LONG-TERM PERIODONTAL CHANGES DURING ORAL APPLIANCE TREATMENT FOR SLEEP APNEA

by

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Craniofacial Science)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

August 2019

The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, a thesis entitled:

Long-Term Periodontal Changes During Oral Appliance Treatment For Sleep Apnea

submitted by Piyush Heda in partial fulfillment of the requirements

the degree of Master of Science

in Craniofacial Sciences

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Abstract

Background: 2 to 4% of estimated population within the age range of 30 to 60 years is diagnosed with obstructive sleep apnea (OSA). Contemporary management of OSA commonly involves continuous positive airway pressure (CPAP) or oral appliance (OAm) therapy. One of the side effects of long-term OAm wear is mesialization of mandibular dentition resulting in the proclination of mandibular incisors. Similar movement of incisors following orthodontic treatment has been associated with gingival recession.

Purpose: The purpose of this retrospective, in-vivo, clinical and cephalometric observational study is to evaluate the periodontal changes associated with OAm treatment of 4.5 or more years, in individuals with OSA.

Research Design: Patients consecutively treated between 2004 to 2014 at UBC Dental Sleep Clinic and an affiliated private practice were screened. Eligible subjects were followed up where periodontal exam was performed. A lateral cephalogram and impressions were also obtained. Clinical crown height was measured on study models. Periodontal exam included PSR (periodontal screening and recording), plaque index, gingival bleeding index, probing pocket depths and facial gingival margin thickness, in addition to clinical attachment level (CAL), recession and width of attached gingiva. Baseline (T1) and follow up (T2) data was compared.

Results: A total of 21 patients (15 males, mean age 57.4±12.0 y.o) were enrolled, with a mean treatment length of 7.6±3.3 years (range = 4.5 to 14.3 years).

At follow up all patients presented with good oral hygiene with mean plaque index of 0.4 and bleeding index of 4.1%. PSR data confirmed absence of active periodontal disease. For mandibular anterior teeth, mean probing depth was 1.4±0.5 mm, recession was -0.6±1.1 mm and CAL was 0.8±1.0 mm.

Compared to baseline there was significant proclination of mandibular incisors (mean increase in IMPA of 5.1º) with the continued use of OAm. Clinical crown height did not change (mean increase of 0.01 mm) over the evaluated time period.

Conclusions: The inclination of mandibular incisors increases significantly with the use of mandibular advancing oral appliance in OSA patients. The positional changes in these teeth was not associated with any measured evidence of increase in periodontal disease or increased clinical crown height.

Lay Summary

Many patients with mild to moderate sleep apnea regularly use oral appliance for their treatment, the side effect of which is progressive shifting of teeth over time. This leads to forward tilting of lower teeth. This type of tooth movement has been associated with recession of gum tissue in orthodontic studies. This research project evaluated changes in the gingival levels in sleep apnea patients who were regularly using oral appliance for many years.

The findings of the study included appreciable forward tipping of front teeth in lower jaw. However, there were no changes in gum levels indicating that the dental side effects did not had any detrimental effect on the gingival levels around these teeth for the studied time period. Additionally, the study showed that patients had significant relief from their sleep apnea as a result of their oral appliance use and they all had meticulous oral hygiene.

Preface

This research project was suggested by Dr. Benjamin Pliska. The research sample was collected from UBC sleep apnea dental clinic and Dr. Fernanda Almeida's private practice. The methodology was finalized in agreement with the committee members Dr. Fernanda Almeida, Dr. Hugh Kim and Dr. Benjamin Pliska.

Data collection, entry and analysis was performed by Piyush Heda. Statistical analysis was completed with the guidance of Dr. Jolanta Aleksejuniene and Ms. Mary wong. Piyush Heda prepared the manuscript with content editing by Dr. Fernanda Almeida, Dr. Hugh Kim and Dr. Benjamin Pliska.

The study was approved by the Clinical Research Ethics Board at the University of British Columbia, ethics certificate number H14-00743.

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List of Abbreviations

AADSM: American academy of dental sleep medicine

AASM: American academy of sleep medicine

AHI: Apnea hypopnea index

BMI: Body mass index

CAL: Clinical attachment level

CPAP: Continuous positive airway pressure

ICC: Intra-class correlation coefficient

ICF: Information and consent form

OAm: Manadibular advancement oral appliance

OSA: Obstructive sleep apnea

PAP: Positive airway pressure

PSR: Periodontal screening and recording

RCDC: Royal college of dentists of Canada

REDCap: Research Electronic Data Capture

RERA: Respiratory effort related arousal

TRD: Tongue retaining device

UBC: University of British Columbia

Acknowledgments

The work with this project has been very instructive. This has been made possible with the help, support, and encouragement from several persons.

First, I would like to thank my supervisor Dr. Benjamin Pliska for recommending this topic to me and for his continuous support throughout this project. His guidance helped me gain valuable research skills, critical thinking, and knowledge in conducting clinical trials.

I would also like to thank my committee members in helping me complete this project. A special thanks to Dr. Fernanda Almeida for her invaluable suggestions as well as for providing me support from her clinic that helped me to better this study. A big thanks to Dr. Hugh Kim whose recommendations helped me in developing a strong clinical protocol for the periodontal component of the patient exam.

I could not have completed this project without the help from Ms. Sandra Harrison, Ms. Eleanor Cawthorne and Dr. Bernardo Peres who helped me with organizing UBC sleep apnea dental clinic patient database, patient recalls, patient exam, records and data management. They were extremely dedicated and generously offered their continuous support.

I also want to acknowledge Dr. Jolanta Aleksejuniene and Ms. Mary Wong for advising me on the statistical analysis for my research. Their help is greatly appreciated.

Last but not least, I cannot thank my family enough for their relentless love, support, and encouragement. I owe a great debt of gratitude to my parents who always entrusted my life's decisions and stayed by my side. It would not have been possible without their love and blessings.

Dedication

To my wife Kiran and my sons Vishrut and Ishan for their countless sacrifices and for believing in me. Thank you for never making me feel how much I had been away from you in the past few years.

Chapter 1: Introduction

1.1 Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a common disorder considered to be the most severe manifestation of sleep disordered breathing[1]. In OSA there is repetitive partial or complete collapse of upper airway causing hypopnea or apnea respectively resulting in cardiovascular and metabolic consequences[2,3]. In order to maintain a patent upper airway, an individual experiences frequent arousals which activates sympathetic nervous system and disrupts sleep[4]. Such sleep fragmentation along with oxygen desaturation is found to significantly increase sympathetic activity in OSA patients not only in sleep but also when they are awake compared to matched controls. This results in significantly high blood pressure levels and tachycardia in OSA patients during sleep. Chronic and untreated OSA therefore may result in adverse cardiac consequences over time.[4] Due to disrupted sleep patient may also experience reduced quality of life, excessive daytime sleepiness and an increased risk of accidents[3,5]. The apnea-hypopnea index (AHI) is commonly used to determine the severity of the disorder that is calculated as mean number of events of apnea or hypopnea for every hour of sleep. OSA has been classified as mild (5-15 events/hr), moderate (15-30 events/hr) and severe (more than 30 events/hr)[6].

1.2 OSA epidemiology

Young and co-workers carried out one of the most comprehensive OSA epidemiological investigations at the University of Wisconsin. Overnight polysomnography of 602 randomly selected subjects with the age range of 30 to 60 years revealed that the prevalence of OSA is 4% in men and 2% in women. The findings of their study reported that 9% women and 24% men

have the apnea hypopnea index (AHI) of 5 or higher. Additionally, male sex and obesity were identified as strong risk factors[7]. Sharma et al[8] in a 2-stage cross-sectional study involving 2150 subjects from Indian population found similar OSA prevalence of 4.9% and 2.1% in males and females respectively between the age range of 30 to 60 years.

In a prospective clinical trial at the University of Wisconsin, Peppard et al[9] estimated the prevalence of OSA by comparing data from the Wisconsin sleep cohort study for the time periods 1988-1994 and 2007-2010. They evaluated 1520 subjects between the ages of 30 to 70 years and demonstrated the higher prevalence of OSA in men, older subjects and those with higher body mass index (BMI). Authors concluded significant increase in OSA prevalence over the last 2 decades with current percentages being 10% and 3% among 30 to 49 year old men and women respectively and 17% and 9% among 50 to 70 year old men and women respectively. Peppard et al[10] had observed that there is 32% increment in OSA risk following 10% weight gain.

According to the American academy of sleep medicine (AASM) guidelines, individuals with following conditions are considered as high risk and should be evaluated for OSA symptoms – obesity, congestive heart failure, atrial fibrillation, refractory hypertension, type-2 diabetes, nocturnal dysrhythmias, stroke, pulmonary hypertension, high-risk driving populations and those undergoing bariatric surgery[11].

1.3 Metabolic changes associated with obstructive sleep apnea

Occurrence of intermittent hypoxia in OSA leads to sympathetic system activation in addition to causing systemic inflammation and associated oxidative stress. Some other conditions linked with OSA include hypertension, hypercoagulability, metabolic dysregulation, endothelial

dysfunction and sleep fragmentation[12]. Patients suffering from severe OSA are at increased risk of having cardiovascular conditions[13] along with obesity, diabetes and metabolic syndrome[14].

In a controlled clinical trial involving 22 patients with 16 controls, it was found that patients with mild to moderate OSA showed increased serum markers of systemic inflammation that improved following 6 months of treatment with OAm[15].

A recent systemic review and meta-analysis reported the possibility of link between OSA and reduced bone mass in adult population but with inconsistent, low quality evidence and not without bias risk[16].

1.4 Management of obstructive sleep apnea

OSA is considered as a chronic disease and therefore requires multidisciplinary long-term care to effectively manage the condition. The suggested primary treatment options include behavioral, medical and surgical management[11].

Contemporary conservative management of OSA commonly involves use of nasal continuous positive airway pressure (CPAP) or oral appliance (OAm). Positive airway pressure (PAP) therapy has been consistent with the AHI reduction and significant improvement in the OSA symptoms[17]. CPAP refers to continuous delivery of the air pressure through nasal, oral or oronasal means[17]. Pressurized air is introduced into the airway while the person is sleeping and ensures adequate ventilation, patent airway and prevents its collapse[11].

CPAP is the recommended treatment for adults with OSA but patient compliance may be an issue[2]. Therefore for those patients who are not able to tolerate the CPAP, mandibular advancement oral appliance (OAm) can be a viable alternative[3,18]. It is also the treatment of choice for mild to moderate OSA as well as snoring[19]. OAm works on the principle of holding

the mandible in advanced position during sleep, thereby expanding the airway thus improving the OSA signs and symptoms[19]. Another variant of oral appliance is the tongue retaining device (TRD), which works by holding the tongue forward. Most TRDs are custom made[20], but tend to be less commonly used than OAm.

1.5 Role of oral appliance (OAm) in sleep apnea patients

American academy of dental sleep medicine (AADSM) defined OAm as: "The purpose of an oral appliance is to treat OSA, primary snoring, and associated symptoms. Oral appliances are intended to decrease the frequency and/or duration of apneas, hypopneas, respiratory effort related arousals (RERAs) and/or snoring events. Oral appliances have been demonstrated to improve nocturnal oxygenation as well as the adverse health and social consequences of OSA and snoring. Oral appliances are indicated for patients with mild to moderate OSA and primary snoring. Oral appliances are accepted therapy for patients with severe OSA who do not respond to or are unable or unwilling to tolerate PAP therapies. Although oral appliances are typically used as a stand-alone therapy, they can serve as an adjunct to PAP therapy and/or other treatment modalities for the management of OSA"[21].

OAm is being used more and more commonly for patients with OSA and snoring. Although studies have shown that CPAP is more efficient in reducing the AHI[3,22]. Li et al[23] in a systematic review and meta-analysis that compared the OSA treatment outcomes between CPAP and OAm, they concluded that polysomnography results were better with CPAP particularly for AHI reduction. But they also observed similar clinical outcomes making OAm a viable treatment alternative especially for patients not compliant with CPAP. In an RCT by Phillips et al to compare the health outcomes of CPAP versus OAm treatment for patients with OSA and

AHI>10, they concluded better efficiency with CPAP than OAm in terms of AHI reduction but the OAm group exhibited better compliance regarding appliance use. Similar health outcomes were observed in both CPAP and OAm groups at the end of the study and the authors concluded that the improved efficacy of CPAP was counteracted by its poor compliance leading to similar effectiveness over time[24].

The mechanism of action of OAm is that the forward posturing of mandible enlarges the upper airway and maintains the patency during sleep. This improves oxygen saturation and reduces AHI thereby improving the signs and symptoms of OSA[20].

The AASM guidelines indicated OAm use in patients with mild to moderate OSA who do not tolerate CPAP well or do not respond to CPAP therapy or previous treatment with CPAP has failed or based on patient preference[3]. They also recommended that OAm should be delivered by qualified dental professional who has received adequate training for the same[3,20].

1.6 Adverse effects of OAm on craniofacial structures

Because of its simple design and non-invasive nature of therapy there is increased patient acceptance leading to more effective overall treatment[25]. At the start of the OAm use however, some adverse effects have been commonly reported[26]. These mild and transient effects include excess salivation, dry mouth, tissue irritation, lip and cheek biting, short term discomfort in jaws and teeth, myofascial pain, jaw stiffness and grinding of teeth[27–30].

When an OAm is inserted in mouth, it tends to hold the mandible in a downward and forward, advanced position. This causes the upper airway to enlarge[19] and the extent of mandibular advancement is directly related to the efficacy of an OAm[31,32]. Initial mandibular advancement position is usually between 50% to 75% of the maximum protrusive movement by

the patient or less if the patient is uncomfortable with this much advancement. The subsequent advancement of the mandible should be customized for each patient based on the improvement of symptoms and patient comfort[20].

OAm use may have to continue through the life of an individual with OSA. Such long term use of OAm leads to various dental and skeletal changes which also depends on the total duration of OAm wear and extent of mandibular advancement[19]. These side effects have been evaluated using cephalometric[27,30,33–36] studies and dental cast[27,34] analysis. Most of the craniofacial changes observed were essentially dental changes or tooth movements[37]. Both cephalometric and dental cast analysis revealed the significant overjet and overbite reduction with mesial mandibular movement[27,34,38]. Maxillary incisors retrocline and mandibular incisors procline following OAm use[27,33,38,39]. Ueda et al[40] in their follow up of over 5 years found significant change in both anterior and posterior occlusal contact area. Norrhem et al[41] in a relatively short follow up period of about 3 years evaluated change in incisor irregularity comparing flexible vs rigid OAm. They found that the irregularity increased with flexible OAm whereas remained unchanged when the rigid OAm was used.

Magnitude of dental change however is a function of time and therefore considering the possible lifelong use of OAm many of these studies had relatively short follow-up periods. Many previous studies also did not have a control group.

Robertson et al[33] in a relatively short follow up period of 30 months for patients using non-titrable OAm found that the tooth movement is progressive. On the contrary, Pantin et al[30] in their 5 year follow up of OSA patients using OAm proposed that the expression of dental side effects may slow down after few years. Martínez-Gomis et al[42] in a similar study which also had

a 5 year follow up period, had observed significant dental changes within first 2 years and some trend towards reversal in the remaining follow up period.

Two studies[19,37,39] with the longest follow up periods however have concluded that the dental changes observed are progressive with OAm wear.

Almeida et al[37,39] in a cephalometric and study model analysis of OSA patients using OAm for a mean duration of 7.4 years observed that the changes are primarily dental clinically manifested as occlusion changes, posterior open bite and anterior crossbite tendency, overjet and overbite reduction, maxillary incisor retroclination and mandibular incisor proclination with progressive resolution of crowding over time. Interestingly, they found unfavorable response in individuals with Class I pre-treatment occlusion/ malocclusion whereas those with Class II malocclusion types pre-treatment had relatively lesser dental changes which were favorable due to distal movement of maxillary dentition and mesial movement and extrusion of mandibular posterior teeth along with transverse dental changes.

Pliska et al[19] in the longest follow up by far of over 11 years of mean treatment duration, have evaluated study models and found similar dental changes that are ongoing with the OAm wear. They also found increase in mandibular transverse dental width between molars and canines.

Of all the dental side effects resulting from OAm therapy, teeth most affected are maxillary and mandibular incisors[39].

1.7 Periodontal changes associated with lower incisor proclination

There is no published study that has evaluated the periodontal change following proclination of mandibular incisors as a consequence of OAm wear, but this has been studied

often when such proclination is the result of an orthodontic treatment. It is important to notice though that for patients using OAm, since the change is progressive and treatment is lifelong, we can anticipate that the mandibular incisors will continue to procline with time. This is not the case in patients undergoing orthodontic treatment where the active tooth movement stops following discontinuation of orthodontic forces.

Several clinical situations in orthodontics necessitates proclination of mandibular incisors e.g. in resolving anterior crowding without extractions which can lead to better esthetics as well as occlusal outcomes[43]. Also in mild to moderate Class II division 1 malocclusions with camouflage treatment, in Class II division 2 malocclusion where mandibular incisors are retroclined pre-treatment and in Skeletal Class III malocclusions where mandibular incisors need to be proclined for dental decompensation pre-surgically.[44]

The periodontal consequences of such tooth movement alone has been a matter of controversy.[45,46] Some studies[43,47–52] have concluded that gingival recession can follow mandibular incisor proclination, whereas others[43,51,53–55] have denied such a correlation. When it occurs, gingival recession can cause other problems such as unaesthetic outcome following treatment, oral hygiene maintenance, dentin hypersensitivity and bone loss to name a few.[47,56] In adults, after 50 years of age the prevalence reported for gingival recession was 90% that worsens with time[57]. The most commonly affected areas are labial surfaces of mandibular incisors and maxillary molars[47,58]. Thin cortical bone on the labial aspect, minimal or absent attached gingiva and mandibular incisors with labially prominent roots are the factors held responsible recession by Dorfman[47]. Such teeth on application of orthodontic forces may show localized areas of gingival recession[59]. However, Dorfman also observed that there is a weak correlation between

this association, and it should be interpreted with caution. As long as the teeth are moved within the confines of their bony envelope, the risk of gingival recession is believed to be minimal[59,60].

Some animal experiments have suggested that when the periodontium is healthy and teeth are moved orthodontically, such that it follows the arch form then the teeth maintains its periodontal support[61,62]. On the contrary, animal studies involving labial movement of mandibular incisors have reported areas of bone dehiscence in monkeys[63] and dogs[64]. In a study of extensive mandibular incisor inclination change due to pre-surgical dental decompensation in cases with mandibular prognathism, they found that recession could not be avoided especially when cortical bone is thin but these changes are seen mainly during active treatment[49]. In a similar recent study also it was found that following significant dental decompensation involving mandibular incisors there is increase in clinical crown height on the labial aspect along with reduced attached gingiva width[65]. In the cephalometric analysis they measured symphysis width and reported its correlation with recession[49]. In another follow up study, where the mandibular incisors were proclined for the correction of Class II malocclusion in adolescent patients, they observed no increased risk of recession[43].

When this deleterious effect does occur following mandibular incisor proclination it can also be caused by lack of adequate oral hygiene maintenance resulting in plaque accumulation[51]. In orthodontic patients the prevalence of gingival recession following treatment can range from 1.3% to 10%[47,66]. Pre-existing mucogingival problems can lead to rapid periodontal deterioration[67], but patients with at least 2 mm of attached gingiva are less likely to develop gingival recession[59,68]. Therefore, pre-existing mucogingival defects should be treated before starting orthodontic treatment so that the periodontium can better withstand orthodontic forces[68]. This is particularly important for mandibular incisors, as due to their anatomic position,

following labial movement the roots can become very prominent with little or no bone on the labial surface with inadequate or no attached gingival tissue[47]. Wennstrom and coworkers however suggested that the quality of gingival tissue is more important than its dimension[60].

Two systematic reviews[45,46] have attempted to answer this question of determination of an association between orthodontic labial movement of mandibular incisors and gingival recession. Both the systematic reviews pointed towards the lack of good quality studies, variable methodology and thus the low level of available evidence. They both concluded that there is either no association or weak association between orthodontic proclination and gingival recession and due to low level of evidence this should be interpreted with caution. Clinically, it cannot be readily surmised that the proclination of mandibular incisor will cause gingival recession. The possible risk factors identified are pre-treatment gingival recession, presence of plaque and associated gingivitis, poor oral hygiene maintenance, minimal or absent keratinized gingival tissue, thin gingival biotype and thin labial cortical bone.

Even though some studies have suggested the possible correlation between the incisor position labiolingually and gingival recession, this association is weak[59] and the available evidence is low and non-conclusive as has been emphasized by the systematic reviews[45,46]. Therefore, considering the risk factors, it is challenging for the orthodontist to identify cases that will be predisposed towards recession or the ones that will not need any periodontal treatment[59]. This makes it judicious to make a referral to periodontist whenever there is inadequate or thin keratinized gingival tissue[69–71].

The etiology for the gingival recession is believed to be multifactorial[59,72], which includes predisposing and precipitating factors which are anatomic and inflammatory causes respectively[54]. It is therefore important to identify these risk factors and inform the patient[59].

1.8 Assessment of periodontal changes following mandibular incisor proclination

There has been variation in the methodology used in different studies to assess the periodontal changes following mandibular incisor proclination as a result of orthodontic treatment. Most studies however used lateral cephalograms and dental casts of patients to determine the degree of proclination and the changes in clinical crown height respectively[43,49,51,53]. Some have also used intraoral color slides or intraoral photographs with or without radiographs and dental casts[43,49,51,53,55].

Few studies[43,49,52] involved direct assessment of patient's gingival tissue at the follow up exam of which two[49,52] did a more comprehensive exam by also measuring plaque index, gingival bleeding index, pocket probing depth and gingival recession. Only few studies had a control group[43,49,55]. Gingival recession was often assessed at different times by different authors that ranged from immediately after orthodontic appliance removal to up to 8 years[43,49,51–53,55].

1.9 Obstructive sleep apnea and periodontitis

Periodontitis is a chronic infection of the supporting tissues of teeth commonly caused by pathogenic bacteria that initiates an inflammatory response[73]. Gunaratnam et al[74] first suggested following a pilot study, the possibility of an association between periodontitis and OSA. This was based on the hypothesis that systemic inflammation is the common feature of both periodontitis and OSA. They found that in OSA patients, periodontitis is four times more prevalent when compared with national average. Other potential mechanisms that may explain this relationship apart from systemic inflammation is dryness of mouth from mouth breathing or medications and oxidative stress following intermittent hypoxia[75].

Many studies[75–83] since then have attempted to determine this association between OSA and periodontitis among various populations and most have observed significant but variable levels of association with the suggestion of the need for further exploration in this area. Al-Jewair et al[79] in a systematic review and meta-analysis, attempted to identify the bidirectional relationship between periodontitis and OSA. But owing to lack of high quality research and heterogeneity among studies, cause and effect relationship remains debatable while the association has been identified. At least one study failed to find an association between OSA and periodontitis[84]. In this cross-sectional study, they evaluated 100 subjects from veterans sleep study center. Subjects were grouped based on severity of AHI and compared with matched controls. Based on their methodology, they found very high prevalence of periodontitis in their study subjects compared to general population and no association between OSA and periodontitis. While the periodontitis prevalence was similar among the groups with mild, moderate and severe AHI and the controls, their results may not be extrapolated to the general population.[84]

1.10 Long-term dental and periodontal maturational changes in healthy adults

The long-term changes in periodontal attachment level in healthy individuals with aging have been investigated. In two population studies that evaluated long-term periodontal changes with age found that there is increase in mean attachment loss over a period of 14 and 28 years respectively, but this change is not significant statistically[85,86]. The 28-year follow up reported 1.34 mm of change in clinical attachment level during the study period. But these studies did not controlled for systemic and oral health and one study[85] was a retrospective radiographic assessment. Although age has been indicated as a risk factor for periodontal attachment loss, no

direct correlation could be established[87]. Locker et al[88] in their review pointed that while aging may be attributed to some attachment loss, the amount of change is not clinically significant. Huttner et al[89] mentioned that these age related changes can be due to cellular and biomolecular alterations within the periodontal ligament as well as systemic hormonal changes.

Ship et al[90] in a 10-year follow up of the Baltimore Longitudinal Study, evaluated 95 healthy subjects between 29 and 76 years of age. Periodontal examination included recession, pocket depth, level of attachment and attachment loss. They concluded that the periodontal attachment loss observed was not dependent on subject's age with no generalized changes taking place. Mean change in recession ranged from 0.11 mm (reduced) to -0.86 mm (increased) with the higher number reaching statistical significance. Interestingly they observed the risk is higher by one third for mandibular teeth in terms of attachment loss but the least amount of change was observed in the incisors which is both clinically as well as statistically insignificant.

In a longitudinal follow up spanning over 40 years, in individuals with normal occlusion, Massaro et al[91] evaluated changes in clinical crown height at 13, 17 and 60 years of age. They observed that this change is not significant for mandibular incisors when compared between 17 to 60 years. They concluded that the clinical crown height for mandibular incisors did not change significantly because the increase in clinical crown height was similar to the extent of incisal wear.

1.11 Research justification

OAm are commonly used in contemporary clinical practice for patients with mild to moderate OSA. One reason for this may be increased patient compliance with the OAm as compared to the CPAP[23]. OAm relieves the OSA symptoms as long as the patient is using the

appliance. This means that a patient needs to use the appliance for the rest of their lives to avoid or minimize OSA symptoms. It has been established by long-term studies that the continuous use of OAm leads to various dental side effects in the form of tooth movement that continues for the duration of appliance use[19]. One of these dental adverse effects is the significant amount of proclination of mandibular incisors over time.

As excessive mandibular incisor proclination is thought to be associated with gingival recession in the orthodontic literature[43,45,46,51,52], an investigation of an association between the excessive mandibular incisor proclination resulting from long-term wear of OAm and potential gingival recession in OSA patients is warranted.

1.12 Study objectives and hypotheses

The specific aims of this study are to:

1. Assess the periodontal parameters, including changes in clinical crown height, in patients wearing OAm for a minimum of 4.5 years.
2. Determine the cephalometric changes in patients wearing OAm for a minimum of 4.5 years.
3. Investigate associations between any occlusal changes and periodontal parameters in a cohort of OSA patients treated with OAm for a minimum of 4.5 years.

The following null hypotheses will be tested:

Null hypothesis 1 (H_0^1): Long-term use of OAm does not result changes in the periodontal health of OSA patients.

Null hypothesis 2 (H_0^2): Changes in incisor inclination following long-term OAm use is not associated with gingival recession.

Chapter 2: Methodology

The protocol for this retrospective observational study was approved by the Ethical Board at the University of British Columbia, Vancouver, British Columbia, Canada (Certificate number: H14-00743).

2.1 Study design

This study consisted of long-term follow up of patients who are using OAm for a minimum of 4.5 years for the treatment of sleep apnea or snoring. Subjects were recruited from two different centers. Case files were screened for availability of good quality baseline study models and lateral cephalogram. Once the inclusion criteria were met, patients were then contacted by either a phone call or an email based on the contact information available on record. Scripted study information was read to them and information and consent form (ICF) document was either mailed or emailed to the patients if they were interested in the study and a clinical visit was scheduled. Two weeks of time period were provided to patient from the time they received the ICF to their enrolment, so their questions can be answered satisfactorily, and a voluntary informed decision can be made. Many patients were already scheduled for routine OAm follow-up visit. They were informed of the study during their clinical visit and ICF was provided.

At the scheduled appointment, ICF is signed and thorough clinical exam is carried out to assess the current periodontal status of the patient. Impressions and lateral cephalogram were also taken at this time unless it was done within last 12 months. Finally, patients are provided with some questionnaires either by email or printed copies. A copy of signed ICF was provided to patient either during this visit or was emailed to them.

To achieve specific aims, comparison of pre-treatment and current lateral cephalograms for mandibular incisor proclination and dental casts to measure clinical crown heights of mandibular anterior teeth was done.

2.2 Sample selection and recruitment

This study was conducted in two different centers. A total of 21 subjects were included from both the centers.

2.2.1 Center 1: University of British Columbia (UBC) sleep apnea dental clinic in Vancouver, British Columbia, Canada

Consecutive sampling was employed. 145 patients received treatment at UBC sleep apnea dental clinic from 2004 to 2014. All patient records and case files were screened for availability of good quality records. Flow diagram for the same is presented in figure 1. Once all the inclusion and exclusion criteria are fulfilled, 13 patients were recruited from this clinic.

2.2.2 Center 2: Private sleep apnea dental clinic in Vancouver, British Columbia, Canada

Random sampling method was used. From the case files of patients who started treatment and received OAm either in 2012 or 2013, 26 patient charts were randomly selected. 8 patients were recruited from this private office after excluding ineligible subjects.

2.2.3 Inclusion criteria

- Patients who are willing to participate and have given their informed consent at the clinical visit.

- Patients using OAm regularly and for a minimum of 4.5 years. Regular wear is defined as use of OAm for minimum 5 nights per week and at least 4 hours per night.
- Availability of good quality pre-treatment records for existing patients.
- Patient at least 19 years of age or older.
- Patient able to understand and communicate in English.

2.2.4 Exclusion criteria

- Patients who refused to participate in the study or declined follow up records.
- Patients who could not be contacted.
- Patients who stopped using OAm or switched to other means of OSA treatment, e.g. CPAP.
- Missing or lack of good quality records.
- Pre-existing periodontal condition e.g. acute or chronic periodontitis.
- Patients with previous history of any mucogingival surgery in sextant 5.
- Patients with a dental implant in sextant 5.

2.3 Data collection

Pre-treatment and current clinical records of included subjects were reviewed for data collection. This included review of patient charts, pre-treatment study models, panoramic and lateral cephalometric radiographs (T1), post-treatment study models, panoramic radiograph and lateral cephalometric radiograph (T2). A clinical and periodontal exam was also performed during patient visit. Patient age, sex, treatment start date, medical history, missing teeth, presence

of dental implants, Angle's classification, overjet, overbite, AHI, BMI and OAm characteristics were recorded at baseline as well as at the recent visit. Patients were provided with following questionnaires: Patient history form, subjective adherence questionnaire and dental side effects questionnaire.

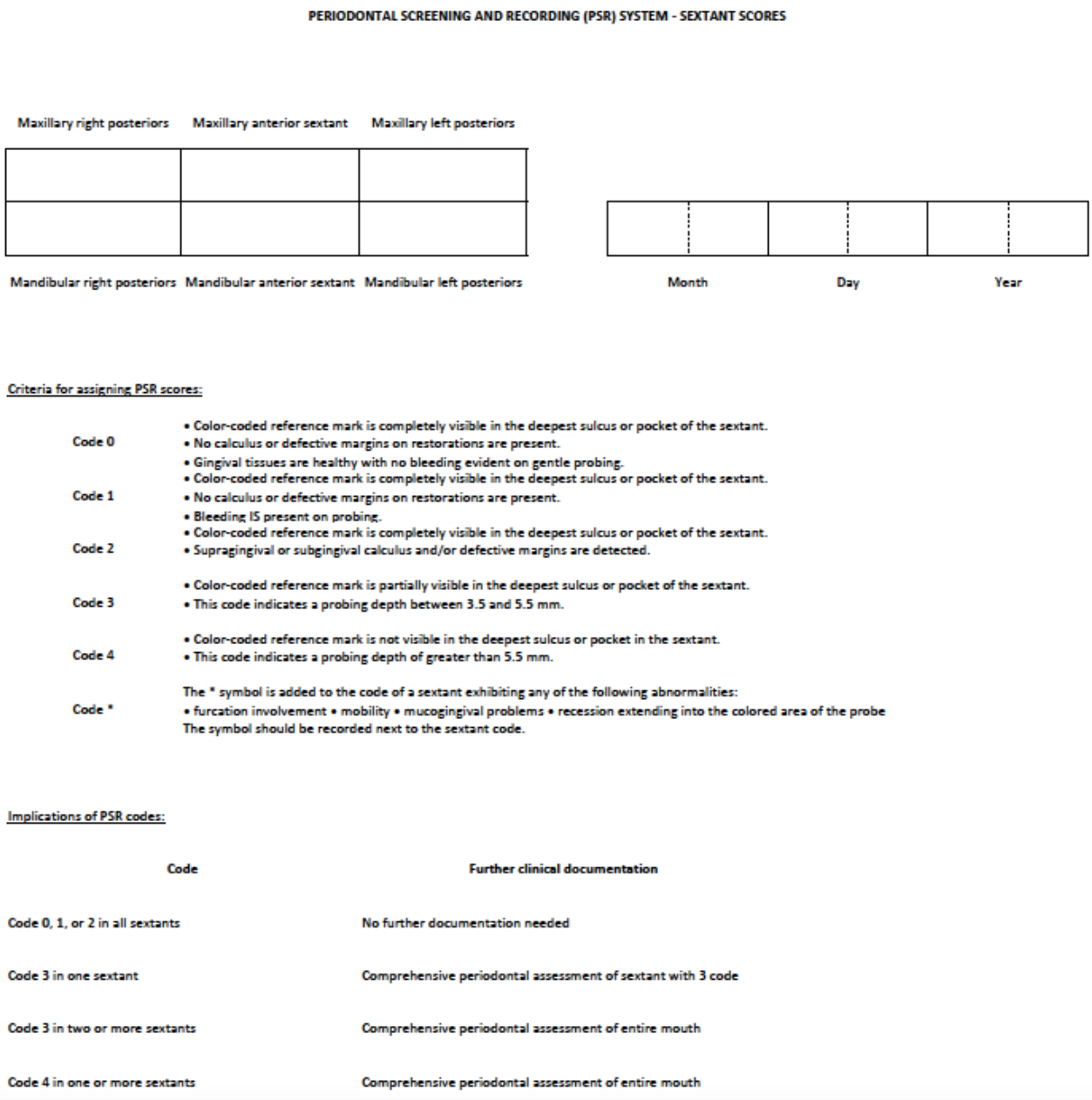
Study data was collected and managed using REDCap electronic data capture tools hosted at The University of British Columbia[92]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources[92].

2.3.1 Periodontal screening data

Periodontal data is collected during patient's clinical visit (T2). Periodontal screening and recording (PSR) system is used as a screening tool to assess the overall periodontal health of the subjects and to identify periodontal disease as well as treatment need if any. PSR codes were scored and documented for each sextant. A metal PSR probe was used for all patients. It has a ball tip of 0.5 mm diameter and a colored band marked at 3.5 mm to 5.5 mm from the tip (See Figure 1 and Figure 2).

In addition to screening, detailed periodontal evaluation is done for mandibular anterior teeth. This included measuring of probing pocket depths, recession (including negative recession), clinical attachment level (CAL), width of attached gingiva and mobility. Facial gingival margin thickness was evaluated as thick or thin based on visibility of probe when inserted into the gingival sulcus. Gingival color, contour, consistency and presence of calculus

are recorded. Plaque index (Silness and Loë[93]) and gingival bleeding index (Ainamo and Bay[94]) were calculated. For probing depths, 3 sites on the facial aspect and 3 on the lingual aspect were measured. Data is recorded on "The Royal College of Dentists of Canada - periodontal case report record" sheet (See Figure 3).



PERIODONTAL SCREENING AND RECORDING (PSR) SYSTEM - SEXTANT SCORES

Maxillary right posteriors | Maxillary anterior sextant | Maxillary left posteriors

Mandibular right posteriors | Mandibular anterior sextant | Mandibular left posteriors

Month | Day | Year

Criteria for assigning PSR scores:

Code 0	• Color-coded reference mark is completely visible in the deepest sulcus or pocket of the sextant. • No calculus or defective margins on restorations are present. • Gingival tissues are healthy with no bleeding evident on gentle probing.
Code 1	• Color-coded reference mark is completely visible in the deepest sulcus or pocket of the sextant. • No calculus or defective margins on restorations are present. • Bleeding IS present on probing.
Code 2	• Color-coded reference mark is completely visible in the deepest sulcus or pocket of the sextant. • Supragingival or subgingival calculus and/or defective margins are detected.
Code 3	• Color-coded reference mark is partially visible in the deepest sulcus or pocket of the sextant. • This code indicates a probing depth between 3.5 and 5.5 mm.
Code 4	• Color-coded reference mark is not visible in the deepest sulcus or pocket in the sextant. • This code indicates a probing depth of greater than 5.5 mm.
Code *	The * symbol is added to the code of a sextant exhibiting any of the following abnormalities: • furcation involvement • mobility • mucogingival problems • recession extending into the colored area of the probe The symbol should be recorded next to the sextant code.

Implications of PSR codes:

Code	Further clinical documentation
Code 0, 1, or 2 in all sextants	No further documentation needed
Code 3 in one sextant	Comprehensive periodontal assessment of sextant with 3 code
Code 3 in two or more sextants	Comprehensive periodontal assessment of entire mouth
Code 4 in one or more sextants	Comprehensive periodontal assessment of entire mouth

Figure 1: PSR scoring sheet with legend

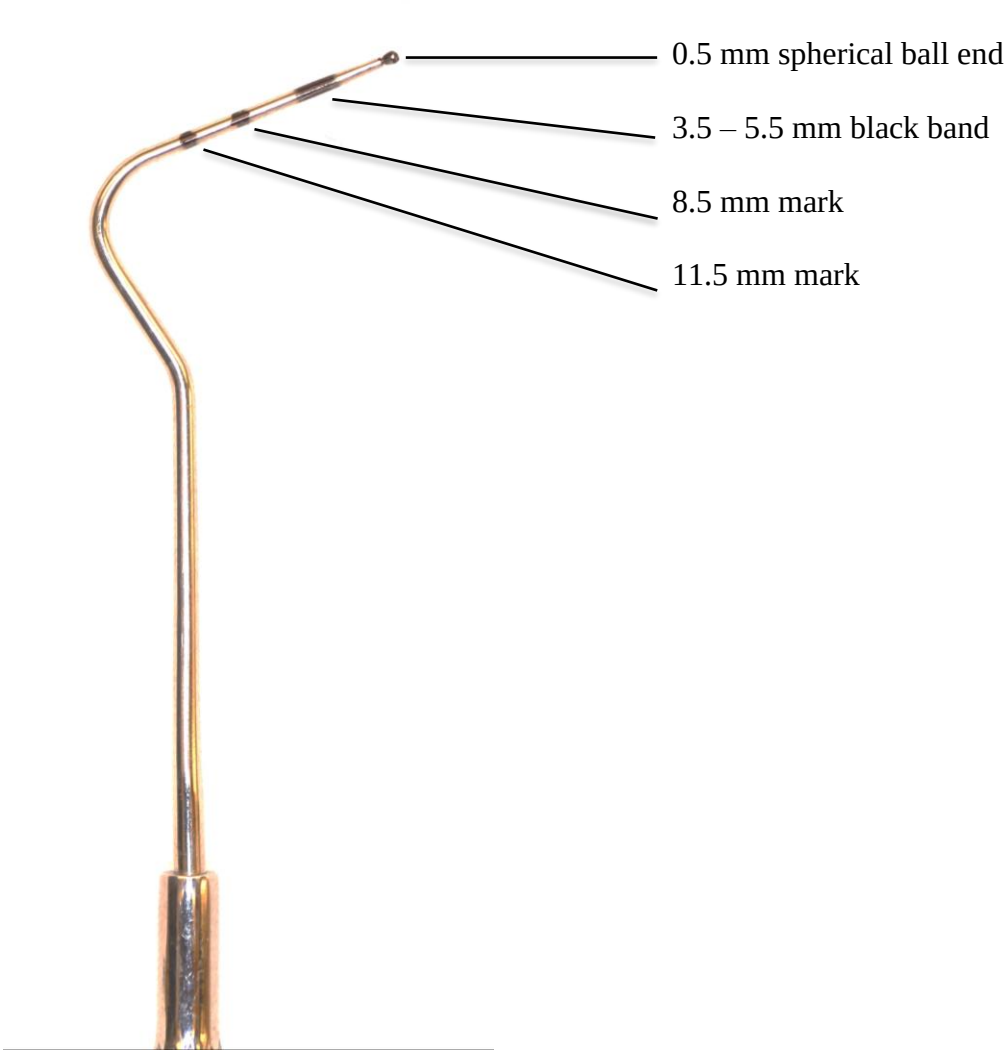


Figure 2: PSR probe used in the study

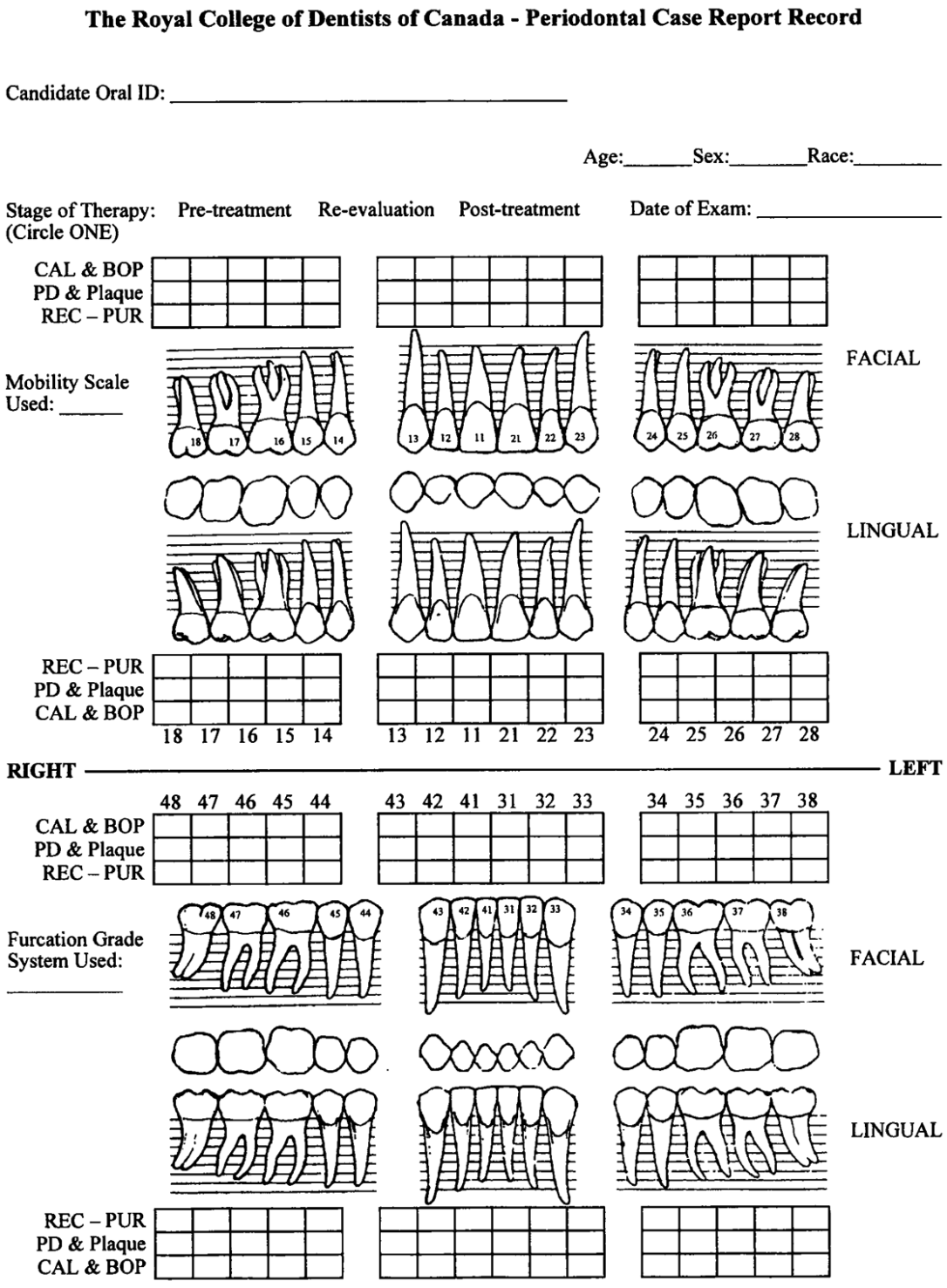


Figure 3: RCDC periodontal case recording sheet

2.3.2 Lateral cephalometric data

Lateral cephalograms were obtained in centric occlusion. Baseline (T1) and current (T2) lateral cephalograms were traced digitally using Dolphin Imaging Software Version 11.7 (Dolphin Imaging and Management solutions, Patterson Dental Supply, Inc., Chatsworth, California, USA). A total of 3 skeletal and 3 dental variables were measured (Table 1). Skeletal variables evaluated anteroposterior and vertical skeletal changes and linear and angular dental variables were used to determine change in mandibular incisor inclination and position from T1 to T2.

Table 1: Description of cephalometric variables used

Variable	***Description***
ANB (°)	Angle between point A-nasion-point B
Sn-GoGn (°)	Angle between SN plane and mandibular plane (Go-Gn)
FMA (°)	Angle between Frankfort's horizontal plane and mandibular plane
IMPA (°)	Angle between long axis of most proclined mandibular incisor and mandibular plane (Go-Gn)
L1-NB (mm)	Linear measurement from line NB to most labial portion of the crown of mandibular incisor
L1-NB (°)	Angle between long axis of mandibular incisor and line from nasion to point B

All but 6 patients had cephalograms from same digital machine at both time points. For these 6 patients, their T1 lateral cephalometric radiographs were analog films that were scanned to digital images and T2 radiographs were digital images from newer machine. In order to

eliminate magnification error, linear parameter (L1-NB in mm) from these 6 patients was not considered in the statistical analysis. Figure 4 illustrates the cephalometric tracing and composite analysis.

Angle ANB was used to evaluate anteroposterior skeletal change whereas angles FMA and Sn-GoGn were used to determine vertical facial change. Among the 3 dental parameters, IMPA and L1-NB (°) measured angular and L1-NB (mm) for linear change in mandibular incisor.

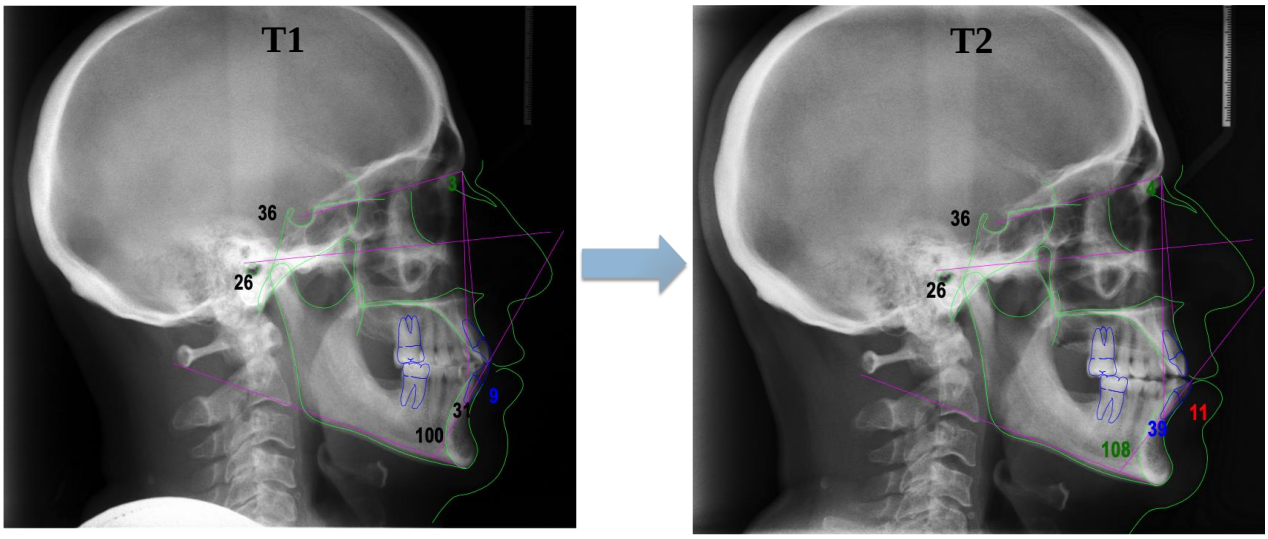


Figure 4: Lateral cephalometric tracings of a patient at T1 and T2 with composite analysis

2.3.3 Study model measurements

Study models were prepared from alginate impressions of patients, taken at T1 and T2. Clinical crown height was measured for all mandibular incisors and canines with a digital caliper (Neiko Tools, USA). Figure 5 illustrates clinical crown height measurement on the study model.

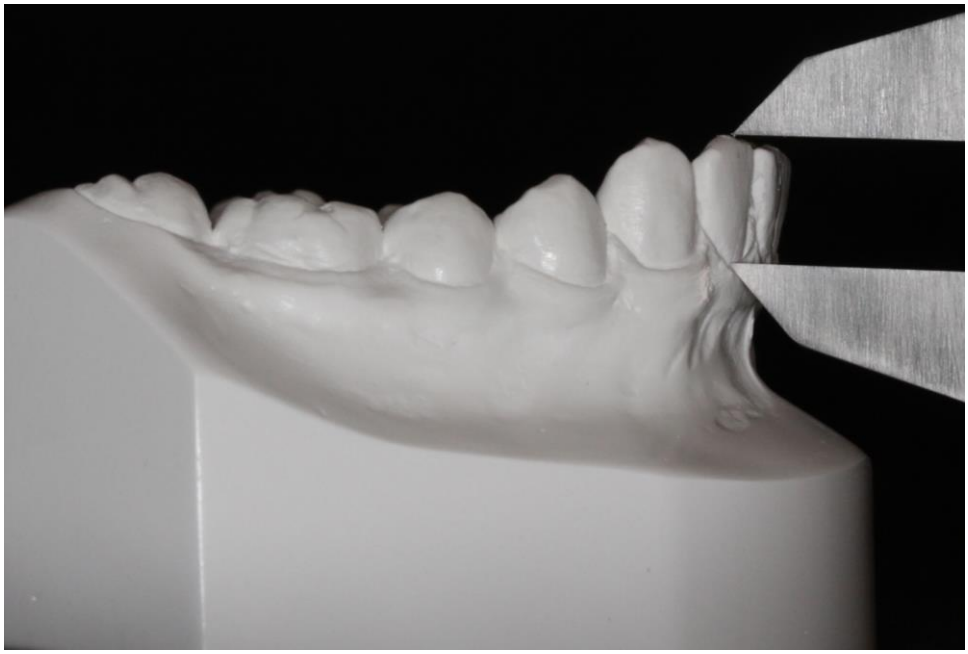


Figure 5: Clinical crown height measurement on study model using digital calipers

2.4 Measurement error and reliability

Lateral cephalograms and models at T1 and T2 for eleven randomly selected cases were scored twice, 6 weeks apart to measure the intra-examiner reliability.

Periodontal probing and measurements for all the patients were performed by one investigator who is extensively trained by a board-certified periodontist.

2.5 Data analysis

Statistical analysis of data was performed with Sigmaplot 14 (Systat Software Inc., IL, USA) and SPSS software 22.0 (SPSS Inc., IL, USA).

To assess the primary data for all the variables, descriptive statistics was used. This included the means and standard deviations. Normal and non-normal distribution of variables were determined. For the collected data, assumptions were made that both normality and equality

of variances existed. Measured data was compiled into tables for both time points, T1 and T2, including the mean and standard deviation for each group measuring age, clinical crown height of mandibular anterior teeth and cephalometric variables.

Paired *t* test was used to compare the means at T1 and T2 for clinical crown height of mandibular incisors and each of cephalometric variables. This was also used to evaluate the comparability of the clinical crown height at two time points. Normality was determined using Shapiro-Wilk test. Data for cephalometric angle ANB showed non-normal distribution and therefore Wilcoxon signed rank test was used to determine the median. Additionally, periodontal measurements PD, recession, CAL and bleeding index presented with non-normal distribution.

The reproducibility of all cephalometric and dental cast measurements was assessed according to intraclass correlation coefficient by repeating measurements for 11 randomly selected patients 30 days apart. Post hoc power analysis was done based on the paired *t*-test data from the 21 study subjects.

Lastly, correlation was determined for change in clinical crown height, mandibular incisor inclination and position, duration in treatment with OAm and gingival recession, using Pearson's correlation coefficient.

Chapter 3: Results

3.1 Subject summary

In this retrospective observational clinical evaluation, a total of 171 patients were screened from 2 centers. Final sample size comprised of 21 subjects, who agreed to participate, met all eligibility criteria and completed their clinical visit.

There were 66 patients who could not be contacted. They either moved or changed their contact information or did not responded. 18 patients had to be excluded as they had some missing baseline records. 2 patients had passed away while 1 patient had full mouth implants placed. Remaining 84 patients were contacted out of which 23 refused to participate. 39 more patients were excluded, as they were not using OAm as they either switched to CPAP or they no longer had sleep apnea. Remaining 22 patients were provided with study details and ICF was either mailed or emailed to them. 1 patient was excluded during clinical visit due to history of gingival grafting in the mandibular anterior region. The study flow diagram is detailed in Figure 6.

3.2 Sample size calculation

Power calculations were conducted for the primary outcome variable, which is change in clinical crown height. Based on the paired *t*-test data from the 21 study subjects, the difference in means of T2 and T1 is 0.017 mm with a standard deviation of 0.568 mm. Assuming a 2-sided type I error of 5% the required sample size to achieve at least 80% power for change in clinical crown height from T1 to T2 was determined to be 8764 participants. Since the change in clinical crown height is negligible, the effect size is only 0.03 and that's why such large sample is needed to achieve statistical significance which is beyond the scope of this study.

Since the observed difference in clinical crown height is not significant both clinically and statistically, in order to determine sample size needed to detect a change that is clinically significant, we performed power analysis assuming the change of 0.57 mm in the clinical crown height and a standard deviation of 0.57 mm. This made the effect size larger and increased it to 1. Again, assuming a 2-sided type I error of 5% the required sample size to achieve 95% power for change in clinical crown height from T1 to T2 is 16 subjects. Thus, the study is powered adequately to detect the clinically significant change.

3.3 Correlation

Pearson's correlation coefficient was used to determine the correlation between change in clinical crown height of mandibular incisors, change in mandibular incisor position and inclination, duration of treatment with the OAm and gingival recession for the mandibular incisors.

There was no correlation found for change in clinical crown height and gingival recession with all the remaining parameters evaluated. Statistically significant correlation was observed only between change in incisor inclination and the duration of treatment.

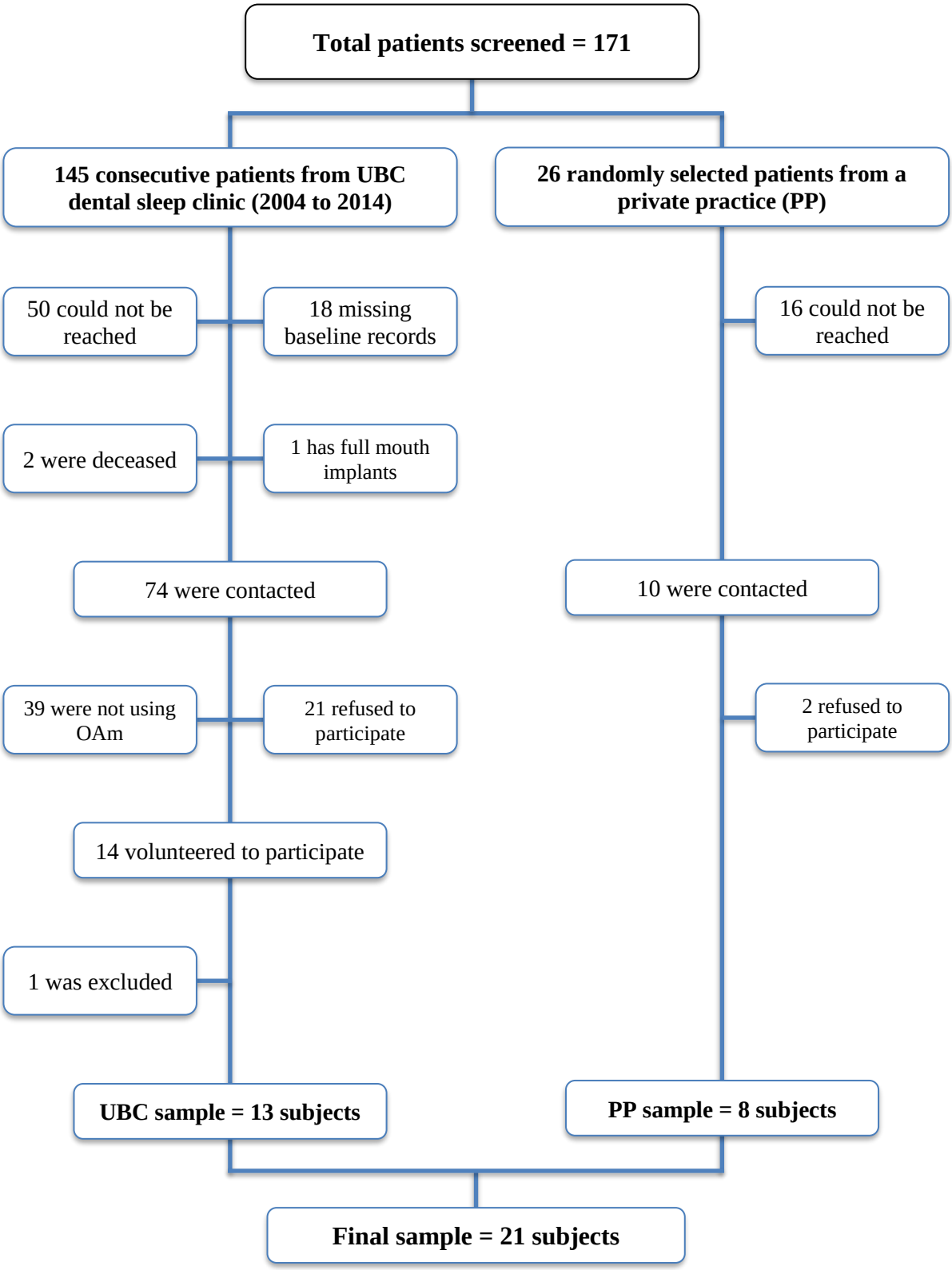


Figure 6: Study flow diagram

3.4 Intra-examiner reliability

The ICC based on 11 randomly selected cases showed excellent intra-examiner reliability for both the cephalometric measurements as well as study models, and it ranged from 0.97 to 0.99 (Table 2 and Table 3).

Table 2: Intra-examiner reliability for crown height measurement on 11 randomly selected cases

Tooth number	**3.3**	**3.2**	**3.1**	**4.1**	**4.2**	**4.3**
Intraclass Correlation	0.97	0.99	0.99	0.99	0.97	0.99

Table 3: Intra-examiner reliability for crown height measurement on 11 randomly selected cases

Cephalometric parameter	**ANB**	**SN-GoGn**	**FMA**	**IMPA**	**L1-NB (mm)**	**L1-NB (deg)**
Intraclass Correlation	0.97	0.99	0.97	0.99	0.99	0.98

3.5 Sample description and characteristics

The distribution of sample with respect to mean age at T1 and T2 as well as sex is presented in table 3.3. Age at the start of treatment (T1) ranged from 25 years 11 months to 69 years 8 months with a mean age of 49.52 ± 11.84 years. Mean age at T2 was 57.41 ± 12.08 years that ranged from 31 years 5 months to 76 years 3 months. Therefore, average treatment duration with OAm was 7.89 ± 3.3 years (see Table 4, Figure 7).

Patients were provided with the subjective adherence questionnaire to determine the duration of appliance wear. Regular use of OAm for minimum 5 nights per week and at least 4 hours per night was desired for them to be included in the study. All patients reported 7

nights/week of OAm use except 1 patient who was using the OAm for 6 nights/week. Furthermore, all patients reported 7-8 hours of OAm wear/night except for 1 patient who reported 4 hours of OAm wear every night.

Of the total 21 patients in the study, 15 (71.43%) were males and 6 (28.57%) were females.

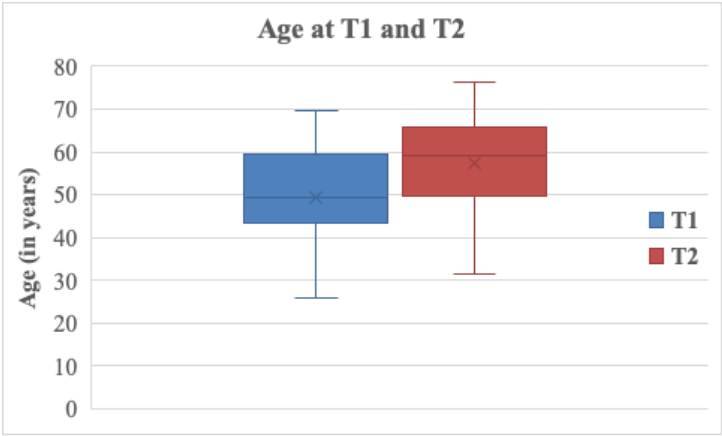


Figure 7: Box plot with mean ages at T1 and T2

Mean overjet at T1 was 3.38 ± 1.65 mm that was reduced to 2.14 ± 1.81 mm at T2. Mean overjet reduction was 1.24 ± 1.59 mm due to dental changes following OAm use.

Similarly, mean overbite at T1 was 3.21 ± 1.4 that reduced to 2.19 ± 1.71 mm at T2. Thus, the mean overbite reduction was 1.02 ± 0.96 mm over the mean treatment duration of 7.89 ± 3.3 years (see Table 4, Figure 8).

Table 4: Sample description for age, OJ and OB

	T1	*T2*	*T2-T1*
Variable	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*
Age (Years)	49.52 ± 11.84	57.41 ± 12.08	7.89 ± 3.3
Overjet (mm)	3.38 ± 1.65	2.14 ± 1.81	-1.24 ± 1.59
Overbite (mm)	3.21 ± 1.4	2.19 ± 1.71	-1.02 ± 0.96

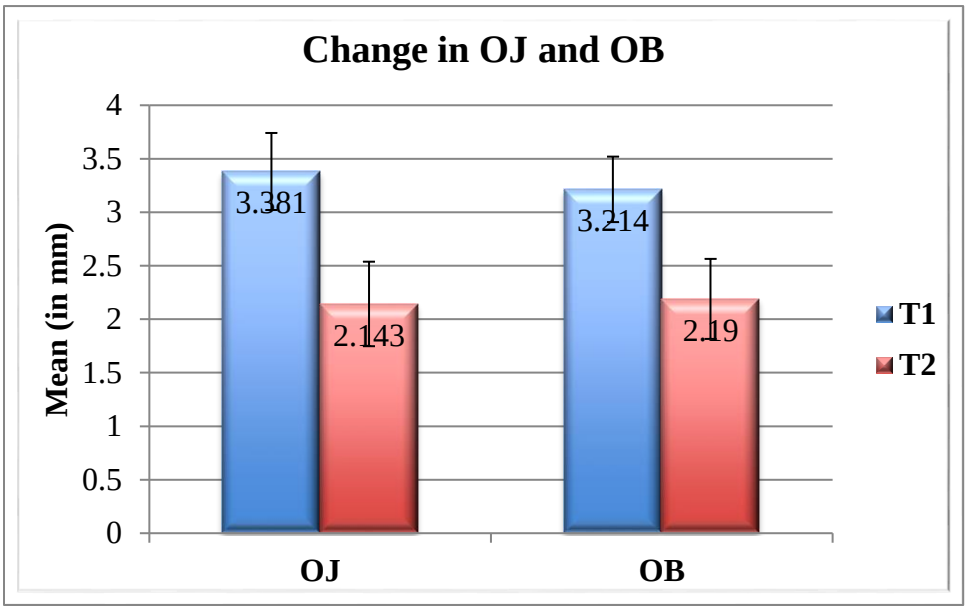


Figure 8: Simple bar graph for mean reduction in OJ and OB with standard error

3.6 Distribution according to type of occlusion

Based on molar and incisor relationship, of the 21 patients, 9 (43%) had a Class I molar relation, 3 (14%) had Class II division 1 and 9 (43%) had a Class II division 2 at T1. Dental changes at T2 changed this to 9 (43%) Class I, 1 (4%) Class II division 1, 9 (43%) Class II division 2 and 2 (10%) patients with Class III molar and incisor relation.

3.7 Distribution according to periodontal characteristics

According to the gingival biotype that was assessed at T2, 14 patients presented with thick gingival biotype over mandibular anterior teeth whereas 7 patients have thin gingival biotype.

The findings from thorough periodontal evaluation and PSR method demonstrated that the probing depths ranged from 1 to 3 mm. The color-coded reference mark was completely visible in the deepest part of the sulcus for all the teeth for all the patients indicating no probing depth was > 3.5 mm. No patient had PSR scores greater than 2 for any sextant indicating excellent oral hygiene maintained by almost all patients in the sample. This is also evident by the mean Plaque index (Silness and Loë[93]) which is 0.44 ± 0.26 and mean gingival bleeding index (Ainamo and Bay[94]) which is 4.14 ± 5.02. Plaque index ranged from as low as 0.04 to as high as 1.04 for the sample and gingival Bleeding index ranged from 0 to 19.13% (see Table 5).

None of the patients were found to have mobility greater than grade 1 for lower anterior teeth. Width of keratinized gingival tissue for mandibular anterior teeth ranged from 1 mm to 6 mm as measured on the labial aspect at mid-buccal area. All patients had excellent oral hygiene, coral pink gingival color, scalloped contour and firm consistency except for one patient who had inflamed and edematous gingiva. 10 patients also had light calculus present in the mandibular anterior region.

Mean values for PD, recession and CAL is represented in Table 5 along with plaque and bleeding indices. CAL ranged from 0 to 4 in descending order with one site having CAL of 6 mm.

Table 5: Mean (of all patients) values of periodontal parameters for mandibular anterior teeth at follow-up (T2)

Periodontal Parameters	*Mean*	*Standard Deviation*	*Range*
Probing Depth (mm)	1.36	0.52	1 to 3
Recession (mm)	-0.59	0.59	-3 to 4
CAL (mm)	0.75	1.04	0 to 6
Plaque Index (Silness and Loë)	0.44	0.26	0.04 to 1.04
Bleeding Index (%) (Ainamo and Bay)	4.14	5.02	0 to 19.13

3.8 Lateral cephalometric changes

Lateral cephalometric radiographs taken at T1 and T2 were traced. In order to determine changes associated with mandibular incisor and related anteroposterior or vertical skeletal changes, 6 cephalometric parameters were assessed. 3 dental parameters focused on the mandibular incisor position and inclination.

Means and changes in skeletal and dental parameters are quantified in Table 6 below and illustrated as simple bar chart in Figure 9 and Figure 10.

When skeletal parameters were compared, mean change from T1 to T2 indicated statistically significant increase in mandibular plane angle and increase in ANB angle, however these changes are not considered to be clinically significant in magnitude. Changes for dental variables were highly significant as expected due to increase in the mandibular incisor proclination over time.

Table 6: Comparison of cephalometric variables at T1 and T2 (paired *t*-test)

	T1	***T2***	***T2-T1***	***Significance***
Ceph Variable	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*p - value*
ANB (°)	4.02 ± 2.5	4.46 ± 2.24	0.44 ± 0.87	0.032
Sn-GoGn (°)	28.81 ± 6.85	29.69 ± 6.72	0.88 ± 1.51	0.015
FMA (°)	23.74 ± 5.73	24.6 ± 5.6	0.85 ± 1.36	0.009
IMPA (°)	95.81 ± 11.26	100.95 ± 11.88	5.13 ± 3.6	<0.001
L1-NB (mm)	4.92 ± 2.25	6.05 ± 2.42	1.13 ± 0.77	<0.001
L1-NB (°)	25.7 ± 7.46	31.1 ± 8.73	5.41 ± 3.89	<0.001

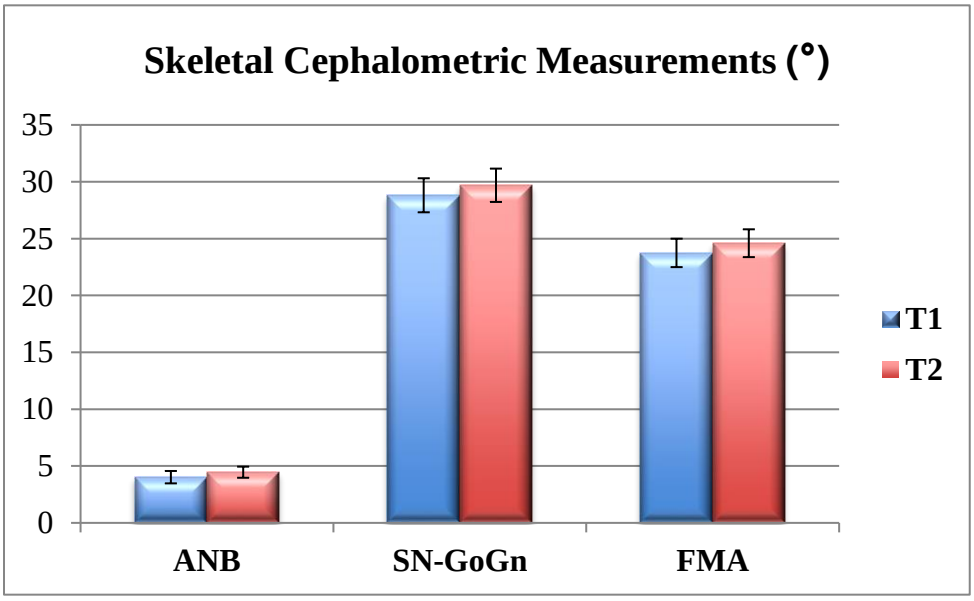


Figure 9: Bar diagram comparing means of skeletal cephalometric variables at T1 and T2

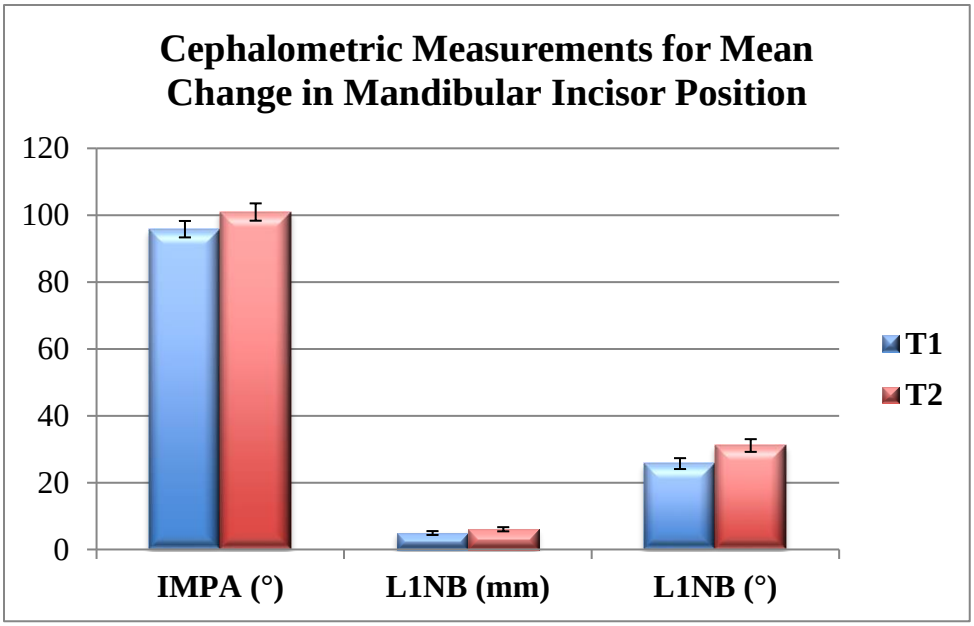


Figure 10: Bar diagram comparing means of dental cephalometric variables at T1 and T2

3.9 Changes in clinical crown height

Clinical crown height was measured for mandibular anterior teeth on mid-buccal region from the incisal edge or cusp tip for canine to gingival margin. One patient had a congenitally missing 4.1. Data for mean clinical crown height and changes between 2 time points is presented in Table 7. There is negligible change in the clinical crown height between 2 time points. This is neither statistically nor clinically significant. This finding is consistent across all the patients and for all the teeth considering the fact the all patients had maintained meticulous oral hygiene and were regular in their routine dental follow up. All patients had good systemic health at the time of clinical exam and one patient reported active smoking. 5 patient had hypertension, 4 patient reported history of cardiovascular incident, 2 patients were diabetic, 3 had hormone related disorders and 2 reported having asthma. All patients were under physician's care and their systemic illnesses were well controlled.

When the preliminary data was gathered for the first 10 patients, we attempted to determine correlation between proclination of mandibular incisor and change in clinical crown height using Pearson's correlation coefficient. Since the change in clinical crown height is minimal, no significant correlation was found between these 2 variables. This result did not change when correlation was determined for the entire sample.

While tracing lateral cephalogram, only the most proclined incisor is traced. Due to the consistency of results, we took mean of clinical crown height of all the mandibular incisors and excluded the canines and paired *t* test was used to compare the means at T1 and T2 (see Table 8). The mean clinical crown height of mandibular incisors at T1 and T2 is 8.17 ± 1.21 mm and 8.19 ± 1.31 mm respectively (see Figure 11). Mean difference in the crown height between T1 and T2 is increase of 0.02 ± 0.57 mm. This change is both statistically as well as clinically insignificant.

Table 7: Clinical crown height for mandibular anterior teeth (in mm) - mean and treatment changes (paired *t* test)

Tooth No.	***N***	***T1***	***T2***	***T2-T1***	***Significance***
		Mean ± SD	*Mean ± SD*	*Mean ± SD*	*P value*
33	21	9.6 ± 1.35	9.84 ± 1.54	0.24 ± 0.45	0.025
32	21	8.24 ± 1.22	8.4 ± 1.31	0.16 ± 0.47	0.136
31	21	7.86 ± 1.19	7.89 ± 1.18	0.03 ± 0.58	0.839
41	20	8.14 ± 1.39	7.97 ± 1.43	0.17 ± 0.60	0.218
42	21	8.45 ± 1.06	8.49 ± 1.29	0.05 ± 0.60	0.730
43	21	9.95 ± 1.42	9.93 ± 1.40	-0.02 ± 0.42	0.828

Table 8: Clinical crown height for mandibular incisors (in mm) - mean and treatment changes (paired t test)

Teeth	***T1***	***T2***	***T2-T1***		***T2-T1***
N = 83	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*P value*	*Range*
Mandibular incisors	8.17 ± 1.21	8.19 ± 1.31	0.02 ± 0.57	0.781	-1.39 to 1.55

Although the mean of difference in clinical crown height is significantly less this also masks the significant changes in individual teeth in our relatively smaller sample. Out of 83 mandibular incisors evaluated, 38 teeth had decrease in clinical crown height (negative value) and remaining 45 teeth had increase in clinical crown height (positive value). While most teeth had less than 0.5 mm of change, 4 teeth were found to have more than 1 mm of decrease and 4 teeth were found to have more than 1 mm of increase in crown height. None of the teeth had greater than 1.5 mm increase or decrease in clinical crown height.

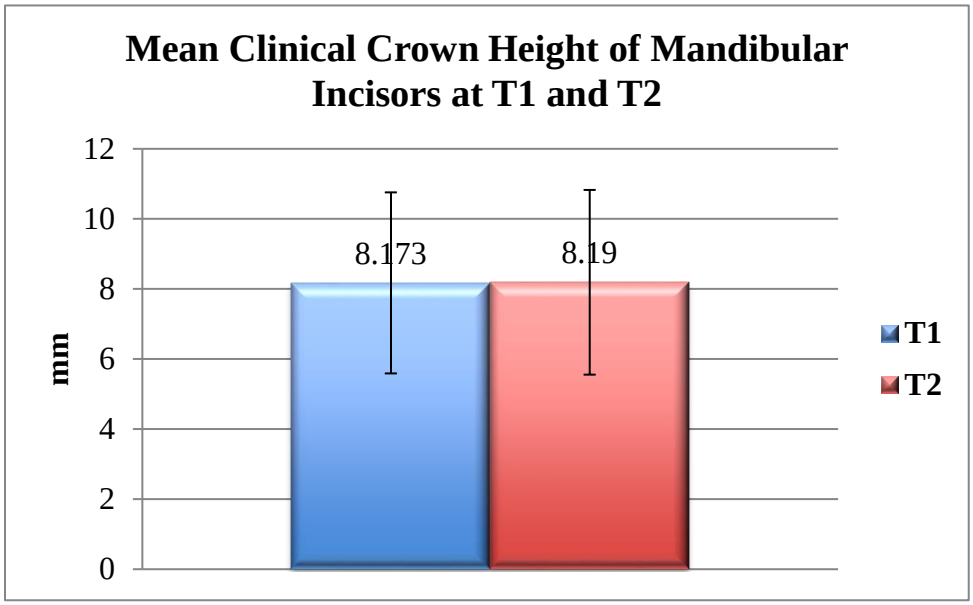


Figure 11: Bar diagram of clinical crown height for mandibular incisors (in mm) - mean and treatment changes (paired *t* test) with standard error

Chapter 4: Discussion

4.1 General discussion

Proclination of mandibular incisors has been associated with gingival recession in the orthodontic literature and has been the basis for many studies[43,45,46,49,51–55,95]. Similarly, in the literature regarding OSA, longitudinal studies[19,39,96] have provided conclusive evidence that OAm treatment leads to the side effect of dental tooth movement, including mandibular incisor proclination. Combining these two observations we investigated whether the progressive proclination of mandibular incisors in OAm patients would lead to similar outcomes for the periodontal tissues supporting these teeth. This clinical trial therefore was performed to assess whether there is any gingival recession secondary to mandibular incisor proclination in OSA patients using OAm for at least 4.5 years. To the best of our knowledge, this association in OSA patients has never been studied before.

The prevalence of OSA is reported to be increasing in the past 2 decades and it also increases with the age and associated risk factors[9,10]. The majority of OSA patients are treated with either CPAP or OAm based on severity of AHI and patient preference. Due to reported higher compliance among OAm patients, the net effectiveness between the two treatment modalities is largely similar[24]. This emphasizes the fact that a significant number of OSA patients are using OAm therapy and this number may rise in the future. The dental side effects of long-term OAm use are known[19,37] but how this will affect the supporting structures of the teeth has not previously been studied. If the findings of similar tooth movement in orthodontic literature were to be extrapolated to OSA patients, some detrimental effects in the form of periodontal breakdown may be anticipated with long-term OAm use.

Interestingly, in our study there was no significant decreases in the average clinical crown height of mandibular anterior teeth at T1 and T2, a period corresponding to greater than 7 years on average. This is in contrast to what would have been expected in the orthodontic treatment following progressive labial movement of mandibular anterior teeth. Therefore, this is a crucial finding and certainly reassuring for the patients using OAm regularly who experience significant dental changes inevitably. But the individual variations were quite significant where 4 teeth had greater than 1 mm of reduction in clinical crown height and 4 teeth showed greater than 1 mm of increase in clinical crown height. No teeth however experienced greater than 1.5 mm of change.

The mandibular incisor inclination however did increase significantly between T1 and T2 as expected, however this was not associated with any observed gingival recession. Our results thus have failed to reject both the null hypotheses. All 3 parameters for change in mandibular incisor inclination and position demonstrated significant proclination of these teeth. The remaining 3 cephalometric parameters to assess anteroposterior and vertical skeletal measurements showed minor but clinically insignificant changes. Additionally, there was significant reduction in mean overjet as well as overbite which is expected with the known dental side effects of long-term OAm use and is in agreement with many previous studies[19,37].

Our study sample came from two centers. Since this was a retrospective long-term follow up, in order to eliminate risk of bias consecutive sampling was done for UBC sleep dental clinic patients. For the second center, which is an affiliated private practice, random sampling was employed for patients who started treatment in 2012 and 2013. We noticed that from patients treated during earlier years, a high number of patients had to be excluded from the UBC sample as they were lost to follow up and could not be contacted either because they moved, or we did not have updated contact information. Therefore to ensure an adequate sample size, we contacted

patients from private practice who had started treatment in the years 2012 and 2013. Our final sample size of 21 patients was relatively small owing to exclusion of a greater number of patients than we initially anticipated. But considering the consecutive sampling, this will not have changed significantly unless a large multicenter trial is planned, that may be challenging. We targeted patients primarily from university clinic that treats only sleep apnea patients, but there are not too many private clinics that limit their practices to treatment of OSA patients only. Many OSA patients probably seek care at dental offices that provide OAm treatment. In order to determine sample size, we first calculated the effect size using the mean of difference and the standard deviation. Owing to the small difference in the means of clinical crown heights at T1 and T2, the effect size is 0.03, which is very small. Based on this post hoc power calculation, the sample size of 8764 participants needed to achieve statistical significance seems impractical. We therefore determined the effect size for a clinically detectable change and found that the study is powered adequately for the same. Also what was noticeable is that within this small sample, all the findings were very consistent without any exception.

It is important to note that generally, the study sample of patients had good oral hygiene and a lack of periodontal disease, as periodontal breakdown can be a result of these factors and not necessarily change in incisor inclination and position. For this reason, thorough periodontal evaluation was carried out during patient's clinical visit (T2). PSR has been reported as an excellent tool for periodontal health estimation in population studies and has been used frequently for the same[97]. Therefore, we used PSR to determine overall periodontal status of the patients. All patients had PSR codes of 0, 1 and 2. None of the patients had PSR score of 3 or 4 or with * indicating good periodontal health in all the study subjects. Also, low values of plaque and bleeding indices further substantiated this finding and indicated the presence of adequate

oral hygiene. In addition, detailed periodontal exam was performed for mandibular anterior teeth. Again, low values for mean PD, recession and CAL with no measurements going beyond 3 mm indicated healthy periodontal tissues with good oral hygiene maintenance by these patients. Additionally, all patients reported regular follow-up with their respective dentist for routine hygiene and dental care. None of the mandibular anterior teeth exhibited any mobility and there was adequate width of keratinized tissue on all the teeth in all the patients. Lastly, gingival biotype, gingival tissue characteristics and presence of calculus were recorded, which were all consistent with the excellent oral hygiene demonstrated by these patients. It was observed that 14 of our study subjects had thick and remaining 7 had thin gingival biotypes as evaluated for the mandibular anterior teeth. All but 1 patient had coral pink gingiva with normal scalloped contour and firm consistency. Areas of redness with rolled bulbous margins and soft and edematous gingival consistency was noted in 1 patient but with no increase in probing depth beyond 3 mm. Calculus was not observed in 11 patients and 10 had light amount of calculus present.

Since our objective was to find out periodontal consequences specifically from incisor proclination, it was important to control for overall well-being of the patients as it may affect oral health secondarily. Patients were provided with medical history questionnaire, subjective adherence and dental side effects questionnaire. Since OSA leads to hypoxia and oxidative stress, the resulting state of systemic inflammation has been associated with chronic periodontitis in addition to other medical conditions[74,76–79,81–84,98]. It is important to note that all our study subjects had significant reduction in AHI due to reported daily regular use of OAm and were also under the regular care of their physician. Among the self-reported medical conditions 5 patients had hypertension that was well controlled, 4 patients reported history of a cardiovascular incident, 3 had hormone related disorders, 2 were diabetics that was under control and 2 had

asthma. Regarding habits, only 2 patients within the study group reported active smoking of less than 10 cigarettes per day and 4 reported history of cigarette smoking that they quit over 2 decades ago. None of the patients reported more than casual consumption of either alcohol or caffeine.

Regular use of OAm causes dental movement that continues as long as the patient is using OAm. Since, OSA treatment is not curative, the OAm needs to be periodically titrated and many patients will ultimately use the OAm throughout their life. Therefore, one may think that the longer the appliance wear, more will be the dental change, which is actually true and has been observed in the longest follow-up study[19] reported so far. In our study sample 4 patients experienced most significant change in molar relationship in which, 2 changed from Class II to Class I and remaining 2 changed from Class I to Class III. It is interesting to note that these 4 patients had the longest follow up periods of >11 years. Also, the correlation analysis was statistically significant for the length of OAm treatment and change in incisor inclination. However, we observed a great deal of individual variation among patients. This is also in agreement with the long-term findings reported by Pliska et al[19]. This time related and progressive dental change in the form of reduction in overjet and overbite as well as change in maxillary and mandibular incisor inclination has also been reported in a recent systematic review and meta-analysis.[99] There is no predictable pattern of dental side effects and this may be attributed to various facial morphological patterns, dental health, missing teeth and pretreatment malocclusion characteristics. So we included patients who were using OAm for at least 4.5 years at the time of data collection in anticipation that they may have had some appreciable dental changes that will enable us to evaluate its effect on the surrounding periodontal tissues. The dental movement resulted not only in a reduction in overbite and overjet, but also a general

mesialization of the mandibular arch. This was evident in the shift in Angle classification of the study sample over time. Based on molar relationship, our sample at T1 had 9 patients (43%) with Class I, 3 (14%) Class II division 1 and 9 (43%) Class II division 2. At T2, following dental changes we had 9 (43%) Class I, 1 (5%) Class II division 1, 9 (43%) Class II division 2 and 2 (10%) Class III. These changes happened as 4 (19%) patients who used OAm for >11 years had significant dental changes. Two patients who started with Class II molar relationship (one was Class II division 1 and other was Class II division 2) at T1 had Class I molar relation at T2 and another 2 patients who started with Class I molars presented with Class III molar relation at T2. Remaining patients whose molar relationship did not changed significantly included 10 patients with Class II (8 Class II division 2 and 2 Class II division 1) and 7 patients with Class I molars. It may be said that in time progressive dental changes will lead to further alteration in occlusion and molar relationship.

If there is a minimum of eight healthy teeth present in each jaw, an OAm can be fabricated. Excluding third molars, in our study sample, 12 patients had all teeth present, 4 patients had at least 1 posterior tooth missing and 1 patient had congenitally missing mandibular right central incisor. One patient had 10 posterior teeth missing and was using a removable partial denture. Remaining patients had no more than 4 missing posterior teeth and no missing anterior teeth.

None of the patients had implants at T1 and 2 patients had one implant each at T2. One was to replace mandibular left first molar and other was for maxillary left central incisor. Presence of implant in either arch may affect the tooth movement in respective arch. An implant is osseointegrated and will not move in response to constant force application like a tooth. Therefore, it may be assumed that the presence of an implant may prevent or minimize the dental

side effects, and this can be beneficial to these patients, but currently there is no evidence available to support this contention. Both these patients with implants did show similar dental changes as the rest of the group and so were included, but it is important to note that they did not had implants at T1, meaning tooth movement could have occurred prior to implant placement, and also each of them had implant that was unilaterally placed.

Two of our study subjects also had history of orthodontic treatment over 3 decades ago. Extraction of four premolars was done in 1 patient for orthodontic treatment. There was no history of recent orthodontic treatment and there is no validated literature regarding variation in tooth movement in response to OAm in patients with previous orthodontic treatment. Therefore, these patients were included in the study as they were not different than the rest of the population.

4.2 Limitations of the study

This study has several limitations. Being a retrospective study, there is always a potential for selection bias. To eliminate this however, we contacted all consecutively treated patients at the UBC sleep apnea dental clinic. Patients selected from the private practice were however selected by random sampling for the same reason. Another drawback of retrospective study is that the periodontal status of patients at T1 is not known. While this can be obtained from their respective dentists, this data will have little meaning in the absence of inter-examiner calibration[100] and such calibration may not be possible owing to the fact that few of the study patients had common dental home.

One of the difficulties with long-term follow-up is the significant patient attrition due to several factors related to the passage of time. Approximately one-third of the patients had to be

excluded simply because they could not be contacted because they either moved or their contact information changed that was not available in our records. In addition, other major reasons for exclusion included missing baseline records and patients who were not using OAm or switched to other treatment options e.g. CPAP. We had higher number of exclusions from our patient pool than initially anticipated, which resulted in smaller sample size. The wide age range of patients at T1 as well as variable follow-up periods further compounded this limitation. Another consideration regarding our finding of no change in clinical crown height from T1 to T2 is that any increase in clinical crown height may have been offset by the attrition of incisal edges of mandibular anterior teeth. This can possibly incorporate methodological error that is difficult to quantify in a retrospective study. We did not find significant gingival recession among the study subjects however this could be controlled for by periodic longitudinal follow-up. By periodic recalls and clinical exam, any gingival or periodontal event will be known as and when it happens, and its etiology can be better identified. Also, none of our patient had any restoration affecting the incisal edge of mandibular anterior teeth. One further limitation of the study protocol was that as we evaluated records at two time points only, baseline and the single follow-up observation period, the time scale of any periodontal changes is unknown. Multiple periodic observations would be required to determine is periodontal changes progress evenly overtime for example, or if changes occur only after a certain threshold of treatment time is met, etc. It's also important to note though that all our patients are healthy individuals with their systemic diseases being well controlled including OSA and associated oxidative stress.

Another potential study limitation was lack of control sample that can also be attributed to the retrospective study design. In a prospective longitudinal study, control group can be followed over time with standard methodology to minimize errors. One potential confounder for

this study is the natural progression of the periodontium attributed to the effect of periodontal diseases in a typical middle-age population and periodontal changes in healthy individuals over time. For this we referred to published data of longitudinal studies. None of our patients had any periodontal disease history and they all presented with healthy periodontal tissues and meticulous oral hygiene. Persson in a review of periodontal diseases in the elderly concluded that owing to high variability in studies it is difficult to assess the prevalence but it can be reasonably assumed to be at least 30%[101]. Ship et al in a 10-year longitudinal follow-up of healthy individuals observed that the attachment loss was least in the incisors[90]. Ismail et al[86] in a 28 year follow-up mentioned age as a risk factor for CAL with mean increase in CAL of only 1.34 mm, however, many studies in contrast have reported that the change in attachment level over time is not age dependent[87,89,90,101,102]. Huttner et al also reported that these changes may be due to aging related epithelial thinning and reduced keratinization but doubted that age alone will cause periodontal tissue damage in healthy elderly persons[89]. Persson et al also reported that CAL progression is significantly reduced in elderly population after 50 years of age[103].

One other study limitation is related to the landmark identification error in 2D lateral cephalometric radiographs. Within our study sample since some films were very old and were from different machine, there was variation in radiographic quality, and some didn't have the ruler for calibration thus introducing magnification and distortion error. For this reason, we eliminated the linear measurement for 6 subjects who had their T1 films that were from different machine. In addition, the overlapping of bilateral structures makes it difficult to accurately identify the cephalometric landmark. For intra-examiner reliability, ICC greater than 0.9 for all coordinates for most landmarks with mean difference of approximately 1 mm have been reported in literature[104]. All of our dental landmarks were easily identifiable than others and we had high

reliability greater than 0.9 for both dental and skeletal structures. We further mitigated this by selecting multiple measurements to determine same parameter and our findings were consistent.

4.3 Future directions

Many of the possibilities regarding future directions have already been discussed with the study limitations above. If this study were to be repeated, consideration should be given to prospective data collection, sample size and methodological improvements for crown height measurement.

Prospective longitudinal study will further minimize bias, and factors like incisor wear, proclination or gingival recession can be better controlled by following over time. This may also allow for uniform follow-up periods for all subjects.

Instead of having measurements at T1 and T2, periodic progress records may detect other transient changes that will not be obvious otherwise e.g. transient change in gingival levels due to local or systemic factors. A larger sample size may improve the generalizability of the results, however due to many variables related to OSA treatment and patient compliance, this will be most challenging. Thin gingival tissue has often been implicated as a risk factor for gingival recession with incisor proclination, and a larger sample may also allow for comparison between groups with different gingival biotypes.

Chapter 5: Conclusion

1. In our cohort of OSA patients, clinically significant proclination of the mandibular incisors was observed with ongoing long-term use of OAm.
2. Clinical crown height did not change over the evaluated time period of >7 years despite the significant proclination of mandibular incisors.
3. Gingival levels were maintained with clinically insignificant changes taking place during the study period.

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