resonance frequency analysis

REC: 2017-05 list 19 (2)

Reference: (Please quote reference on all correspondence)

Dear Dr. Madeley,

Thank you for your correspondence in which you responded to the concerns of the SJH/AMNCH Research and Ethics Committee.

The Chairman has reviewed this correspondence, is happy with the responses therein and has given ethical approval for this study to proceed.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

PARTICIPANT INFORMATION LEAFLET

Longitudinal analysis of treatment of peri-implantitis utilising magnetic resonance frequency analysis.

You are being invited to participate in a research study:

In order to make an informed judgment on whether you want to be part of this research study, you should understand its potential risks and benefits. This is called informed consent. This leaflet gives you information about the research study, which will be discussed with you. Ask us if there is anything that is not clear or if you would like more information. Once you understand the study, you will be asked to sign a consent form if you wish to participate. Should you not wish to participate, simply do not return the consent form

Study Summary:

This study will collect information on the healing of the tissues around your implant following treatment for implant-disease. We aim to measure the stability of your implant in the bone and the healing of the surrounding tissues following treatment for peri-implant disease.

Background information:

Unfortunately dental implants are susceptible to a disease process similar to gum disease seen on natural teeth, known as either Peri-Implant Mucositis or Peri-Implantitis.

Peri-Implant Mucositis is an inflammation of the gums surrounding your implant(s) and Peri-Implantitis is an inflammation, which in addition, results in some loss of the bone surrounding your implant(s).

If left untreated Peri-implant mucositis may lead to Peri-implantitis, which may eventually result in pain, swelling and potentially loss of the implant(s). Treatment of peri-implant disease consists of improving your oral hygiene regime, most often cleaning around the implant(s) and if indicated surgical treatment of the implant(s).

Magnetic Resonance Frequency Analysis (MRFA) is a technology that has become available in the past two decades and has been adapted to allow your dental clinician to test the stability of your implant(s). A small magnetic peg is fixed to the top of your implant and a sensor shows how stable the implant is. This process is quick, pain free and does no lasting damage to your implant(s).



Fig 1: The Osstell™ machine

Study Overview:

This study aims to assess if the Osstell™ Machine can be used as an effective method of assessing the success of treating disease around implants. Measurements will be taken before and after any required treatment. Following completion of the treatment and study the results of the Osstell™ measurements and clinical measurements will be compared to see if healing can be detected by the Osstell™ machine.

All treatment will be carried out as normal based on the specific type of disease of the implant and therefore the treatment received by yourself will be unaffected by the study; the only difference to standard treatment is that all measurements taken pre- and post-treatment will be recorded for use in statistical analysis.

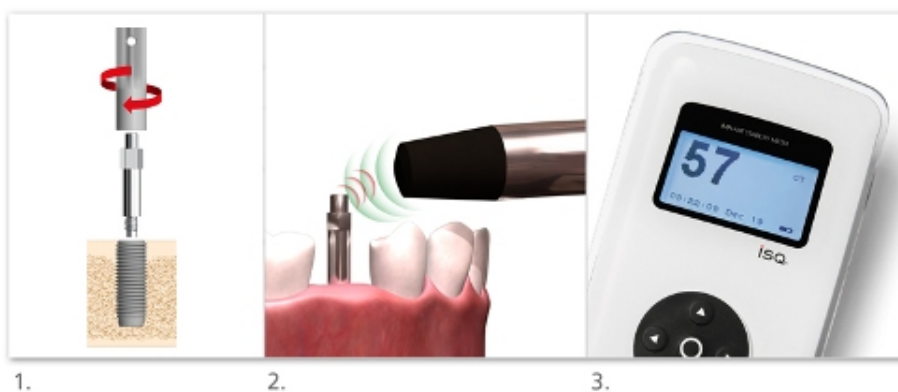


Fig 2: How the Osstell™ machine attaches to an implant.

Are you suitable for this study?

To be included in the study you must fulfill the criteria below:

- Be 18 years old or over.
- Require treatment of peri-implant mucositis or peri-implantitis (disease around your implant(s)).
- Be in good general health and able to tolerate minor dental surgeries.
- Be able to give consent to participate in this study and sign a consent form approved by the Research Ethics Committee, St James' Hospital.
- Be able to attend all the appointments described below. If you are initially included in the study but you fail to complete all stages of the treatment due to poor attendance, you will have to be excluded from the study.

Study Appointments:

Screening appointment: You will be invited to attend an initial screening appointment to confirm you are suitable for treatment and that you fit the criteria for the study. If you are suitable you will be invited to participate. You will be given a detailed description of the study and some written information to take home.

Study visit 1: Pre-surgery. A consent form will be signed to show you understand and agree to participate. If necessary, x-rays will be taken at this time (This is the normal procedure for any implant treatment).

Study visit 2: This will include any necessary treatment of your implant(s); which may be as simple as cleaning around the implant to surgery on the tissues surrounding the implant.

Maintenance visits: Following the treatment of the implant(s) we will need to see you for 1 appointment each month to check the implant is kept clean and is healing well. At 3,6 and 12 months we will also retake our Osstell™ measurements.

The types of dental treatments provided in this study are an alternative to:

No treatment – allowing the peri-implant disease to progress.

Dental treatment is associated with risk. The risks associated with this type of treatment include:

- Pain following treatment.
- Bleeding following surgery.
- Swelling of the gums after the surgery.
- Bruising of the face following the operations.
- Failure of the treatment.
- Loss of the implant through deterioration of the pre-existing condition.

Other information of relevance to the study:

- Participants will have to pay for their treatment. However, monthly maintenance appointments and any measurements appointments will be provided free of charge.
- Other dental treatments such as fillings cannot be provided in the study.
- If for any reason we have to exclude you from the study but you would like to continue with your treatment in the Dublin Dental Hospital, you can.
- Your identity will remain confidential. Your name will not be published.
- If you decide to participate in this study, you may withdraw at any time.
- If you decide not to participate, or withdraw, you will not give up benefits that you had before entering the study.
- You understand that the investigators may withdraw your participation in the study at any time without your consent.

Contact details

If you have any questions please contact the principal researcher, Dr. Ed Madeley

Email: Edward.Madeley@dental.tcd.ie

Emergency contact number: 01 6127250

Informed Consent Form

Longitudinal analysis of treatment of peri-implantitis utilising magnetic resonance frequency analysis.

Staff Conducting Research

Dr. Ed Madeley

Dr. Ioannis Polyzois

Dr. Peter Harrison

Study Summary:

This study will collect information on the healing of the tissues around your implant following treatment. We aim to measure the stability of your implant and the nature of the surrounding tissues following treatment for peri-implant disease.

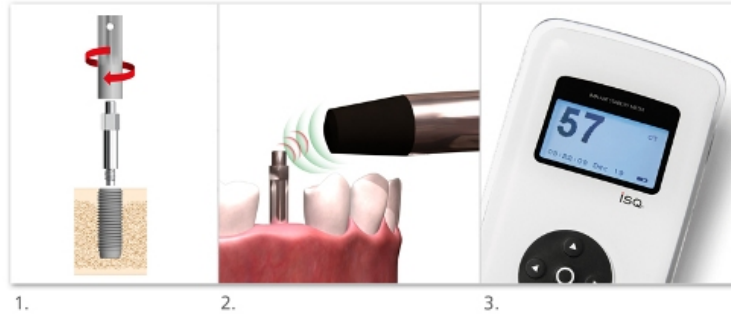
Background information:

The invention of dental implants has revolutionized modern day dentistry and provides a solution when teeth have previously been lost. However, unfortunately dental implants are susceptible to Peri-Implant Mucositis and Peri-Implantitis; which are diseases much a kin to gingivitis and periodontitis (gum disease) seen around natural teeth.

Peri-Implant Mucositis is an inflammation of the gums surrounding your implant(s) and Peri-Implantitis is an inflammation, which in addition, results in some loss of the bone surrounding your implant(s)/

If left untreated Peri-implant mucositis may lead to Peri-implantitis, which may eventually result in pain, swelling and potentially loss of the implant(s). Treatment of peri-implant disease consists of improving your oral hygiene regime, most often cleaning around the implant(s) and if indicated surgical treatment of the implant(s).

Magnetic Resonance Frequency Analysis (MRFA) is a technology that has become available in the past two decades and has been adapted to allow your dental clinician to test the stability of your implant(s). A small magnetic peg is fixed to the top of your implant and a sensor shows how stable the implant is. This process is quick, pain free and does no lasting damage to your implant(s).



The aim of the study:

To assess if MRFA in the form of the Osstell™ machine can be used to test the stability around healing implants following treatment and to see if the treatment results in improved implant stability readings.

Confidentiality:

Your name will not be used to identify the sample and no-one outside the study group will have access to your details to ensure your confidentiality.

Consent:

Having read the participant information leaflet, if you wish to participate please sign the declaration below. Should you not wish to take part in this study, it will have no impact on the care you receive from the hospital and do not sign the declaration below.

Declaration:

I have read, or had read to me, the information leaflet for this project and I understand the contents. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, without prejudice to my legal and ethical rights. I understand that I may withdraw from my study at any time and I have received a copy of this agreement.

_____ I consent to my records including radiographs or photographs being used for research purposes.

_____ I agree to the further use of data (e.g. radiographs and photographs) collected during this study in possible future studies, without the need for my additional consent.

_____ I agree to the possible publication of results from this study

_____ I understand that any of the research or educational purposes referred to above will preserve my anonymity and my name will not be linked to any of these activities or publications.

_____ I understand that I may withdraw from this study at any time I wish

Participant's name:..... Contact
details:..... Participant's signature:
..... Date:.....

I have explained the nature and purpose of this research study, the procedures to be undertaken and any risks that may be involved. I have offered to answer any questions and fully answered such questions. I believe the participant understands my explanation and has freely given informed consent.

Investigator's signature: Date:.....

Appendix 3: Data Collection Sheet

Patient Name													
Chart													
Implant Location													
Restoration Type													
SmartPeg Required													
Treatment provided													
Operator													
CLINICAL MEASUREMENTS													
Time point		Baseline (Day of Treatment)			3 months (Not for Regenerative)			6 months (All)			12 months (All)		
Date													
Lingual	Plaque												
	BOP												
	Rec												
	PD												
Buccal	PD												
	Rec												
	BOP												
	Plaque												
IMPLANT STABILITY ANALYSIS													
Time point		Baseline(All)			3 months (All)			6 months (All)			12 months (All)		
Ostell Readings		1	2	Mean	1	2	Mean	1	2	Mean	1	2	Mean
PerioTest Readings													
KERATINIZED TISSUE WIDTH PRESENT													
KT Width													

Appendix 4: Bone level changes based on subgroup analysis.

Bone Loss (mm)	Baseline	12 month Change	
Treatment Modality I	14	14	N
	3.40 (2.13)	-0.29 (bone gain) (0.56)	Mean (SD)
	0	-4.25 (bone gain)	Min
	11.90	4.25 (bone loss)	Max
	.141		Sig.
Treatment Modality II	9	9	N
	2.79 (2.18)	0.48 (bone loss) (1.58)	Mean (SD)
	0.00	-0.75 (bone gain)	Min
	6.70	4.25 (bone loss)	Max
	.628		Sig.
Treatment Modality III	17	17	N
	4.25 (1.05)	0.21 (bone loss) (1.45)	Mean (SD)
	2.20	-4.25 (bone gain)	Min
	5.80	3.30 (bone loss)	Max
	.528		Sig.
Treatment Modality IV	12	11	N
	5.84 (2.11)	-0.58 (bone gain) (1.55)	Mean
	1.40	-3.05 (bone gain)	Min
	9.20	1.55 (bone loss)	Max
	.807		Sig.

Appendix 5: Subanalysis of periodontal outcomes based on treatment modalities with post-hoc analysis where appropriate based on statistical significance. – Deepest PPD

Deepest Probing Depth (mm)	Baseline	3 Month Change	6 Month Change	12 month Change	
Treatment Modality I	16	16	16	16	N
	4.86 (1.25)	-1.81 (2.00)	-1.06 (1.18)	-1.12 (0.88)	Mean (SD)
	3.00	0	0	0	Min
	8.00	-8.00	-5.00	-3.00	Max
	.01				Sig.
Treatment Modality II	9	9	9	9	N
	4.44 (1.59)	-1.00 (1.12)	-1.67 (1.32)	-1.44 (1.13)	Mean (SD)
	2.00	0.00	0.00	0.00	Min
	6.00	-3.00	-3.00	-3.00	Max
	.011				Sig.
Treatment Modality III	18		17	18	N
	6.17 (2.64)		-2.44 (2.74)	-1.89 (2.82)	Mean (SD)
	6.00		-2.00	-1.50	Median
	3.00		1.00	3.00	Min
	13.00		-10.00	-10.0	Max
	.004				Sig.
Treatment Modality IV	12		11	12	N
	7.42 (3.60)		-1.91 (3.24)	-2.58 (3.63)	Mean (SD)
	3.00		1.00	1.00	Min
	17.00		-10.00	-11.00	Max
	.031				Sig.

ANOVA (1 way) Tukey Post-Hoc test – Deepest PPD – TMI

	Baseline	3 Months	6 Months	12 Months
Baseline		1.81mm $p=.012$	Non-significant	Non-significant
3 Months	-1.81mm $p=.012$		Non-significant	Non-significant
6 Months	Non-significant	Non-significant		Non-significant
12 Months	Non-significant	Non-significant	Non-significant	

ANOVA (1 way) Tukey Post-Hoc – Deepest PPD – TMII

	Baseline	3 Months	6 Months	12 Months
Baseline		Non-significant	1.67mm $p=.011$	1.44mm $p=.033$
3 Months	Non-significant		Non-significant	Non-significant
6 Months	-1.67mm $p=.011$	Non-significant		Non-significant
12 Months	-1.44mm $p=.033$	Non-significant	Non-significant	

Kruskal-Wallis Post-Hoc – Deepest PPD – TMIII

	Baseline	3 Months	6 Months	12 Months
Baseline			$p=.008$	Non-significant
3 Months			Non-significant	Non-significant
6 Months	$p=.008$	Non-significant		Non-significant
12 Months	Non-significant	Non-significant	Non-significant	

ANOVA (1 way) Tukey Post-Hoc – Deepest PPD – TMIV

	Baseline	3 Months	6 Months	12 Months
Baseline			Non-significant	2.58mm $p=.027$
3 Months			Non-significant	Non-significant
6 Months	Non-significant	Non-significant		Non-significant
12 Months	-2.58mm $p=.027$	Non-significant	Non-significant	

Appendix 6: Subanalysis of periodontal outcomes based on treatment modalities with post-hoc analysis where appropriate based on statistical significance. – Average PPD

Average PPD (mm)	Baseline	3 Month Change	6 Month Change	12 month Change	
Treatment Modality I	16	16	16	16	N
	4.03 (1.21)	-1.72 (1.29)	-0.94 (1.09)	0.90 (0.86)	Mean (SD)
	2.83	-0.33	0.67	1.00	Min
	11.90	-5.50	-4.5	-3.00	Max
	<.001				Sig.
Treatment Modality II	9	9	9	9	N
	3.56 (1.38)	-0.74 (0.89)	-1.15 (1.11)	-1.07 (1.13)	Mean (SD)
	1.50	1.00	0.50	0.33	Min
	5.83	-2.00	-3.00	-2.67	Max
	.062				Sig.
Treatment Modality III	18		17	18	N
	5.19 (2.29)		-2.19 (2.26)	-1.77 (2.42)	Mean (SD)
	1.50		0.59	2.83	Min
	10.83		-8.00	-8.17	Max
	.001				Sig.
Treatment Modality IV	12		11	12	N
	6.43 (3.61)		-1.95 (3.41)	-2.25 (3.85)	Mean (SD)
	3.00		0.83	1.67	Min
	16.83		-11.17	-12.50	Max
	.056				Sig.

ANOVA (1 way) Tukey Post-Hoc test – Average PPD – TMI

	Baseline	3 Months	6 Months	12 Months
Baseline		1.72mm $p < .001$	.94mm $p = .034$	0.90mm $p = .05$
3 Months	-1.72mm $p < .001$		Non-significant	Non-significant
6 Months	-0.94mm $p = .034$	Non-significant		Non-significant
12 Months	-0.90mm $p = .05$	Non-significant	Non-significant	

ANOVA (1 way) Tukey Post-Hoc – Average PPD – TMII

	Baseline	3 Months	6 Months	12 Months
Baseline			2.19mm $p = .001$	1.77mm $p = .013$
3 Months			Non-significant	Non-significant
6 Months	-2.19mm $p = .001$	Non-significant		Non-significant
12 Months	-1.77mm $p = .013$	Non-significant	Non-significant	

Appendix 7: Subanalysis of periodontal outcomes based on treatment modalities with post-hoc analysis where appropriate based on statistical significance. – Average Attachment level

Attachment (mm)	Baseline	3 Month Change	6 Month Change	12 month Change	
Treatment Modality I	16	16	16	16	N
	4.21 (1.12)	-1.81 (1.25)	-1.05 (1.12)	-0.95 (0.87)	Mean (SD)
	2.83	-0.33	0.67	1.00	Min
	7.00	-5.50	-4.5	-3.00	Max
	<.001				Sig.
Treatment Modality II	9	9	9	9	N
	4.11 (1.66)	-0.07 (0.59)	-0.98 (0.85)	-0.52 (1.08)	Mean (SD)
	1.50	0.00	0.00	0.67	Min
	6.17	-1.50	-2.50	-2.57	Max
	.608				Sig.
Treatment Modality III	18		17	18	N
	5.82 (2.24)		-1.89 (2.12)	-1.25 (2.37)	Mean
	2.50		1.00	2.83	Min
	10.833		-7.50	-7.50	Max
	.010				Sig.
Treatment Modality IV	12		11	12	N
	6.99 (3.49)		-2.31 (3.06)	-2.48 (3.46)	Mean
	3.00		-0.33	-0.17	Min
	16.83		-11.00	-12.00	Max
	.030				Sig.

ANOVA (1 way) Tukey Post-Hoc – Average Attachment loss – TMI

	Baseline	3 Months	6 Months	12 Months
Baseline		1.81mm $p < .001$	Non-significant	Non-significant
3 Months	-1.81mm $p < .001$		Non-significant	Non-significant
6 Months	Non-significant	Non-significant		Non-significant
12 Months	Non-significant	Non-significant	Non-significant	

ANOVA (1 way) Tukey Post-Hoc – Average Attachment loss – TMIII

	Baseline	3 Months	6 Months	12 Months
Baseline			1.89mm $p = .008$	Non-significant
3 Months			Non-significant	Non-significant
6 Months	-1.89mm $p = .008$	Non-significant		Non-significant
12 Months	Non-significant	Non-significant	Non-significant	

ANOVA (1 way) Tukey Post-Hoc – Average Attachment loss – TMIV

	Baseline	3 Months	6 Months	12 Months
Baseline			Non-significant	2.48mm $p=.025$
3 Months			Non-significant	Non-significant
6 Months	Non-significant	Non-significant		Non-significant
12 Months	-2.48mm $p=.025$	Non-significant	Non-significant	

Appendix 8: Subanalysis of periodontal outcomes based on treatment modalities with post-hoc analysis where appropriate based on statistical significance. – Bleeding on Probing Scores

Bleeding on Probing (%)	Baseline	3 Month	6 Month	12 month	
Treatment Modality I	16	16	16	16	N
	53.00% (46)	20.00% (29)	24.00% (29)	28.00% (36)	Mean (SD)
	50.00%	8.00%	17.00%	17.00%	Median
	0.00	0.00	0.00	0.00	Min
	100.00	100.00	100.00	100.00	Max
	.173				Sig.
Treatment Modality II	9	9	9	9	N
	85.00% (18)	24.00% (29)	26.00% (22)	46.00% (41)	Mean
	50.00	0.00	0.00	0.00	Min
	100.00	83.00	67.00	100.00	Max
	<.0001				Sig.
Treatment Modality III	18		17	18	N
	49.00% (51)		37.00% (39)	32.00% (35)	Mean
	42.00%		33.00%	17.00%	Median
	0.00		0.00	0.00	Min
	100		100	100	Max
	.807				Sig.
Treatment Modality IV	12		11	12	N
	81.00% (31)		59.00% (37)	40.00% (40)	Mean
	100.00%		50.00%	42.00%	Median
	0.00		17.00	0.00	Min
	100.00		100.00	100.00	Max
	.084				Sig.

ANOVA (1 way) Tukey Post-Hoc – Average BOP scores – TMII

	Baseline	3 Months	6 Months	12 Months
Baseline		61% $p < .0001$	59% $p = .001$	39% $p = .037$
3 Months	-61% $p < .0001$		Non-significant	Non-significant
6 Months	-59% $p = .001$	Non-significant		Non-significant
12 Months	-39% $p = .037$	Non-significant	Non-significant	

Appendix 9: Subanalysis of periodontal outcomes based on treatment modalities with post-hoc analysis where appropriate based on statistical significance. – Bleeding on Probing Scores

Plaque score (%)	Baseline	3 Month	6 Month	12 month	
Treatment Modality I	16	16	16	16	N
	45% (50)	7% (25)	18% (22)	56% (51)	Mean (SD)
	8%	0%	0%	100%	Median
	0	0	0	0	Min
	100	100	50	100	Max
	.018				Sig.
Treatment Modality II	9	9	9	9	N
	100% (0)	52% (39)	41% (46)	76% (38)	Mean (SD)
	100	0	0	0	Min
	100	100	100	100	Max
	.008				Sig.
Treatment Modality III	18		17	18	N
	80% (40)		43% (40)	43% (45)	Mean (SD)
	100		33%	33%	Median
	0		0	0	Min
	100		100	100	Max
	.016				Sig.
Treatment Modality IV	12		11	12	N
	92% (29)		47% (50)	43% (51)	Mean (SD)
	100%		50%	42%	Median
	0		0	0	Min
	100		100	100	Max
	.020				Sig.

Kruskal Wallis Post-Hoc – Average Plaque score – TMI

	Baseline	3 Months	6 Months	12 Months
Baseline		Non-significant	Non-significant	Non-significant
3 Months	Non-significant		Non-significant	$p=.002$
6 Months	Non-significant	Non-significant		Non-significant
12 Months	Non-significant	$p=.002$	Non-significant	

Kruskal Wallis Post-Hoc – Average Plaque Score – TMII

	Baseline	3 Months	6 Months	12 Months
Baseline		$p=.033$	$p=.014$	Non-significant
3 Months	$p=.033$		Non-significant	Non-significant
6 Months	$p=.014$	Non-significant		Non-significant
12 Months	Non-significant	Non-significant	Non-significant	

Kruskal Wallis Post-Hoc – Average Plaque score – TMIII

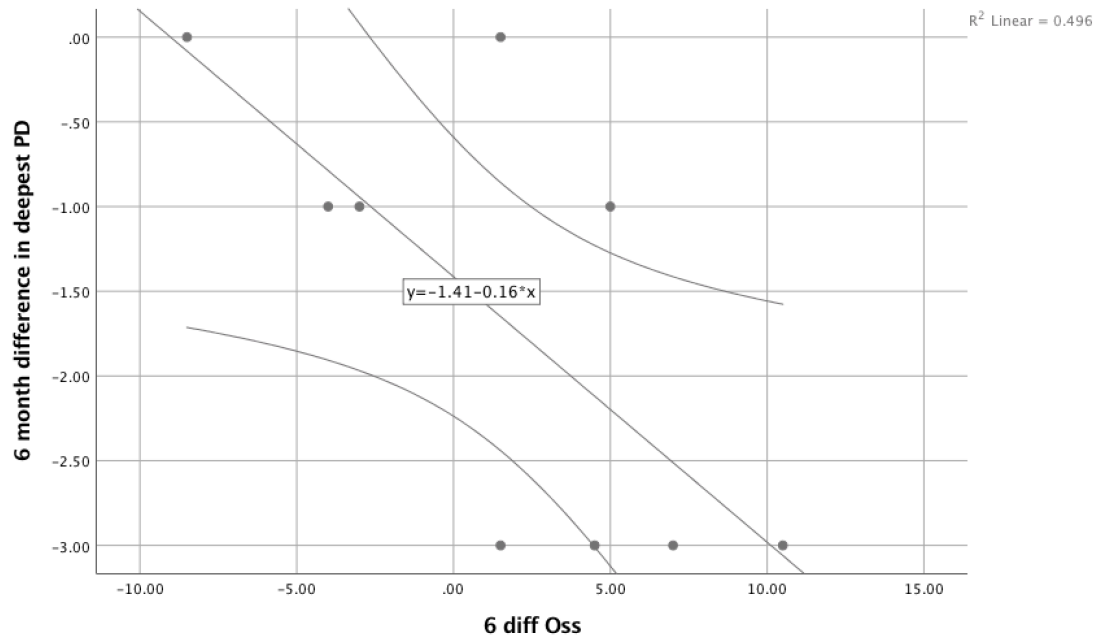
	Baseline	3 Months	6 Months	12 Months
Baseline			$p=.009$	$p=.020$
3 Months			Non-significant	Non-significant
6 Months	$p=.009$	Non-significant		Non-significant
12 Months	$p=.020$	Non-significant	Non-significant	

Kruskal Wallis Post-Hoc – Plaque score – TMIV

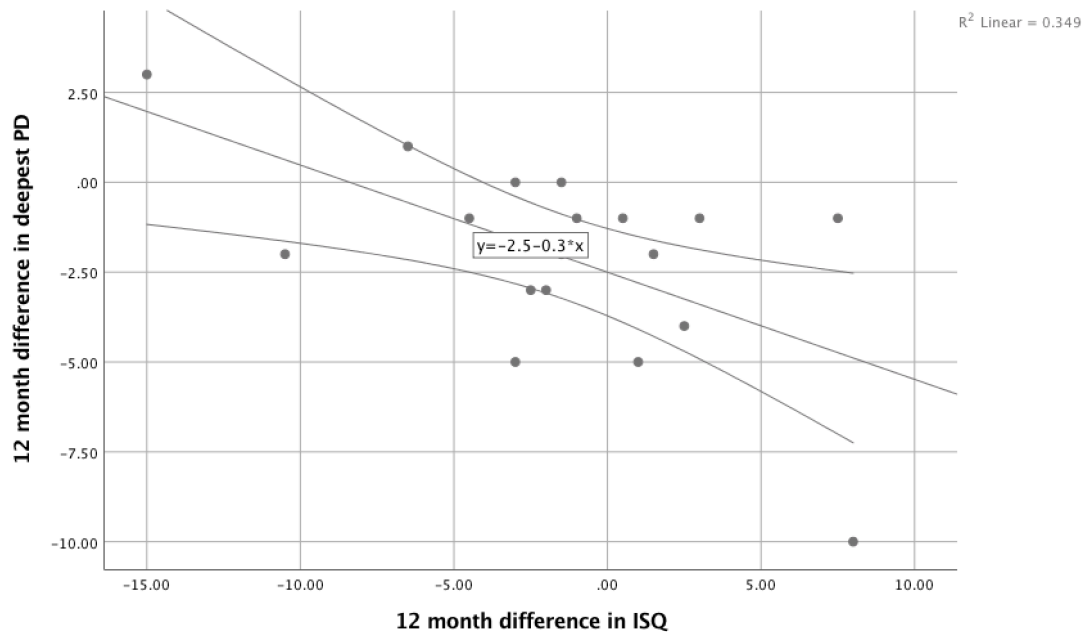
	Baseline	3 Months	6 Months	12 Months
Baseline			$p=.018$	$p=.013$
3 Months			Non-significant	Non-significant
6 Months	$p=.018$	Non-significant		Non-significant
12 Months	$p=.013$	Non-significant	Non-significant	

Appendix 10: Scatterplots of significant relationships in subanalysis of changes in deepest probing depth vs changes in ISQ based on treatment modality.

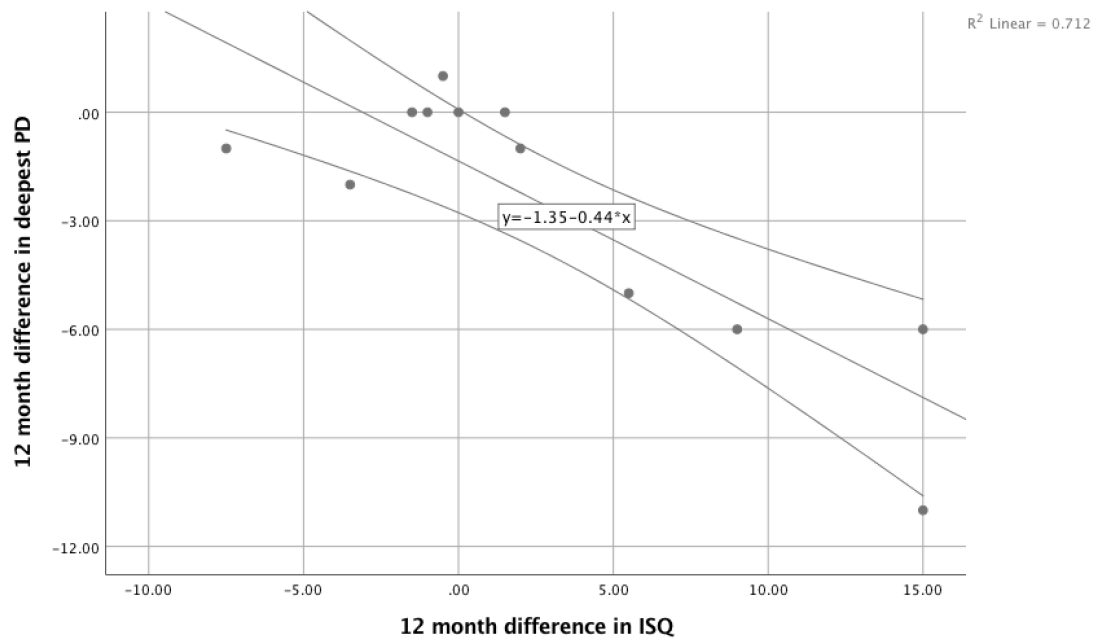
1) TMII – 6 month correlation between changes in deepest probing depth and changes in ISQ.



2) TMIII – 12 month correlation between changes in deepest probing depth and changes in ISQ.



3) TMIV – 12 month correlation between changes in deepest probing depth and changes in ISQ.



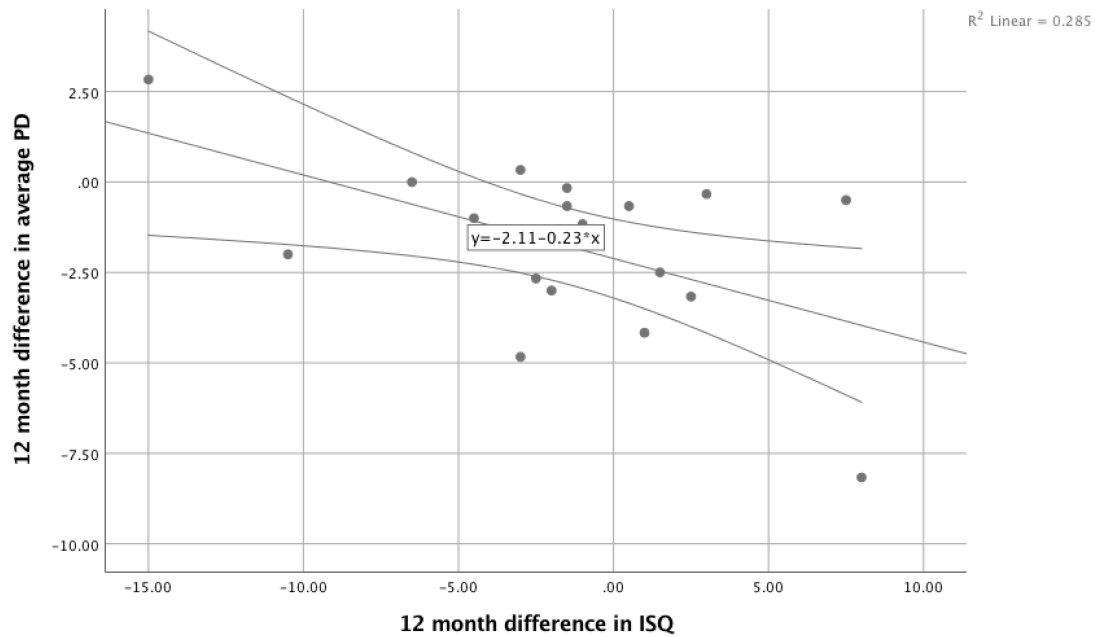
Appendix 11: Scatterplots of significant relationships in subanalysis of changes in deepest probing depth vs changes in ISQ based on treatment modality.

Pearsons Correlation: ISQ vs Average PPD (mm)	3 Month	6 Month	12 month	
All	-1.37mm (1.24)	-1.59mm (4.58)	-1.51 (2.35)	Mean PPD difference (Standard Deviation)
	-0.91 (4.66)	0.51 (4.58)	0.18 (5.60)	Mean ISQ difference (Standard Deviation)
	-.002	-.165	-.493**	Pearson Correlation
	.994	.243	0.000153	Sig. (2-tailed)
Treatment Modality I	-1.72mm (1.29)	-0.95mm (1.10)	-0.91mm (0.86)	Mean PPD difference (Standard Deviation)
	-0.94 (3.48)	1.23 (2.45)	0.17 (3.72)	Mean ISQ difference (Standard Deviation)
	.124	.259	.164	Pearson Correlation
	.649	.352	.560	Sig. (2-tailed)
Treatment Modality II	-0.74mm (0.88)	-1.15mm (1.11)	-1.07mm (1.13)	Mean PPD difference (Standard Deviation)
	0.28 (6.25)	1.61 (5.95)	0.06 (5.73)	Mean ISQ difference (Standard Deviation)
	-.240	-.509	-.064	Pearson Correlation
	.533	.162	.871	Sig. (2-tailed)
Treatment Modality III		-2.19mm (2.26)	-1.77mm (2.42)	Mean PPD difference (Standard Deviation)
		-1.41 (4.92)	-1.50 (5.58)	Mean ISQ difference (Standard Deviation)
		-.162	-.534*	Pearson Correlation
		.533	.023	Sig. (2-tailed)
Treatment Modality IV		-1.95mm (3.41)	-2.25mm (3.85)	Mean PPD difference (Standard Deviation)
		1.59 (4.71)	2.83 (7.02)	Mean ISQ difference (Standard Deviation)
		-.378	-.706*	Pearsson Correlation
		.252	.010	Sig. (2-tailed)

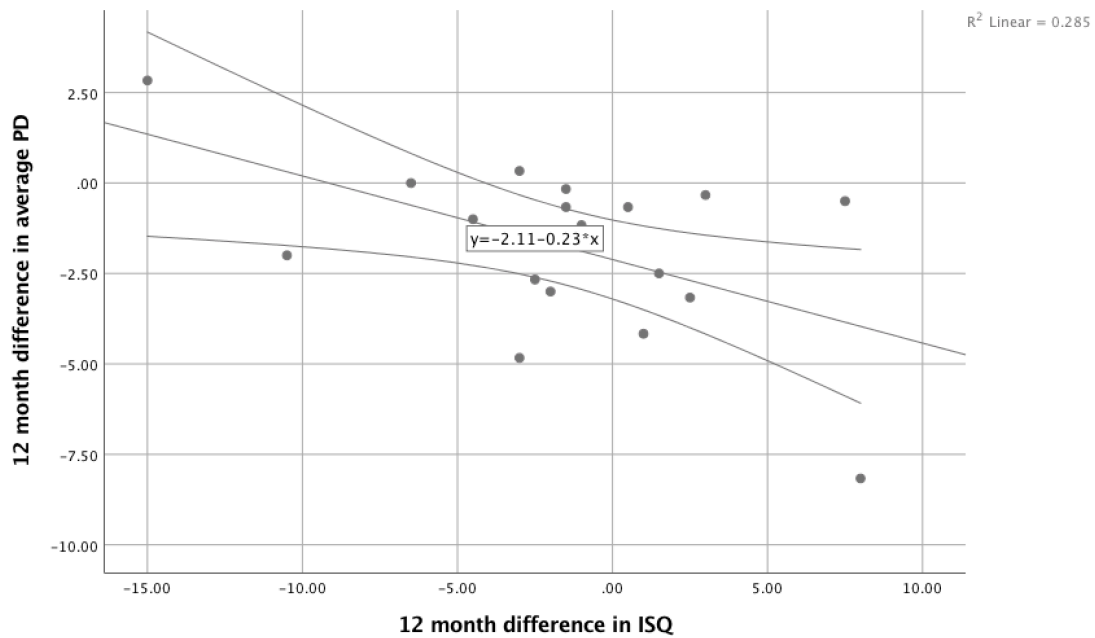
*. Correlation is significant at the 0.05 level (2-tailed)

**. Correlation is significant at the 0.01 level (2-tailed)

- 1) TMIII– 12 month correlation between changes in average probing depth and changes in ISQ.



- 2) TMIV – 12 month correlation between changes in average probing depth and changes in ISQ.

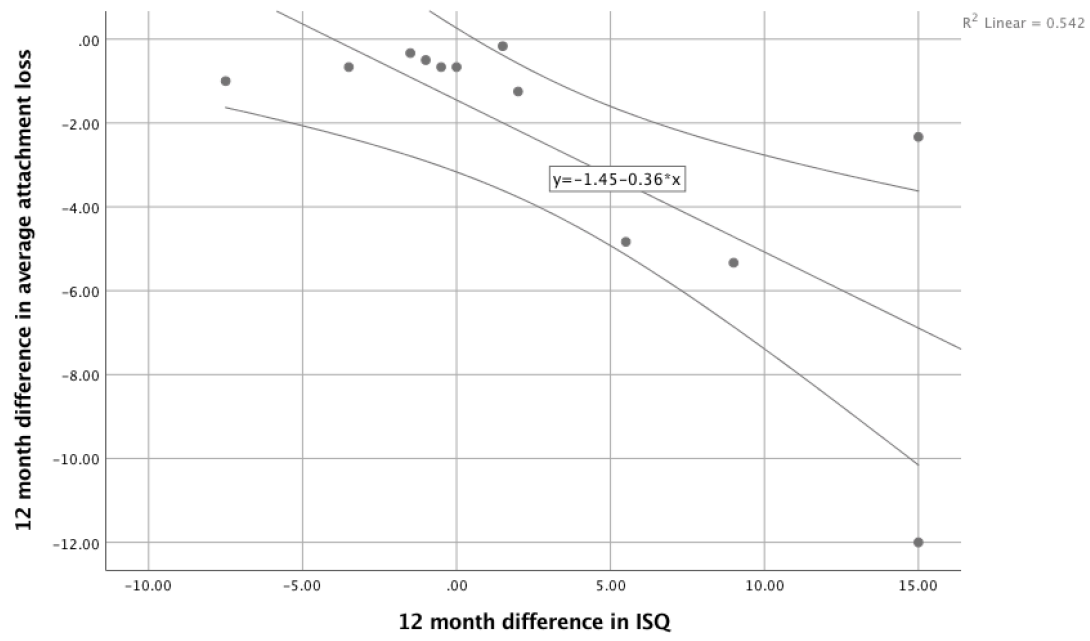


Appendix 12:

Table and scatterplots of significant relationships in subanalysis of changes in average attachment level vs changes in ISQ based on treatment modality.

Pearson Correlation: ISQ vs Attachment level (mm)	3 Month	6 Month	12 month	
All	-1.41mm (1.18)	-1.57mm (1.99)	-1.31mm (2.24)	Mean CAL difference (Standard Deviation)
	-0.91 (4.66)	0.51 (4.58)	0.18 (5.60)	Mean ISQ difference (Standard Deviation)
	.038	-.151	-.496**	Pearson Correlation
	.859	.285	0.00136**	Sig. (2-tailed)
Treatment Modality I	-1.81 (1.25)	-1.05 (1.12)	-0.95 (0.87)	Mean CAL difference (Standard Deviation)
	-0.94 (3.48)	1.23 (2.45)	0.17 (3.72)	Mean ISQ difference (Standard Deviation)
	.193	.486	.194	Pearson Correlation
	.475	.066	.488	Sig. (2-tailed)
Treatment Modality II	-0.70mm (0.59)	-0.98mm (0.85)	-0.52mm (5.73)	Mean CAL difference (Standard Deviation)
	0.28 (6.25)	1.61 (5.95)	0.06 (5.73)	Mean ISQ difference (Standard Deviation)
	-.346	-.629	-.084	Pearson Correlation
	.362	.070	.830	Sig. (2-tailed)
Treatment Modality III		-1.89mm (2.12)	-1.25mm (2.37)	Mean CAL difference (Standard Deviation)
		-1.41 (4.92)	-1.5 (5.58)	Mean ISQ difference (Standard Deviation)
		-.094	-.436	Pearson Correlation
		.721	.071	Sig. (2-tailed)
Treatment Modality IV		-2.31mm (3.06)	-2.48mm (3.46)	Mean CAL difference (Standard Deviation)
		1.59 (4.71)	2.83 (7.02)	Mean ISQ difference (Standard Deviation)
		-.383	-.736**	Pearson Correlation
		.245	.006	Sig. (2-tailed)

** . Correlation is significant at the 0.01 level (2-tailed)



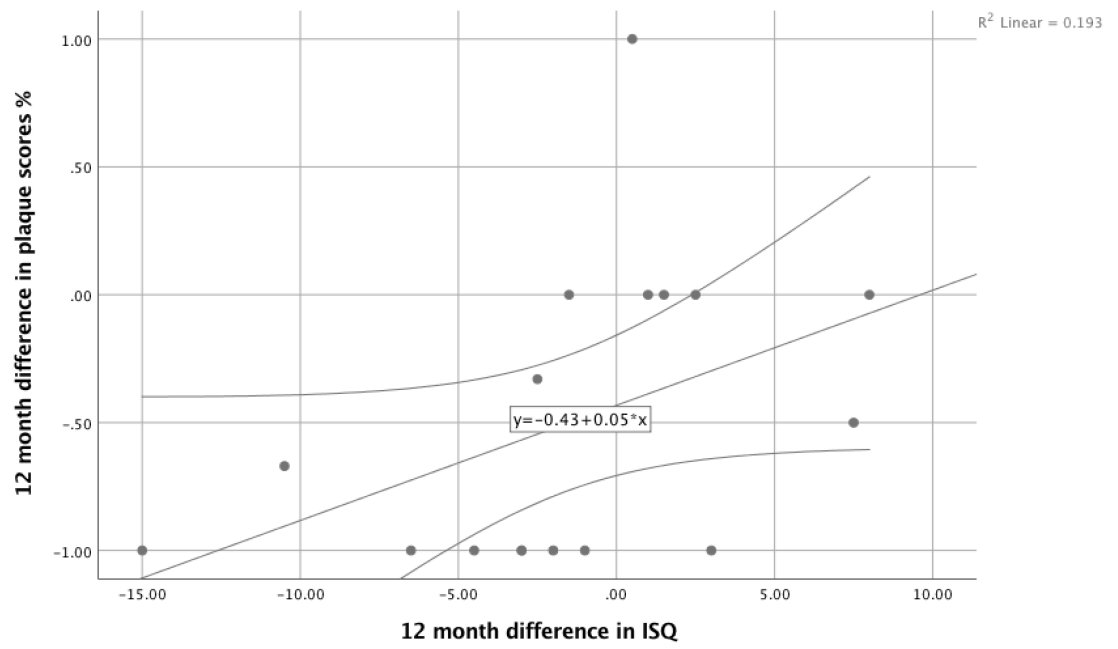
Appendix 13: Table and scatterplots of significant relationships in subanalysis of changes in plaque scores and bleeding on probing vs changes in ISQ based on treatment modality.

Spearman correlation: ISQ vs Bleeding on Probing (% change)	3 Month	6 Month	12 month	
All	-43% (55)	-26% (54)	-28% (54)	Mean BOP difference (Standard Deviation)
	-0.91 (4.66)	0.51 (4.58)	0.18 (5.60)	Mean ISQ difference (Standard Deviation)
	.130	-.257	-.259	Spearman Correlation
	.534	.066	.059	Sig. (2-tailed)
Treatment Modality I	-33% (59)	-29% (41)	-25% (55)	Mean BOP difference (Standard Deviation)
	-0.94 (3.48)	1.23 (2.45)	0.17 (3.72)	Mean ISQ difference (Standard Deviation)
	.308	.370	.164	Spearman Correlation
	.246	.175	.560	Sig. (2-tailed)
Treatment Modality II	-61% (45)	-59% (25)	-39% (32)	Mean BOP difference (Standard Deviation)
	0.28 (6.25)	1.61 (5.95)	0.06 (5.73)	Mean ISQ difference (Standard Deviation)
	-.128	-.106	-.522	Spearman Correlation
	.742	.786	.150	Sig. (2-tailed)
Treatment Modality III		-9% (65)	-17% (65)	Mean BOP difference (Standard Deviation)
		-1.41 (4.92)	-1.5 (5.58)	Mean ISQ difference (Standard Deviation)
		-.472	-.298	Spearman Correlation
		.056	.230	Sig. (2-tailed)
Treatment Modality IV		-20% (61)	-40% (49)	Mean BOP difference (Standard Deviation)
		1.59 (4.71)	2.83 (7.02)	Mean ISQ difference (Standard Deviation)
		-.189	-.463	Spearman Correlation
		.578	.130	Sig. (2-tailed)

Spearman Correlation: ISQ vs	3 Month	6 Month	12	
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Plaque Score (% change)			month	
All	-41% (45)	-40% (49)	-23%	Mean P difference (Standard Deviation)
	-0.91 (4.66)	0.51 (4.58)	0.18 (5.60)	Mean ISQ difference (Standard Deviation)
	.108	-.161	.041	Spearman Correlation
	.607	.254	.767	Sig. (2-tailed)
Treatment Modality I	-38% (48)	-27% (51)	11% (70)	Mean P difference (Standard Deviation)
	-0.94 (3.48)	1.23 (2.45)	0.17 (3.72)	Mean ISQ difference (Standard Deviation)
	.158	-.300	-.289	Spearman Correlation
	.559	.277	.297	Sig. (2-tailed)
Treatment Modality II	-48% (39)	-59% (46)	-24% (38)	Mean P difference (Standard Deviation)
	0.28 (6.25)	1.61 (5.95)	0.06 (5.73)	Mean ISQ difference (Standard Deviation)
	.169	-.139	-.158	Spearman Correlation
	.664	.722	.684	Sig. (2-tailed)
Treatment Modality III		-41% (43)	-50% (57)	Mean P difference (Standard Deviation)
		-1.41 (4.92)	-1.50 (5.58)	Mean ISQ difference (Standard Deviation)
		-.176	.563*	Spearman Correlation
		.498	.015	Sig. (2-tailed)
Treatment Modality IV		-41 (58)	-26% (75)	Mean P difference (Standard Deviation)
		1.59 (4.71)	2.83 (7.02)	Mean ISQ difference (Standard Deviation)
		-.247	-.471	Spearman Correlation
		.464	.122	Sig. (2-tailed)

*. Correlation is significant at the 0.05 level (2-tailed)



Appendix 14:

Correlation between baseline keratinised tissue and periodontal parameters.

Pearson Correlations: Baseline Keratinised tissue (mm)		
Baseline Deepest Probing Depth	5.86mm (2.63)	Mean Deepest PPD (Standard Deviation)
	1.91mm (1.79)	Mean Baseline KT (Standard Deviation)
	.041	Pearson Correlation
	.765	Sig. (2-tailed)
Baseline Average Probing Depth	4.92mm (2.47)	Mean Average PPD (Standard Deviation)
	1.91mm (1.79)	Mean ISQ difference (Standard Deviation)
	.040	Pearson Correlation
	.772	Sig. (2-tailed)
Baseline Average Attachment loss	5.48mm (2.56)	Mean Attachment loss (Standard Deviation)
	1.91mm (1.79)	Mean ISQ difference (Standard Deviation)
	-.084	Pearsson Correlation
	.537	Sig. (2-tailed)
Baseline Bleeding score	63% (44)	Mean BOP%
	1.91mm (1.79)	Mean Baseline KT (Standard Deviation)
	-.217	Spearman Correlation
	.108	Sig. (2-tailed)
Baseline Plaque Score	76% (42)	Mean Plaque Score % (Standard Deviation)
	1.91mm (1.79)	Mean Baseline KT (Standard Deviation)
	-.260	Spearman Correlation
	.053	Sig. (2-tailed)
Baseline Bone Level	-.081mm (1.44)	Mean PPD difference (Standard Deviation)
	1.91mm (1.79)	Mean Baseline KT (Standard Deviation)
	-.020	Pearsson Correlation
	.891	Sig. (2-tailed)