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The Effect of Oral Appliance Therapy on Glycemic Control in Type II Diabetic Patients with Obstructive Sleep Apnea: A pilot Randomized Controlled Trial

par
Emily Santini

Département de santé buccale, section d'orthodontie
Faculté de médecine dentaire

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Ce mémoire intitulé:
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Présenté par :
Emily Santini

A été évalué par un jury composé des personnes suivantes :

Président-rapporteur :
Dr Patrick Arcache

Directrice de recherche :
Dre Nelly Huynh

Co-directrice de recherche :
Dre Andrée Montpetit

Membre du jury :
Dre Sushmita Pamidi

Abstract

Introduction: Obstructive sleep apnea (OSA) is a disorder that is highly prevalent among patients with type 2 diabetes mellitus (T2DM) and the literature supports a strong link between OSA and glucose dysregulation. However, current randomized trials assessing the effect of OSA treatment on metabolic outcomes have been limited to continuous positive airway pressure (CPAP) therapy, and one of the main limitations of these studies is poor compliance. A mandibular advancement device (MAD) is an alternative treatment option for OSA that is generally better tolerated and accepted by patients than CPAP. **Objectives:** The main objective of this study is to evaluate if 3 months of treatment with a MAD will improve glycemic control in patients with OSA and T2DM as compared to a Placebo Device. Secondary objectives will be: 1) to evaluate the feasibility of a MAD to treat sleep apnea in a diabetic population, 2) to compare subjective side effects of the MAD and Placebo Device, 3) to compare subjective changes in quality of life and sleep with both devices, and 4) to compare subjective and objective compliance in both groups. **Methods:** 17 patients participated in this randomized controlled pilot study, comparing treatment of OSA using a MAD (Somnodent®, n=7) and a placebo device (mandibular Essix®, n=10). Blood samples measuring glycemic control by glycated hemoglobin levels were collected before and after treatment. Three polysomnographies were performed (at baseline, after a 2-month titration period and after a 3-month treatment period). All patients answered a side-effects questionnaire after the titration period, and the following questionnaires were compared before (V1), during (V4) and after treatment (V6): Epworth Sleepiness Scale (ESS), the Functional Outcomes of Sleep Questionnaire (FOSQ), the Pittsburg Sleep Quality Index (PSQI), and the Hospital Anxiety and Depression Scale. Patients recorded subjective compliance in a daily journal, and objective compliance was measured by a microchip. **Results:** No significant difference was found in glycated hemoglobin levels between groups (p=0.75). The MAD group showed a significant decrease in OSA as measured by the Apnea-Hypopnea Index (p=0.02) and the Oxygen Desaturation Index (p=0.02). No significant difference was found when comparing Side Effects Questionnaires between groups, more specifically for discomfort in jaws (p=0.15) and changes in occlusion (p=0.41). Frequency of complications were low in both groups and showed no significant differences (p=1.00). Overall patient satisfaction was high in both groups and showed no significant differences (p=1.00). Both groups showed significant improvements in FOSQ scores (p=0.004 between V1-4, and p=0.026 between V1-6), significant decreases in ESS (p= 0.023 between V1-4), significant decreases in Anxiety scores (p=0.003 between V1-4, and p=0.041 between V1-6), as well as a significant decrease in Depression scores (p=0.025 between V1-6). Patients in the MAD group significantly over-reported their subjective compliance as compared to the objective compliance measured by a microchip (p=0.02). **Conclusion:** MAD is a feasible treatment for OSA in patients with T2DM as it was able to significantly improve OSA while demonstrating high overall satisfaction and minimal complications. A strong "placebo effect" was noted with the Placebo Device and reinforces the importance of randomized and controlled studies in the field of OSA treatment. Microchips to measure objective compliance should be used as they offer more reliable data than subjective records. Further large-scale randomized and controlled trials are required, as well as future analyses of Continuous Glucose Monitoring Systems which may allow for more precise evaluation of glycemic outcomes; investigating possible metabolic phenotypes in patients which may respond better to OSA treatment will be important.

Keywords: obstructive sleep apnea, type II diabetes mellitus, glucose dysregulation, mandibular advancement device, placebo device, compliance.

Résumé

Introduction : Le syndrome de l'apnée obstructive du sommeil (SAOS) est un trouble très prévalent chez les patients atteints du diabète de type 2 (DT2) et la littérature préconise un lien étroit entre le SAOS et la dysfonction glycémique. Cependant, les essais randomisés actuels évaluant le traitement du SAOS et les effets métaboliques chez les patients diabétiques sont limités au traitement par pression positive continue (PPC) – parcontre, une limitation majeure de ces études est une faible compliance. L'orthèse d'avancée mandibulaire (OAM) est une option de traitement alternative pour le SAOS qui est généralement mieux tolérée et acceptée par les patients que la PPC. **Objectifs :** L'objectif principal de cette étude est d'évaluer si un traitement de 3 mois avec une OAM améliore le contrôle glycémique chez les patients atteints du SAOS et le DT2 comparé à celui avec un appareil placébo. Les objectifs secondaires sont : 1) d'évaluer la faisabilité d'une OAM comme traitement du SAOS chez une population diabétique, 2) comparer les effets secondaires subjectifs ressentis lors du port de l'OAM ou de l'appareil placébo, 3) comparer les changements subjectifs dans la qualité de vie et sommeil avec les deux appareils, 4) comparer la compliance subjective et objective dans les deux groupes. **Méthodes :** 17 patients ont participé à cette étude pilote contrôlée et randomisée comparant le traitement du SAOS à l'aide d'une OAM (Somnodent®, n=7) et d'un appareil placébo (appareil Essix® mandibulaire, n=10). Des échantillons de sang mesurant le contrôle glycémique par les taux d'hémoglobine glyquée ont été prélevés avant et après le traitement. Trois polysomnographies ont été réalisées (au départ, après une période de titration de 2 mois et après une période de traitement de 3 mois). Tous les patients ont répondu à un questionnaire sur les effets indésirables après la période de titration. Les questionnaires suivants ont été comparés avant (V1), pendant (V4) et après (V6) le traitement : échelle de somnolence d'Epworth (ESS), questionnaire sur les résultats fonctionnels du sommeil (FOSQ), indice de qualité du sommeil de Pittsburg (PSQI), et l'échelle hospitalière d'anxiété et de dépression (HADS). Les patients ont rapporté leur compliance subjective dans un journal quotidien, et la compliance objective a été mesurée par une micropuce. **Résultats :** Aucune différence significative n'a été observée pour l'hémoglobine glycquée après 3-mois de traitement entre les deux groupes ($p = 0.75$). L'OAM a présenté une diminution significative du SAOS mesurée par l'indice d'apnée-hypopnée ($p = 0.02$) et l'indice de désaturation en oxygène ($p = 0.02$). Aucune différence significative n'a été constatée lors de la comparaison des questionnaires sur les effets secondaires entre les groupes, plus précisément pour l'inconfort au niveau des mâchoires ($p = 0.15$) et des changements occlusaux ($p = 0.41$). La fréquence des complications était faible dans les deux groupes et n'a montré aucune différence significative ($p = 1.00$). La satisfaction globale des patients était élevée dans les deux groupes et ne montrait aucune différence significative ($p = 1.00$). Les deux groupes ont présenté des améliorations significatives des scores FOSQ ($p = 0.004$ entre V1-4 et $p = 0.026$ entre V1-6), des diminutions significatives pour ESS ($p = 0.023$ entre V1-4), des diminutions significatives des scores d'anxiété ($p = 0.003$ entre V1-4 et $p = 0.041$ entre V1-6), ainsi qu'une diminution significative des scores de dépression ($p = 0.025$ entre V1-6). Les patients du groupe avec OAM ont sur-rapporté de façon significative leur compliance subjective par rapport à la compliance objective mesurée par les micropuces ($p = 0.02$). **Conclusion :** L'OAM est un traitement faisable pour le traitement du SAOS chez les patients atteints du DT2 et a démontré des effets secondaires minimes et un taux de satisfaction élevé. Un « effet placébo » important a été observé avec l'appareil placébo, ce qui souligne l'importance des études randomisées et contrôlées dans le domaine du traitement du SAOS. Les micropuces utilisées pour mesurer la compliance objective offrent des données plus fiables que les rapports subjectifs des patients. D'autres essais randomisés et contrôlés à grande échelle sont nécessaires, et des analyses futures d'un système de mesure de glucose en continue pourrait être plus précis pour évaluer les effets de l'OAM sur le contrôle glycémique ; l'investigation de phénotypes métaboliques chez certains patients qui pourraient mieux répondre au traitement de leur SAOS serait aussi important.

Mots-clés : syndrome de l'apnée obstructive du sommeil, diabète de type II, dysfonction glycémique, appareil d'avancée mandibulaire, appareil placébo, compliance.

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Abbreviations

AHI: Apnea-Hypopnea Index

APAP: Autotitrating Positive Airway Pressure

BPAP: Bilevel Positive Airway Pressure

CGMS: Continuous Glucose Monitoring System

CO_2: Carbon dioxide

CPAP: Continuous Positive Airway Pressure

CSA: Central Sleep Apnea

DM: Diabetes Mellitus

EDS: Excessive Daytime Sleepiness

ESS: Epworth Sleep Scale

FOSQ: Function Outcome of Sleep Questionnaire

FPG: Fasting Plasma Glucose

FSI: Fasting Serum Insulin

HADS: Hospital Anxiety and Depression Scale

HbA1c: Hemoglobin A1c (glycated hemoglobin)

HOMA: Homeostatic Model Assessment

HPA: Hypothalamic Pituitary Adrenal

HTN: Hypertension

IFG: Impaired Fasting Glucose

IGT: Impaired Glucose Tolerance

IL: Interleukin

IR: Insulin resistance

MAD: Mandibular advancement device

NF-KB: Nuclear Factor Kappa-light-chain-enhancer of activated B cells

O_2: Oxygen

ODI: Oxygen Desaturation Index

OGTT: Oral Glucose Tolerance Test

OSA: Obstructive Sleep Apnea

PAP: Positive Airway Pressure

PG: Plasma Glucose

PSG: Polysomnography

PSQI: Pittsburgh Sleep Quality Index

RAAS: Renin Angiotensin Aldosterone System

RCT: Randomized Controlled Trial

REM: Rapid Eye Movement

SAO_2: Oxyhemoglobin Saturation

SpO_2: Peripheral oxygen saturation

SCD1: Stearoyl Coenzyme A Desaturase 1

SDB: Sleep-Disordered Breathing

T2DM: Type II Diabetes Mellitus

TMJ: Temporo-Mandibular Joint

TNF-α: Tumor Necrosis Factor alpha

VLDL: Very Low-Density Lipoprotein

Pour mes parents; merci pour votre soutien remarquable pendant tout mon parcours.

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Literature Review

Introduction: Obstructive Sleep Apnea

Upper Airway Anatomy

The upper airway, starting at the nares and lips and extending down to the oesophagus and larynx, serves as more than just a passage for food, air and water. As it is surrounded by a complex anatomy of muscle, cartilage and soft tissue, it plays a crucial role in breathing, speech, and gastrointestinal functions (1). The pharynx is divided into three subdivisions: the nasopharynx, the oropharynx, and the hypopharynx (2).

The nasopharynx begins at the nasal conchae and ends at the soft palate. A site of airway resistance can sometimes be found in the anterior portion of the nose, affected by the alae nasi muscles. Airway size in this area can also be affected by the thickness of the nasal mucosa, vascular congestion, as well as nasal bone structure itself (1).

The oropharynx extends from the soft palate all the way down to the epiglottis. Airway resistance in this zone can be affected by the structure of the facial bones, specifically of the maxilla and the mandible. Muscle activity, size of the lymphoid tissue and of the tongue, as well as fatty deposits in the walls of the airway can also affect resistance in this area (1).

The hypopharynx extends from the epiglottis to the beginning of the larynx. The combined space of the oropharynx and the hypopharynx makeup what is called the retroglossal space. The position of the mandible and the activity of the biggest airway dilator muscle, the genioglossus, will be the main determinates of resistance and anteroposterior dimension of this part of the pharynx (1).

The airway is not supported by any bony structure, with exception of the posterior wall of the pharynx. Due to this lack of bony support, the airway is susceptible to collapse when negative pressure during inspiration occurs. Amongst other functions, some muscles surrounding the upper airway work to maintain airway patency (3). Three major muscle groups of airway dilators exist: The palatal muscles (levator veli palatini, tensor veli palatini, muscularis

uvulae, the palatoglossus and the palatopharyngeus) work to keep airway muscle tonicity and shape intact at the retropalatal area; these muscles determine the position of the soft palate and can alter the size of the airway in this area. The genioglossus, the largest dilator muscle of the upper airway which is attached to the mandible, will work to open the retroglossal space by moving the tongue anteriorly. Finally, the hyoid muscles (mainly the geniohyoid and the sternohyoid (1), but also including the stylohyoid, mylohyoid, and thyrohyoid) determine hyoid bone position and are important in swallowing; if activated simultaneously, they will contribute to opening the airway (3) and stabilize the anterior portion of the hypopharynx (1). Pharyngeal constrictors (superior, middle and inferior) will also serve to close the airway during swallowing. Refer to Figure 1, adapted from Jordan and White for images of upper airway anatomy (3).

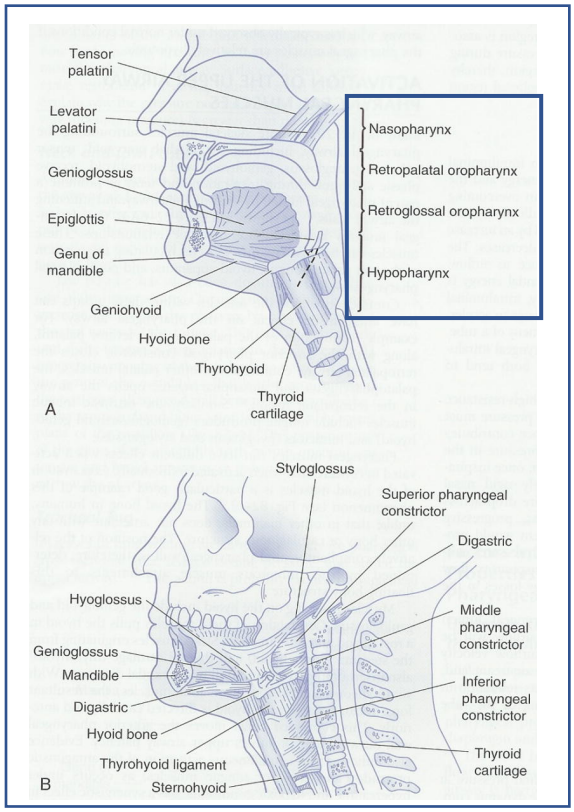

Figure 1. Anatomy of the upper airway.

Adapted from Jordan and White (3).

Breathing during sleep

During sleep in the supine position, certain changes occur in the airway simply due to the force of gravity. The mandible and hypopharyngeal structures are pushed back, collapsing the size of the airway, and blood flow increases to the nasal mucosa (1).

The airway and its muscles no longer receive the same input as they did in a state of wakefulness (4). When awake, muscles of the airway are under both voluntary and involuntary control; however, when asleep, involuntary control takes over. Because of this, airway muscle activity drops and there is a decrease in muscle chemosensitivity to oxygen (O_2) and carbon dioxide (CO_2). As muscle activity and tonicity fall, a small increase in both airway resistance and negative pressure occurs and leads to a gradual rise in CO_2. This prompts a compensation mechanism by certain dilator muscles, specifically the genioglossus, to increase their muscle activity and open the airway (3). However, this normal function of the airway during sleep may be disrupted in some people (1) and certain populations may be at higher risk of developing obstructive sleep apnea (OSA) (5).

Pathogenesis and Risk Factors

OSA is a complex disorder with multiple risk factors and various causes. These factors may interact and contribute to the disease in different ways amongst individuals and also vary according to the severity of their OSA (6). Anatomical issues such as airway anatomy and collapsibility are the predominant factors affecting OSA. In fact, the normal decrease in airway muscle activity during sleep paired with anatomical anomalies can make the airway susceptible to collapse. Non-anatomical factors may also exist and include low arousal threshold (mild pharyngeal narrowing leading to premature awakening), impaired function of airway dilator muscles and unstable ventilatory control (high loop gain) (7).

Anatomical issues of the pharynx such as a narrow airway, specific variations in airway shape and longer airway length are also often associated to airway collapsibility (7). Airway size may differ greatly between patients, but it has been demonstrated in several studies that OSA patients usually have smaller size airways than control subjects. A relationship was also

found to exist between OSA severity and the cross-sectional area of the airway, showing people with severe OSA having smaller sized lumen versus those with mild to moderate OSA (6).

Airway collapsibility may also vary amongst patients with different levels of OSA severity (6). For example, airway collapse can occur at one or several sites (7) ; Patients with mild OSA were found to have collapse in the retropalatal area, whereas patients with severe OSA were found to have collapse in both the retroglossal and retropalatal areas; the amount of collapse was also more important in these patients. Knowing that the site of collapse is not always the same in patients with different levels of OSA severity may be important in treatment selection when trying to target certain anatomical abnormalities (6).

Other airway structures have been compared between OSA patients and healthy controls. OSA patients were found to have increased tongue size with higher fat content, enlarged soft palates, and an increased thickness in the lateral walls of the pharynx. Also, when compared to patients with mild to moderate OSA, patients with severe OSA had lower hyoid bone placement, increased length of pharyngeal airway, increased thickness in soft palates, and longer lengths between the mandibular plane and hyoid bone (6). Several studies also identify certain craniofacial characteristics as being associated with OSA as they may affect upper airway anatomy, such as a narrow maxilla, a small and retrusive maxilla or mandible, vertical growth pattern and a clockwise rotation of the mandibular plane (8).

Another important risk factor for OSA is obesity. An increase in fatty deposits in structures surrounding the airway could directly affect its anatomy and increase its susceptibility to collapse. For example, increased amounts of fat in the tongue which have been found during imaging exams may potentially impair genioglossus function. Being male is also a risk factor for OSA, however the reason why is less understood. A possibility explaining this may be that men usually have a more central pattern of weight gain then women do and larger amounts of fat may be stored in the abdomen and in the surrounding structures of the upper airway. On the other hand, certain studies have also shown that men tend to have larger or same size cross-sectional areas of the airway than women, and an increase in fatty deposits surrounding the area may not have a significant impact on the airway collapsibility. Other studies explain the male sex risk factor for OSA being related to the fact that airway length is often longer in men than in women, increasing its susceptibility to collapse. However, interestingly, the prevalence of

OSA is similar in men and post-menopausal women who have not undergone hormone replacement therapy (9). Increasing age is also another risk factor for OSA as elastic recoil in the lungs may decrease. The airway may also be more prone to collapsing due to a loss of collagen and a decrease in the efficiency of upper airway dilator muscles (10).

Diagnosis

The diagnostic test of choice for OSA is a Level 1 polysomnography (PSG) in an overnight laboratory setting, measuring the number of apnea and hypopnea events per hour of sleep: the apnea-hypopnea index (AHI) (10). A level 1 PSG is supervised by a technician (11) and can collect a minimum of seven data channels and will monitor both respiration and sleep, providing a comprehensive overview of the patient's night (12). Sleep and wake states will be monitored by an electroencephalogram, right and left electrooculograms and a chin electromyogram. Respiration will be monitored by recording breathing effort using plethysmography bands around the thorax and abdomen, airflow by measuring nasal air pressure, temperature, as well as arterial oxygen saturation. An electrocardiogram will monitor heart activity, limb movements can be monitored by electromyography of the anterior tibialis, and body position can also be assessed (10). However, laboratory PSGs may have certain inconveniences such as long wait-times and high costs, while other diagnostic options such as home sleep studies exist (12).

The commonly used Level 3 portable home sleep study is an appropriate alternative for diagnosing OSA and may be less expensive and more accessible than a laboratory PSG. It collects a minimum of 3 data channels such as airflow, oxygen saturation and breathing effort, but may also evaluate snoring, heart rate and body position (11). It however will not monitor sleep-wake states, sleep duration, or other sleep disorders that are non-breathing-related (12). Its specificity (test accurately identifies those who do not have OSA) and sensitivity (correctly identifies those who do have OSA) levels are high, however, as OSA severity increases, its specificity improves but its sensitivity decreases (12) and as many as 17% can be false negatives (11). It therefore may not be the diagnostic test indicated for all patients.

Laboratory PSG still remains the gold standard test for OSA and its use is important when testing patients with comorbidities such as cardiopulmonary issues (e.g.: congestive heart

failure and lung disease) neurological or neuromuscular diseases, risks of hypoventilation, or a risk of having central sleep apnea (CSA). Also, considering the higher rate of technical failures and false negatives associated with home-sleep studies, a laboratory PSG should be used when a home-sleep study yields a negative result for a patient in whom the treating physician still has high clinical suspicions of OSA (11).

Classification

The classification of OSA severity is described in Table 1 (11); classification is based on the AHI once the appropriate diagnostic test is performed (level I PSG or home sleep study).

Severity	AHI
Mild OSA	≥ 5 to <15 events per hour of sleep
Moderate OSA	≥ 15 to <30 events per hour of sleep
Severe OSA	≥ 30 events per hour of sleep

Table 1: Severity classification of OSA in accordance with the AHI.

Prevalence

With the rise of the obesity epidemic and considering the important link between obesity and OSA, the prevalence for OSA has greatly increased over the past 20 years in the general population. Prevalence differs upon age category and AHI severity. Described in Table 2, information was taken from the Wisconsin Sleep Cohort Study of 2007-2010 to identify the prevalence of OSA in the age groups of 30 to 49 years old, and 50 to 70 years old for American men and women with moderate to severe OSA (AHI ≥ 15). The prevalence of mild OSA (AHI ≥ 5 and <15) associated to daytime sleepiness was also estimated to be 14% of men and 5% of women (13).

Age (years)	Gender	Prevalence
30-49	Male	10%
50-70	Male	17%
30-49	Female	3%
50-70	Female	9%

Table 2: Prevalence of OSA in American men and women ages 30-49 and 50-70 with moderate to severe OSA.

When comparing results of the Wisconsin Cohort Sleep Study done in 1988-1994, the increase in prevalence ranges from 14% to 55% depending on the age group studied. Considering the important cardiovascular, endocrinological and neurological comorbidities associated to OSA, this rise in prevalence is alarming (13). When the prevalence of OSA was estimated in the type 2 diabetes mellitus (T2DM) population based on the average of findings from five different studies on nearly 1200 patients, the overall prevalence of OSA was found to be 71% (14).

Consequences of Obstructive Sleep Apnea

Several studies have shown strong associations between OSA and major health issues such as cardiovascular disease, hypertension, cognitive impairment, insulin resistance and T2DM ((15), (16)). The fundamental mechanisms linking these debilitating diseases to OSA remain to be fully understood and further research is needed (15). It is hypothesized that the repeated episodes of sleep fragmentation, intermittent hypoxia and micro-arousals in OSA cause an increase in systemic inflammatory markers, endothelial dysfunction and an increase in activity of the sympathetic nervous system. These systemic abnormalities which have a role to play in the pathophysiology of many diseases are thought to be at cause (17).

Cardiovascular effects

Cardiovascular disease is thought to be mainly caused by the cumulative effects of intermittent hypoxia in patients with OSA. Observations in mice experiencing intermittent hypoxia have shown that atherosclerotic effects such as formation of fatty deposits and mature plaques in parts of the aorta and an increase in size of atherosclerotic plaques occurred when other risk factors for atherosclerosis, such as a fatty diet, were present. This somewhat parallels the reality of most clinical situations in humans, as atherosclerosis is a multifactorial disease (15).

Intermittent hypoxia has also been linked to dyslipidemia, increasing circulating levels of unhealthy cholesterol in the blood. Upregulation of stearoyl coenzyme A desaturase 1 (SCD1), a lipid-synthesizing liver enzyme, has been observed during intermittent hypoxia and is in turn linked to an increase in very low-density lipoprotein (VLDL) levels, an unhealthy type of cholesterol. In fact, a direct correlation was observed in patients with higher levels of nocturnal hypoxia with OSA and increasing levels of SCD1 and VLDL. Intermittent hypoxia has also been suggested to decrease the capacity for lipoprotein clearance, another contributing factor to the development of dyslipidemia. One human study found a direct relation between increasing severity of OSA and a decrease in lipoprotein lipase activity, a major enzyme in lipoprotein metabolism (15).

Several studies have also found associations between intermittent hypoxia, oxidative stress (18) and endothelial dysfunction with increased markers of systemic inflammation in patients with OSA, such as interleukin (IL)-6, IL-8, C-reactive protein, Tumor necrosis factor-α (TNF-α) and others; these markers also play a role in the development of atherosclerosis (15).

Well known risk factors for OSA such as obesity and increasing age are also predisposing factors to many cardiovascular diseases. It can therefore be difficult to separate these confounding factors and find independent correlations between them. However, research has shown that independent associations between OSA and many of these diseases do exist, including heart failure, cerebrovascular disease, cardiac arrhythmias and ischemic heart disease. A higher frequency of potentially deadly cardiovascular events during sleep have also been

noted, such as myocardial infarction, angina and arrhythmias leading to sudden cardiac death, potentially due to catecholamine surge during sleep (18).

Several studies also demonstrate a strong link between OSA and hypertension (18). The causal mechanism linking these together still requires further research, as it is complex and depends on several factors such as endothelial dysfunction, sympathetic activity, disturbances in baroreceptor reflexes and the renin-angiotensin-aldosterone system. Repetitive apneic events linked to acute sympathetic activity and cardiopulmonary issues can cause diurnal hypertension. Intermittent hypoxia stimulates carotid body chemoreceptors, which will cause a reflex stimulation of the sympathetic medullary cardiorespiratory centers. A catecholamine surge and an increase in heart rate and blood pressure will manifest, and can be more important during post-apneic hyperventilation, sometimes reaching levels as high as 240/130mmHg. Another study demonstrated that the effects of intermittent hypoxia during sleep also increased daytime ambulatory blood pressure. It also found that exposure to intermittent hypoxia increased muscle sympathetic nerve activity and decreased baroreflex inhibition, potentially contributing to an increase in blood pressure. Intermittent hypoxia has also been shown to potentially increase activity of the renin-angiotensin aldosterone system (RAAS). Periods of hypoxia could likely increase expression of Angiotensin I and also stimulation of the angiotensin II receptor in the carotid; increases in renin and aldosterone were also seen in animal studies. A meta-analysis comparing 13 studies also found that OSA patients, relative to healthy controls had increased levels of Angiotensin II, and that OSA patients with hypertension (HTN) were also found to have higher levels of aldosterone than OSA patients without HTN. Following treatment with CPAP, a decrease in blood pressure was seen, along with a decline in both markers (18). Studies have also found CPAP and oral appliance therapy to be effective in reducing both systolic and diastolic blood pressure (19) and also inflammatory markers such as C-reactive protein and IL-6 (15).

Cognitive impairments

Excessive daytime sleepiness (EDS) is a common characteristic of patients with OSA, however, it is not experienced by everyone, and nor is it proportional to the severity of OSA based on AHI. It can be a serious and debilitating issue caused by sleep fragmentation, micro

arousals and repetitive interruption of normal sleep architecture. Other neurological and cognitive effects have been related to EDS, such as loss of memory, a lesser ability to concentrate, psychosis, changes in mood, decreased libido and irritability. These impairments can possibly affect quality of life and may explain why some patients with EDS also have a higher incidence of depression. In fact, the comorbidity of OSA and depression may also indicate that both diseases share certain neurobiological factors. The serotoninergic system has an important role in regulating mood and controlling airway muscle tone during sleep. A decrease in serotoninergic neurotransmission can be seen in depression and is usually a cause for sleep alteration. On the other hand, serotonin reuptake inhibitors, a commonly prescribed antidepressant, can also be used to help improve OSA as it may act on muscle tone during sleep (16).

The importance of identifying signs of depression in the OSA population is crucial as it can have a significant impact on patient well-being. Commonly used questionnaires such as the Beck Depression Inventory (measuring depression level) and the Epworth Sleepiness Scale (ESS) (measuring daytime sleepiness) can be used to asses this. In a recent controlled study by Yosunkaya et al. (16), there was no significant difference found between BDI scores in patients with and without OSA. However, a positive correlation was found between higher scores in the BDI, ESS, and the amount of time spent under 90% arterial oxyhemoglobin saturation (SaO_2) in patients with OSA. The study therefore concluded that patients with OSA who spent a large portion of the night under 90% SaO_2 experienced more EDS and were more likely to express symptoms of depression. They do also state that symptoms of depression and EDS were not related to the severity of OSA based on the AHI, as some patients with very severe OSA did not experience EDS. The authors however mention a study performed by Klonoff et al. (20), where symptoms of depression in the OSA population were not more frequent than in those with other chronic illnesses. It can therefore not be stated that OSA causes depression, however the importance of screening OSA patients for depression should be noted (16).

Effects on glycemic regulation

A large number of studies have linked OSA to the development of T2DM, insulin resistance, and altered glucose metabolism. Before exploring the mechanisms linking OSA to these health issues, an overview of Diabetes Mellitus (DM) will be presented.

Definition of Diabetes Mellitus

DM being one of the most common endocrine disorders (21) is a metabolic condition affecting the regulation of blood glucose leading to hyperglycemia. A lack of insulin secretion, defective insulin action, or a combination of both of these issues can be the cause of hyperglycemia (22).

Classification of Diabetes Mellitus

Several types of DM exist based on different causal factors. Types 1 and 2 will differ in terms of management and it is therefore important to differentiate between these types (22).

Type 1 Diabetes Mellitus (T1DM)

The major cause of T1DM is pancreatic β-cell destruction often caused by an autoimmune process or due to an unknown cause (22). Certain environmental and genetic factors may also be involved (23). Onset usually occurs at a much younger age than T2DM (24) and patients may be more prone to ketoacidosis (22), a severe and acute complication resulting from insulin deficiency, lipid breakdown and the accumulation of ketones, leading to potentially fatal acidosis of the blood (25).

Type 2 Diabetes Mellitus

T2DM is a chronic endocrine condition with major contributing factors such as obesity, excessive caloric intake and insufficient physical activity (14). It presents a range of issues from major insulin resistance with relative insulin deficiency to an important problem with insulin secretion with insulin resistance (22).

Gestational Diabetes Mellitus (GDM)

GDM occurs when glucose intolerance appears for the first time during pregnancy (22). If left untreated, it may lead to an increased risk in maternal and perinatal morbidity (26).

Prediabetes

The term prediabetes can be used to indicate people who have a higher risk of developing DM and is characterized by having an impaired glucose tolerance, an impaired fasting glucose, or a glycated hemoglobin of 6.0 to 6.4%. Not everyone with prediabetes will develop DM and it is possible for someone with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) to even revert back to normal glycemic levels. People with prediabetes do not have a higher risk of developing microvascular disease like people with DM do, however, they are at higher risk of developing cardiovascular disease. A stronger link was found between IGT and cardiovascular disease than with IFG, and people diagnosed with both IFG and IGT have a greater risk of developing DM and cardiovascular disease (22).

Risk factors for T2DM

Risk factors for developing T2DM include being over the age of 40 years, having a family history of T2DM (such as a relative of first degree) and having a high-risk ethnic background (African, Asian, Aboriginal, Hispanic or South-Asian). Having a history of prediabetes, GDM, or giving birth to a child with a significantly high birth weight (macrosomic infant) are also predisposing factors to developing T2DM. Patients with certain vascular issues may also be at risk of developing T2DM, such as an high-density-lipoprotein (HDL) cholesterol level <1.3 mmol/L in females and <1.0 mmol/L in males, triglyceride levels ≥ 1.7 mmol/L, having a diagnosis of hypertension, being overweight, or presenting abdominal obesity as measured by waist circumference. Patients also taking certain medications such as glucocorticoids, atypical antipsychotics or highly active antiretroviral therapy for HIV may also be at risk of developing T2DM (23).

The metabolic syndrome

The metabolic syndrome is known as a cluster of conditions predisposing the patient to an increased risk of developing cardiovascular disease. A minimum of three of the following conditions are required for its diagnosis: abdominal obesity, dyslipidemia, hypertension and increased blood glucose levels. Patients with prediabetes and T2DM often have the metabolic syndrome, and patients with the metabolic syndrome that do not yet have diabetes are at high risk of developing it. Research suggests that an aggressive approach should be taken to promptly diagnose and treat people with the metabolic syndrome in order to reduce cardiovascular morbidity and mortality (22).

Pathogenesis of T2DM

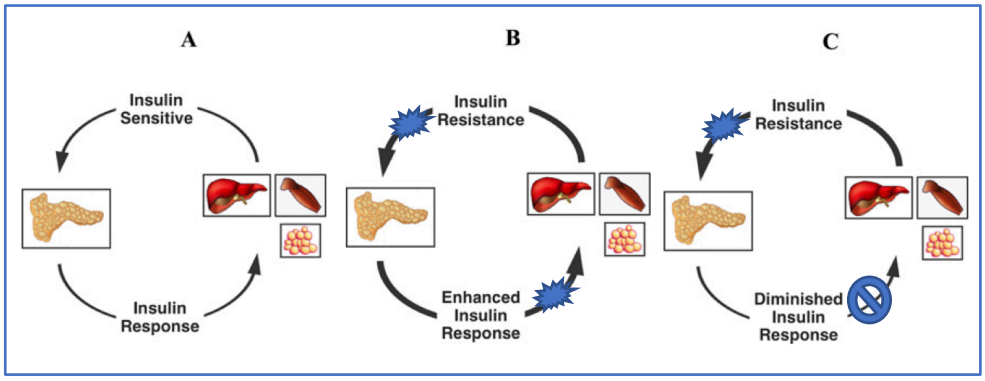

Figure 2. The development of insulin resistance.

Adapted from Kahn et al (27).

In healthy patients, a feedback mechanism exists in order to maintain proper glucose homeostasis in the body. Figure 2A: Pancreatic β-cells release insulin, a hormone which mediates proper uptake of glucose, amino acids and fatty acids by specific insulin-sensitive organs such as muscles and adipose tissues. Insulin also has an effect on the liver and inhibits further glucose production. The quantity of insulin that is secreted to maintain glucose homeostasis depends on the amount of insulin required from these tissues and the level of insulin sensitivity. Figure 2B: As often seen in obese patients, insulin resistance can develop in these insulin-sensitive tissues and consequently, β-cells increase their insulin secretion in order to

maintain normal glycemic levels and a normal glucose tolerant state. Figure 2C: As insulin resistance persists, the β-cells can no longer keep up and are unable to increase insulin secretion; plasma glucose levels begin to rise and the system is in a state of impaired glucose tolerance. With time, as pancreatic β-cells continue to malfunction, glycemic levels continue to increase and diabetes ultimately develops (27). T2DM is therefore a process which involves two steps: insulin resistance and impaired insulin secretion; the impact it will have on patient health can be serious and is associated with many life-long complications, such as cardiovascular disease, retinopathy, nephropathy and issues with the nervous system (14).

Prevalence of Diabetes Mellitus

In the year 2000, an estimated 150 million people world-wide were diagnosed with diabetes; in 2012, that number rose to 371 million people, and by 2030, that number is expect to increase to 552 million or can be viewed as a diagnosis of DM for 1 in every 10 adults. The estimated prevalence in Canada in 2009 was about 6.8% of the population or 2.4 million people. By 2019, the projected estimate is supposed to increase to 3.7 million Canadians (28).

The prevalence of T2DM in the OSA population has also been investigated in several studies. Cross-sectional analyses of current research show that a higher prevalence of T2DM is found in people with OSA versus those without it. The estimated prevalence ranges from 15-30% and varies due to factors such as the studied patient population, the T2DM diagnostic method and the definition used for OSA severity. Whether OSA may cause T2DM over time still requires further investigation (14).

Monitoring hyperglycemia

Some of the most common methods used to measure glucose tolerance, insulin sensitivity and insulin secretion are described in Table 3 (14):

Method assessing glucose metabolism	Description
Fasting Plasma Glucose (FPG) and Fasting Serum Insulin (FSI)	- After fasting, plasma glucose and serum insulin levels are measured - A diagnosis for IFG can be given if FPG levels are between 100-125 mg/dl
Hemoglobin A1c (HbA1c)	- Used in the clinical management of DM and is the primary target for glycemic control - Measure taken in one blood sample and indicates glucose control over the past 2-3 months
Homeostatic model assessment index (HOMA-index)	- Index confirmed as a reliable estimate of insulin resistance - Follows a formula: (Fasting serum insulin x FPG) ÷ 22.5 - The higher the value, the higher the level of insulin resistance
Oral Glucose Tolerance Test ((OGTT) - *2h plasma glucose (PG) in a 75g OGTT*))	- One of the clinical tests used to diagnose T2DM - Requires the consumption of 75g of glucose, then assesses glucose tolerance by measuring levels of glucose and insulin in blood samples every 30 minutes, for 2 hours.
Continuous Glucose Monitoring System	- Test used to assess daily glucose fluctuations, specifically post-prandial and nocturnal glycemic levels - Subcutaneous sensor used to measure glucose concentrations in the interstitial fluid. - Continuous monitoring records levels every 5 minutes (total of 288 readings in 24h)
Hyperinsulinemic euglycemic clamp	- Gold standard test for insulin sensitivity

	- Insulin sensitivity is determined and quantified by the rate of intravenous glucose infusion
Intravenous glucose tolerance test	- Mathematic model and confirmed test to verify glucose tolerance, β-cell responsiveness and insulin sensitivity - Measures glucose and insulin concentrations while fasting and then after intravenous glucose injections at different intervals for 4 hours

Table 3: Various methods used to assess glucose metabolism by the American Thoracic Society.

Diagnostic criteria

Criteria used for the diagnosis of prediabetes and DM are shown in Table 4 and Tale 5 respectively (22):

Test	Result	Category of prediabetes
FPG	6.1-6.9 mmol/L	Impaired fasting glucose
2hPG in a 75g OGTT	7.8-11.0 mmol/L	Impaired glucose tolerance
HbA1c	6.0-6.4%	Prediabetes

Table 4: Different tests and results required for the diagnosis of prediabetes.

Test	Result
FPG *(Taken after a minimum of 8 hours of fasting)*	≥7.0 mmol/L
HbA1c	≥ 6.5%
2hPG in a 75g OGTT	≥11.1 mmol/L
Random PG *(Taken at any time of the day, does not consider last food intake)*	≥11.1 mmol/L

Table 5: Different tests and results required for the diagnosis of DM.

Each test may have different advantages and disadvantages and selection is left up to the discretion of the clinician in charge. If only one test is performed and results are in the diagnostic range of diabetes and the patient does not present any symptoms of hyperglycemia, a second test on another day must be performed to confirm the diagnosis of DM. When confirming this, it is ideal to repeat the same test, unless a random PG was performed, in which case another diagnostic test should be chosen to finalise the diagnosis. Once two separate tests confirm the results are above normal levels, a diagnosis of DM can be confirmed. If ever the results of these tests are conflicting, the test with the positive result for DM should be repeated. In cases where patients present symptoms of hyperglycemia, the diagnosis can be made and a confirmation test is not necessary before beginning treatment. Also, a confirmation test should not delay treatment in patients with T1DM who are often younger, lean or present symptoms of hyperglycemia (22).

Management and current treatment of T2DM

A multitude of different pharmacological treatments are currently available to help manage and treat T2DM. Treatment regimens and therapeutic goals must be customized for each patient as so many factors can affect the success and outcome of any therapy. The severity of the patient's hyperglycemia, the possibility of inducing hypoglycemia, the effectiveness of alleviating associated micro and macrovascular complications of T2DM, encountered side effects and any pre-existing medical conditions must all be considered by the treating physician. Also, as β-cell function is likely to decrease over time and glycemic levels may become worse, T2DM therapy must be re-evaluated and may require a different approach with time (29).

Certain recommendations have been listed for the clinical management of hyperglycemia in T2DM. When HbA1c is under 8.5%, weight loss therapy and lifestyle management should be initiated immediately. If the glycemic target is not achieved after 2-3 months of doing this, treatment with an antihyperglycemic agent should begin and Metformin is the recommended drug for initial use in patients who are overweight. The treating physician may also decide to begin Metformin immediately (29).

When HbA1c is ≥8.5%, an antihyperglycemic agent should be started immediately and the use of two different agents should be considered; one of the agents may be insulin. Also, when a patient has symptomatic hyperglycemia, insulin should be a part of the patient's initial therapeutic regime. Furthermore, different classes of antihyperglycemic agents will need to be combined to metformin and/or insulin if target HbA1c is not met after 3-6 months (29).

Research has shown that combining adequate lifestyle management and the use of metformin and other agents have been effective in decreasing the incidence of T2DM. Nonetheless, these forms of treatment become less effective over time and the disease remains an important economical and public health issue. Progress and development of new treatment modalities to help prevent or postpone the onset of T2DM are tremendously needed (14).

The link between T2DM and OSA

Insulin resistance can contribute to the development of T2DM and both are important risk factors for cardiovascular disease (30). The exact mechanism linking OSA and metabolic

dysfunction has yet to be fully elucidated, however substantial amounts of research indicate that intermittent hypoxia, a main component of OSA which is characterized by repeated episodes of desaturation and then re-oxygenation, plays a major role in its development. The mechanisms by which intermittent hypoxia (IH) affect glucose metabolism are numerous (31).

Both animal and human studies document the activation of the sympathetic nervous system in response to episodes of IH. Catecholamines are released and are known to reduce insulin sensitivity, insulin-mediated glucose absorption and also stimulate hepatic gluconeogenesis. Some studies have also found IH to have direct effects on the hypothalamic pituitary adrenal (HPA) axis, in turn increasing cortisol secretion. The effects of cortisol on glucose metabolism are also well documented, such as insulin resistance and inhibiting insulin secretion (31). Sleep fragmentation was also found to increase the activity of the HPA axis, increasing cortisol levels and inducing atypical glucose metabolism. Animal studies have also shown an association between sleep fragmentation and both glucose intolerance and insulin resistance (32).

IH has also been found to activate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB). NF-kB is a key regulator of the inflammatory response and unravels a strong production of inflammatory mediators such as TNF-α, IL6, IL8, and monocyte chemoattractant protein (MCP1), which are known to decrease insulin sensitivity in the liver and fatty tissues. Excessive production of reactive oxygen species was also documented during periods of IH, increasing oxidative stress, which was shown to increase lipid peroxidation in liver and pancreatic β-cells, increasing β-cell dysfunction and decreasing insulin secretion (31). Other animal studies have also linked IH to decreased β-cell function, increasing levels of fasting glucose and developing insulin resistance (32).

Strong evidence suggests the link between OSA, T2DM and insulin resistance in overweight and obese patients. Whether this link exists independently of obesity and other confounding factors is possible, however, needs further examination. A recent study by Pamidi et al. investigated glucose metabolism in non-overweight men with and without OSA. Both groups were clear of cardiometabolic disease and other health issues, had normal systolic and diastolic blood pressures as well as fasting lipid measures. Using men between the ages of 18 and 30 with body mass indexes (BMI) ranging from 18 to 25 kg/m^2, this is one of the first studies

to investigate the effects of OSA on glucose metabolism in healthy, young and lean men. OSA and control subjects were matched according to similar age, BMI, fitness level, family history of diabetes and diabetes risk based on ethnicity. After an oral glucose tolerance test, patients with OSA were found to have 27% lower insulin sensitivity and 37% higher levels of total insulin secretion than controls; however, glucose levels did not differ significantly. These signs of insulin resistance as well as increased levels of insulin secretion are compatible with T2DM's natural progression, where initial stages involve insulin resistance, normal glycemic levels and compensatory hyperinsulinemia. The results also support the hypothesis that OSA may alter glucose metabolism at a young age, even in patients who are not obese and do not have any cardiovascular disease (33).

Results for fasting glucose and insulin levels as well as the insulin sensitivity index (the HOMA-IR, which is also based on fasting glucose and insulin levels) did not differ significantly between groups. In contrast, other previous studies had indeed found a link between OSA, its level of severity and the HOMA-IR; these studies were however conducted in a lean, middle-aged Asian population presenting health conditions for which they were already being treated, such as hypertension, dyslipidemia and T2DM (33).

One particularity of Pamidi's study (33) on young lean men is its way of defining the AHI: calculating the total number of apneas and hypopneas per hour, however considering a hypopnea as a drop in nasal pressure of ≥50% of its original value and associated with either a ≥3% oxygen desaturation or an arousal. In certain larger population-based studies, hypopneas followed a stricter definition of reduced airflow with ≥4% desaturation and without considering arousals in their criteria. When data was recalculated using the latter definition of a hypopnea (≥4% desaturation, without considering arousals), the number of patients diagnosed with OSA (AHI>5) was significantly reduced. This suggests that when using only desaturation data and disregarding arousals, OSA may not be properly identified in the young and lean population (33). A previous study by Guilleminault et al. supports the relevance of arousal use in OSA diagnostic criteria in this specific population, since lean patients tend to desaturate less than obese patients. This is thought to be due to lean patients having better functional reserve capacities and less ventilation perfusion mismatch, leading them to have less important oxygen desaturation per hypopnea, however still presenting other key features of reduced airflow and

arousals. This is therefore an important consideration when diagnosing OSA in lean patients (34).

Another important point in Pamidi's study (33) on young lean men is that most patients in the sample were found to have mild OSA and physiological events during sleep were essentially related to arousals, not extreme oxygen desaturation; this led to an increase in sleep fragmentation and less deep slow-wave sleep. Two previous studies ((35), (36)) also found similar results in healthy, young individuals when evaluating the effects of sleep fragmentation and reduced amounts of deep slow-wave sleep on glucose metabolism, where an approximate 25% reduction in insulin sensitivity was found. These two studies also showed that sleep fragmentation increased sympathetic nervous system activity, possibly explaining the mechanism linking insulin resistance to changes in sleep quality (33). Evidence in other studies also found that IH induced in heathy patients increased blood pressure via sympathetic nervous system activity and also decreased insulin sensitivity ((37),(38),(39)). Further research is required to assess if changes in insulin and glucose levels in patients with OSA may progress into long-term clinical T2DM, or if treatment of OSA may help reverse these negative effects (33).

A recent study by Seicean et al. (40) performed an analysis on a subset of data taken from The Sleep Heart Health Study (41), a multi-center cohort study from 1994 to 1999. Seicean et al. found an association between OSA and a greater prevalence of prediabetes and occult diabetes in the non-overweight but older population. Although the number of non-overweight patients in the study was limited, the results still demonstrated an independent link between sleep-disordered breathing (SDB) and distinct measures of impaired glucose metabolism (IFG, IGT, IFG+IGT and occult diabetes) in both overweight and non-overweight groups, independently of BMI or waist circumference. In fact, both overweight and normal weight groups showed similar strengths of association between SDB and glucose irregularities, supporting the hypothesis that the mechanism linking the two together is not dependent on adiposity. As previously stated, the effects of certain physiological events during OSA such as intermittent hypoxia, sleep fragmentation, hypercapnia and micro-arousals may be at cause (40).

The study by Seicean et al. also found that occult diabetes and combined measures of IFG and IGT were found to be significantly more prevalent in patients with SDB than those

without it. The presence of combined IFG and IGT appears to have a significant clinical impact as data suggests that this issue may present more severe dysfunction in insulin secretion, action and endogenous glucose production relative to problems with IGT or IFG alone. It has also been shown that patients with combined IFG and IGT have a higher risk of rapid progression of cardiovascular disease, T2DM as well as premature death (40).

A correlation also seems to exist between higher OSA severity and poorer glucose control. A study by Aronsohn et al. in diabetic patients evaluated the relationship between untreated OSA and its level of severity with HbA1c levels, compared to patients without OSA and after controlling for confounding factors such as BMI, age, race, total number years with diabetes, total number of medications used for diabetes, sex, level of physical activity and total hours of sleep (42). Results showed that patients with mild OSA had levels of adjusted mean HbA1c that was increased by 1.49% versus patients without OSA. Patients having moderate OSA had an increase by 1.93%, and patients with severe OSA had an increase by 3.69%. A positive correlation was also found between increasing levels of HbA1c and measures of OSA severity, such as total AHI, rapid eye movement (REM) sleep-AHI, and ODI during total and REM sleep (42).

Obstructive Sleep Apnea Treatment

Over the past few decades, important progress in the field of sleep medicine has led to better diagnosis and treatment of OSA. Multidisciplinary management is often required, and several different treatment options exist, such as positive airway pressure therapy, oral appliance therapy, positional therapy, behaviour management, weight loss and bariatric surgery, a variety of surgical procedures of the upper airway and maxillomandibular advancement surgery (43). Several factors such as OSA severity, patient preference, airway anatomy and different health factors should all be considered before selecting the appropriate treatment option (44).

Weight loss

As previously discussed, studies have shown obesity to be an important risk factor for OSA as over 70% of OSA patients suffer from obesity. An important relationship exists between AHI and BMI and losing weight should be encouraged as a first form of treatment for all

overweight patients with OSA (43). Although weight loss may improve AHI, the cure rate by diet alone remains low and should be associated to another form of treatment for OSA. A sleep test should be performed after important weight loss (over 10% of body weight) to identify if treatment by positive airway pressure (PAP) – *discussed below* – is still required or if PAP levels need to be adjusted. Studies have also shown that bariatric surgery may improve or even eliminate OSA and may be indicated in people with severe obesity and with whom conventional weight-loss techniques were unsuccessful. Long-term follow-up remains important as the rate of remission for OSA is 40% two years post bariatric surgery (44).

Treatment with Positive Airway Pressure

Treatment with positive airway pressure was first introduced by Sullivan in 1981 and is currently the gold standard treatment for moderate to severe OSA (45). PAP is either delivered through the nasal passages, the oral cavity, or both, and acts as a pneumatic splint to prevent airway collapse during sleep (44). Refer to Figure 3, adapted from Gordon and Sanders for illustration (46). The amount of pressure needed to maintain patency differs amongst patients and OSA severity and must be increased above the airways' "critical value" in order to prevent collapse from occurring (43). The ideal pressure level should be determined individually for each patient by either a full-night or split-night titration study. Other PAP systems exist for CPAP intolerant patients, such as the bilevel mode (BPAP), or the autotitrating mode (APAP). BPAP may be an alternative for patients requiring high PAP levels but find it difficult to exhale against the continuous and fixed pressure delivered by CPAP (44). APAP mode may provide more comfort and has a slightly better compliance rate than CPAP as it automatically titrates the pressure it delivers according to specific factors such as sleep stage, posture and nasal congestion (43).

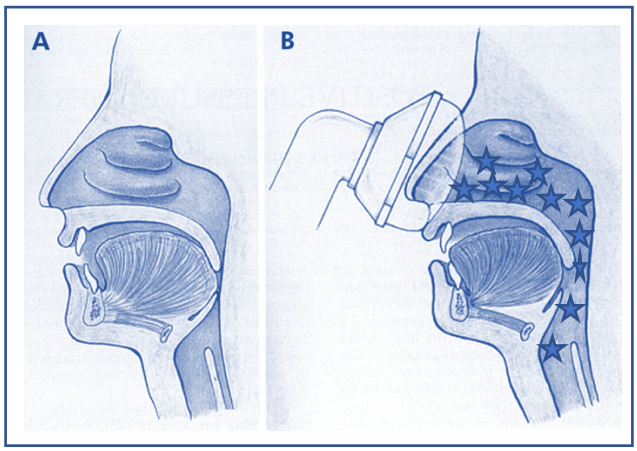

Figure 3. A – Airway collapse during sleep. B – Airway maintained open by positive pressure via nasal passage.

Adapted from Gordon and Sanders (46).

In cases of mild OSA (AHI ≥5 and <15), treatment by PAP is indicated if the patient presents symptoms affecting mood, excessive daytime sleepiness, cognitive dysfunction, or in the presence of comorbidities such as hypertension, coronary artery disease, or a past cerebrovascular accident. In the presence of moderate to severe OSA (AHI ≥ 15), treatment by PAP is indicated as the first choice of treatment regardless of patient symptoms or associated comorbidities. Substantial amounts of research have shown the effectiveness of CPAP in controlling the symptoms and consequences of OSA, however, its efficacy is highly dependent on its continued use. Symptoms may recur only 1-3 days after stopping treatment, therefore patient compliance is of extreme importance (43). Certain unwanted side effects may diminish patient acceptance if they are not rapidly addressed. One of the most frequent reasons for abandoning CPAP treatment is mask discomfort. Other side effects include conjunctivitis and noise due to mask air leaks, nasal congestion, dryness of the mouth, skin irritation, swallowing air and bloating (47). Whether it is due to discomfort caused by side effects or the unwillingness to sleep while attached to the machine, adherence is a major problem and patient compliance with CPAP varies from 50% to 80% (43).

Oral Appliance Therapy

Although not as efficient in as many treatment outcomes as CPAP (44), oral appliance therapy has become increasingly popular over the past decade and is now recognized as an important alternative to CPAP treatment for patients with mild to moderate OSA, as well as patients with severe OSA who are intolerant to CPAP (43).

The most frequently used appliance is the mandibular advancement device (MAD), which anchors itself on both maxillary and mandibular dental arches and serves to advance and hold the lower jaw in an anterior position. In doing so, the base of the tongue also moves forward and pharyngeal fat pads move laterally away from the airway, allowing the upper airway to widen in its lateral aspect and also improves the function of dilator muscles, specifically the genioglossus. Airway collapsibility and the AHI are therefore reduced when MADs are used on appropriately selected patients. Some common but temporary side effects may include hypersalivation, gingival irritation or dry mouth. Other side effects may last longer and include pain in the TMJs, changes in occlusal relationship and tooth pain (43). Conversely, studies have shown the usefulness of mandibular exercises in reducing temporomandibular joint (TMJ) pain (48), as well as minimizing the effects of occlusal changes and improving bite force during MAD therapy (49).

Potential MAD candidates must be thoroughly examined by a qualified dental professional to evaluate the health of the teeth, soft tissues, periodontium and TMJ before receiving an appliance; all elements of the exam must be in good condition in order to support the MAD. Panoramic or intra-oral radiographs may also be taken, dental occlusion must be examined and the patient must have acceptable mandibular range of motion. Another oral appliance is the tongue retaining device which will only maintain the tongue in an anterior position without repositioning the lower jaw (44). These devices are more recent and although they show some promising results, further research is required before they become a recommended form of treatment for OSA (43).

Patients should also be closely monitored once mandibular advancement therapy begins in order to ensure patient compliance, comfort, proper activation of the appliance and manage any unwanted side effects or pain (44). A dependant relationship is generally observed between

progressive appliance activation and improvement in AHI (50). Once the appliance is fully adjusted and the patient is comfortable, patients should undergo a sleep study to evaluate treatment efficacy and its impact on AHI and oxyhemoglobin saturation; resolution of clinical signs and symptoms must also be assessed. Once proper titration, fit and efficiency of the device are obtained, a follow up every 6 months during the first year is suggested, after which annual check-ups are sufficient (44). Although the efficacy and success of MADs have been well demonstrated when used on appropriately selected patients, up to one third of patients still fail to respond to treatment. Younger non-obese women with milder and non-positional OSA seem to have better responses to MADs, however, predictive factors used to select patients best suited for MADs are still unclear, and further research is required to identify them (43). Obese patients (BMI > 24 kg/m^2) with moderate OSA and Mallampati class 4 were found to be unlikely to respond to MADs by one study (51), and certain investigators believe that a BMI > 35 kg/m^2 is a contraindication for MADs (52).

Although MADs were found to be less effective than CPAP on certain levels, many studies have shown better patient compliance and preference with oral devices (53). However, when comparing compliance data, results are not unanimous and research on patient preference in OSA treatment is lacking (52). Certain studies have even shown similar levels of preference between the two, or even more preference for the CPAP (43). A qualitative study showed that a patient's experience with CPAP and MADs was not only based on physical aspects of the devices, but also depended on their lifestyle needs. Some of the most important factors that impacted treatment preference were device effectiveness, its ability to be transported, potential embarrassment with device use, and cost. Physicians should be considerate of patient's preferences in order to select the most appropriate treatment option for them and hopefully increase their compliance (54).

Surgical treatment

Some of the first techniques developed to treat OSA involved surgery of the upper airway in order to provide a permanent solution for patients suffering from this condition (44). Surgical treatment looks to enlarge the width of the airway and eliminate the cause of obstruction in order to improve OSA. Various techniques exist and operate on different

anatomical structures such as the tongue, the nose and tissues of the oropharyngeal tract. Unfortunately, success rates may be limited and surgical treatment of this kind remains controversial to this day (43).

Maxillofacial surgery such as bi-maxillary advancement works by advancing the skeletal structures of the maxilla and mandible in order to produce forward displacement of the tongue, soft palate and also widen the airway space. This type of surgery may be extremely effective as AHI was found to be reduced by an average of 87% in two studies ((55),(56)). This form of treatment may be interesting for patients who have failed with all other forms of treatment or who have specific craniofacial characteristics. Long-term follow up after any surgical procedure also remains essential as treatment efficiency tends to reduce as patients become older and gain weight with time (43).

Impact of treatment on patient health

Numerous benefits have been associated with the treatment of OSA and vary depending on the type of treatment selected. Differences in treatment efficacy and patient compliance may also affect the quality of improvement on patient health (57).

In a randomized controlled trial (RCT) by Phillips et al., the effects of MADs and CPAP were measured on patients with moderate to severe OSA. After 1 month of optimal use, they found that CPAP was more effective in reducing AHI than MADs, however, compliance was reported to be higher with the oral appliances. When comparing effects of excessive daytime sleepiness, driving performance, and quality of life, both treatments improved each factor similarly; four factors of quality of life were actually even reported to be superior with MADs. When comparing 24-hour mean arterial pressure, both CPAP and MADs were equivalent, yet neither of them improved blood pressure. Effects on health were therefore similar between both treatments and may be explained by CPAP's superior efficacy offset by the lower patient adherence when compared to MAD therapy (51). On the other hand, in a systematic review and meta-analysis by Bratton et al., the effects of CPAP versus MADs on patient blood pressure were also compared; blood pressure was successfully reduced by both MAD and CPAP with no significant difference between treatments (19).

The effects and benefits of OSA treatment on T2DM are less clear, despite research suggesting a strong association between the two disorders. Over a decade ago, West et al. performed an RCT studying the effects of CPAP treatment on HbA1c and insulin resistance in men with poorly controlled T2DM and OSA. After a 3-month period of CPAP treatment and an average nightly compliance of only 3.6 hours, no beneficial effects were observed. Two more RCTs have been published recently and studied the effects of 6-month treatment with CPAP on glycemic control in T2DM patients, using HbA1c as their primary outcome as well. CPAP treatment was found to have no effect in the first study by Shaw et al. (58), however, the second study by Martinez-Ceron et al. (59) reported a clinically significant reduction of 0.4% in HbA1c. Both studies had similar patient populations when considering sex, BMI, age and OSA severity (60).

Factors that did vary between these studies were the types of treatments patients received for their T2DM and also their initial degree of glycemic control. In Shaw's study (58), baseline HbA1c was lower by about 0.3%, and approximately half of the patients did not use any diabetes medication; patients using insulin were also excluded from the study. Conversely, in the Martinez-Ceron study (59), virtually all patients received oral anti-diabetic treatment and 42% of patients used insulin treatment; they found that patients treated by oral agents alone showed significant improvements in HbA1c, however patients using oral agents in combination with insulin did not. A patient's metabolic phenotype and their medication regimen may therefore affect the way they respond to OSA treatment and require further investigation as they may impact the success rate in improving glycemic control (60).

CPAP adherence was similar in both of these studies as well, averaging around 5 hours per night. While there is no established threshold for CPAP use that dictates effectiveness on glycemic control, a dose-response relationship was reported between the number of hours of CPAP use and amelioration in insulin sensitivity. A recent RCT by Pamidi et al. showed that 8-hour CPAP use in a controlled laboratory setting for a 2-week period led to improved insulin sensitivity and lower glucose levels in pre-diabetic patients (61). Another study by Mokhlesi et al. found significant improvements in glycemic control in patients with T2DM who underwent one week of CPAP treatment in a laboratory setting with a full 8-hour use per night (62). These studies support the importance of adequate compliance needed to improve metabolic health (60).

The effects of MADs on metabolic health have yet to be fully investigated as well. A small uncontrolled prospective study was performed, measuring the effects of a mandibular advancement device on arterial stiffness and glucose metabolism in patients with mild to moderate OSA. After 1 year of MAD therapy, they found significant reductions in fasting plasma glucose, fasting plasma insulin, and improved HOMA-IR in patients without T2DM or cardiovascular disease. Fasting plasma insulin and HOMA-IR were also significantly improved after only 3 months of MAD therapy. Although patients did not have higher than normal values of fasting plasma glucose and fasting plasma insulin at baseline, 33% of patients did demonstrate signs of impaired glucose tolerance after an OGTT, indicating initial signs of pre-diabetes. The study also showed that MAD therapy improved arterial stiffness, decreased AHI, ODI, EDS and minimum SpO_2 (63).

Objectives and Hypothesis

Statement of problem

The overall prevalence of 71% of OSA in the T2DM population is alarming (14). As the literature supports the link between OSA and glucose dysregulation, optimal treatment of OSA may actually improve cardiometabolic outcomes in T2DM patients. Promising data already exists on CPAP treatment showing blood sugar improvements in as little as one week in T2DM patients (62), and also in two weeks in prediabetic patients (61). However, both studies were performed under optimal conditions, where compliance was monitored in an all-night laboratory setting. Results from other RCTs assessing the effects of CPAP on metabolic outcomes are often not as consistent likely due to their poor compliance, leaving many patients partially or completely untreated (43). As MADs may be better tolerated and accepted by patients than CPAP, better compliance may result in more optimal treatment and potentially deliver more consistent improvements in metabolic outcomes (53). However, to date, no RCTs have assessed whether MADs can improve health outcomes in this population (53). In the same way that MAD therapy was shown to reduce blood pressure similarly to CPAP (19), further research is merited to investigate the effects of MADs on metabolic outcomes in patients with T2DM. Since Hba1C is the primary target for glycemic control and indicates the average glucose concentration over

the past 2-3 months (14), MAD therapy lasting 3 months can be set to assess possible glycemic changes.

Hypothesis

Research hypothesis

The overall hypothesis of this study is that 3 months of MAD therapy in patients with both OSA and T2DM will improve glycemic control when compared to a control group using a placebo oral appliance.

Null hypothesis

Three months of MAD therapy in patients with both OSA and T2DM will not improve glycemic control when compared to a control group using a placebo oral appliance.

Study objectives

Given the extent of the study and time restrictions within the scope of this thesis project, **this paper represents a sub-study** and will evaluate and discuss specific criteria only; for the purpose of simplicity, objectives will be separated into "sub-study objectives" and "main-study objectives".

Sub-study objectives

This thesis project will only focus on the following objectives:

- **Primary objective:**
    - To evaluate if 3 months of treatment with a MAD will improve glycemic control as measured by the HbA1c in patients with OSA and T2DM as compared to a Placebo Device.
- **Secondary objectives:**
    - To evaluate the feasibility of a MAD to treat OSA in the T2DM population.
    - To compare subjective side effects of the MAD and Placebo Device.

- To evaluate overall treatment satisfaction and frequency of complications experienced with both devices.
- To compare subjective changes in quality of life and sleep with both devices.
- To compare subjective and objective compliance with both devices.

Main-study objectives

This thesis project will not focus on the following objectives, unless specified in the previous "Sub-study objectives" section.

- **Primary objective:**

- The primary aim of this study is to determine if the MAD vs. the placebo device will reduce day-to-day glucose variations and peaks in glucose above normal range, particularly at night time, using a continuous glucose monitoring system (CGMS) in patients with T2DM and OSA.

  - The CGMS can be more informative than either the HbA1c or self-monitoring of blood glucose as it provides data on the direction, magnitude, duration and frequency of glucose level fluctuations (64). In fact, higher levels of glucose variability are linked to poorer vascular outcomes, independent of the HbA1c (65).

- **Secondary objectives:**

- To assess changes in the following parameters of cardiometabolic health before and after treatment in both groups:

  - Clinical blood pressure
  - Microalbuminuria (an indicator of renal microvascular complications of T2DM)
  - Lipid abnormalities (triglycerides, LDL-C, HDL-C)
  - Total daily insulin doses in patients on insulin therapy, as a secondary outcome of their glycemic control

- To determine if MAD therapy will improve glycemic control, as measured by HbA1c.

- HbA1c reflects mean fasting and postprandial glycemia over a 2-month period and is commonly used to guide clinicians in therapeutic decisions in patients with T2DM (66); it is also a frequent primary endpoint in clinical trials of T2DM (67).
- Increases in HbA1c are linked to a greater risk for macrovascular and microvascular complications, as well as increased mortality in patients with T2DM (67). Also, observational studies have found an association between increasing severity of OSA and elevated values of HbA1c, an indication of a worsening glycemic status (42).

- To improve subjective excessive daytime sleepiness, quality of life and depression scores.

- To determine whether improving glucose control and other metabolic parameters may be linked to changes in key biomarkers of inflammation, such as highly-sensitive C-reactive protein (hs-CRP), and/or sympathetic activity (measured by heart-rate variability), hypothesized mechanisms underlying the association between OSA and adverse metabolic health outcomes ((5), (68)).

Materials and methods

Study type

This study is a pilot randomized controlled trial.

Study population

17 patients with T2DM who screened positive for OSA after undergoing a home sleep study. Patients were then randomized to either the treatment group (MAD), or the control group (Placebo device).

Inclusion criteria

- Over 18 years of age
- T2DM diagnosis (under current Canadian Diabetes Association Guidelines)

- Medication regimen stable for at least 1 month before randomization. Agreement also made with treating physician to not modify anti-diabetic medication during study, unless otherwise necessary
- OSA diagnosis with AHI ≥ 5 episodes/hour (under current American Academy of Sleep Medicine criteria for scoring respiratory events)

Exclusion criteria

- Use of medication that alters blood glucose levels (e.g.: steroids)
- Having received any form of treatment for OSA in the past 3 months
- Patients with severe subjective sleepiness (Epworth sleepiness scale (ESS) > 15)
- Professional drivers or patients having a higher risk of driving-related incidents based on clinical interview
- Sleep apnea presenting any of the following characteristics:
    - Very severe OSA (AHI > 50 and oxygen desaturation index (ODI) >50)
    - Severe hypoxemia (blood oxygen saturation (SpO_2) <80% for over 10% of recorded time)
    - Central sleep apnea or Cheyne-Stokes respirations with a central apnea index > 10 episodes/hour
- Patient already has another sleep disorder other than OSA
- Active cardiovascular disease (includes arrhythmia, congestive heart failure, angina)
- Body Mass Index (BMI) > 35
- Current pregnancy
- Habitual use of narcotics or sedatives
- Dentition unable to support the MAD
    - Insufficient number of teeth to allow proper appliance retention
    - Extensive tooth mobility
    - Extensive tooth restauration required
    - Signs of active infection
    - Pain in teeth or of the soft tissues

- Pain of the temporomandibular joint (TMJ) or limited mandibular range of motion

Recruitment

Patients with T2DM were recruited by the following means:

- Public announcements in:
    - The *Journal 24h*
    - *Kijiji*
- Brochures were distributed in the following clinics:
    - MUHC Family Medicine Clinic
    - MUHC Cardiovascular Clinic
    - Queen Elizabeth Health Complex
    - Roper Clinic
    - *Diamant* Medical Clinic
    - *Santé medic* Clinic
- Via a referring doctor or in person at:
    - MUHC's Royal Victoria Hospital Endocrinology Clinic
    - MUHC's Montreal Chest Institute Sleep Disorders Clinic

Ethical considerations

This research project was approved by the Research Ethics Board of the MUHC (Project number: 2017-2769, approved 2016-12-21) and the *Comité d'éthique de la recherche en santé* of the University of Montreal (Certificate number: 17-003-CERES-P, approved 2017-01-30).

No serious adverse effects were expected from the use of either appliance; possible side effects due to appliance use were described in the Informed Consent Form (See Annex – Informed Consent Form). Patients were also informed that either appliance may or may not have the desired effect of adequately treating their OSA. Participants with sleep test results indicative of exclusion criteria at any point throughout the study were excluded and immediately referred

to the MUHC Sleep Clinic and offered CPAP treatment. Patients in the control group were only informed of the inefficient nature of their treatment at the end of the study and were subsequently offered the MAD. After the end of the study, all participants were offered long-term follow-ups at the MUHC Sleep Clinic for their OSA, and at the Orthodontic Clinic of the University of Montreal for their MAD.

Interventions

Randomization and blinding

Participants who screened positive for OSA were randomized 1:1 to either MAD vs. placebo device. Randomization was by blocks of 2 or 4 with two strata of sleep apnea severity (AHI<15 and AHI ≥15). Participants were told that the study would compare two different oral appliances for OSA treatment and were thus blinded to the presence of a placebo device.

Study groups

- **MAD group:** The SomnoDent Flex™ Mandibular Advancement Device as illustrated in Figure 4. The appliances were made by the Somnomed® company, using upper and lower casts with bite registration at 60% of maximal mandibular protrusion. Each device has a compliance microchip (Braebon Dentitrac®) embedded in the acrylic of the mandibular piece. The device is titratable, and patients can advance beyond the 60% of their maximal mandibular protrusion according to their level of comfort.

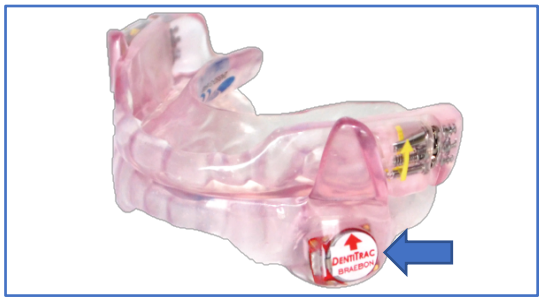

Figure 4. SomnoDent Flex™ device with embedded Dentitrac® microchip.

Photo adapted from Somnomed Compliance Recording (https://somnomed.com/ca-en/dentists/compliance-recording/).

- **Placebo group:** Mandibular Essix® device as illustrated in Figure 5. The appliances were made by the Orthodontic Resident (Emily Santini) in the following way:
    - The microchip was placed at a minimum of 2mm from the occlusal surface of the teeth to avoid any interference. Then 1mm of Orthodontic Resin (Dentsply Caulk®) was placed around the chip which will secure it to the appliance.
    - A vacu-form shell (ACE VAC .035 Essix® Plastic Dentsply) was then formed around the mandibular cast and microchip with surrounding orthodontic resin.

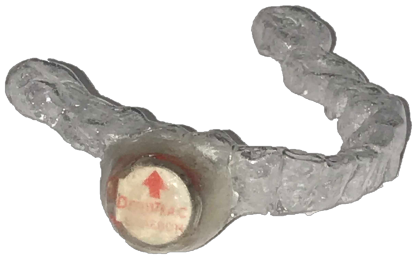

Figure 5. Mandibular Placebo device (Essix® with Dentitrac® microchip).

Photo by Emily Santini.

Procedures

Screening

1- Initial screening: Prior to performing a sleep test, general eligibility was assessed using a pre-screen questionnaire that addressed medical history as well as work, sleeping and travel habits. The ESS was also administered to assess daytime sleepiness. Questionnaires were completed over the phone or in person. The information was only kept if participants later signed the information consent form. Eligible participants were invited to come to a screening visit at the MUHC where consent was obtained and eligibility for the sleep test was confirmed.

2- OSA screening - Home sleep study: At the time of the sleep test, diabetes medication had to be stable for at least 2 weeks and expected to remain stable. Patients then underwent a level III home sleep study to be screened for OSA. The research coordinator went over instructions on how to set up the sleep recording device (Portable sleep recording Medibyte® Braebon or the Embletta® MPR) and patients installed the equipment themselves before going to sleep. Data was scored by a Registered Polysomnographic Technologist (RPSGT) according

to the American academy of sleep medicine recommendations. Those positive for OSA (until July 30th 2018: AHI≥10, as of July 31 2018: AHI≥5) and negative for all exclusion criteria related to sleep were informed they were eligible to participate and were then sent for a dental screening to be evaluated for MAD eligibility.

3- Dental screening: Patients were then seen by the Orthodontic Resident in the Orthodontic Clinic at the University of Montreal. Upon intra-oral/extra-oral examinations (See Annex – Oral exam) and a panoramic radiograph, patient eligibility was determined. If eligible to receive the MAD, the following was recorded:

a. Alginate (Jeltrate®, fast set) impressions of the upper and lower dental arches

- Impressions were then poured in Microstone (Whipmix®)

b. Bite registration at 60% of maximal mandibular protrusion (using the George Gauge™) was taken with Thixotropic Vinyl Polysiloxane Regular Set (Blu-Mousse®)

Study visits and data collection

Visit 1 – Baseline measurements: Patients were seen at the MUHC by the research coordinator in order to obtain baseline data:

a. Blood was drawn by a nurse and sample analyses were performed at the Royal Victoria Hospital Central Laboratory in order to measure HbA1c levels.

b. Weight

c. Record of any changes in medication or health

d. Administration of the following questionnaires: (See Annex - Questionnaires)

- The Epworth Sleepiness Scale (ESS); done during screening-recruitment
- The Functional Outcomes of Sleep Questionnaire (FOSQ)
- The Pittsburgh Sleep Quality Index (PSQI)
- The Hospital Anxiety and Depression Scale (HADS)

Visit 2 – Appliance fitting: The appropriate appliance was delivered by the Orthodontic Resident according to patient randomization. Using an acrylic bur, adjustments were made until patients felt comfortable with their appliance and were able to insert and remove it properly.

Patients were instructed to wear appliance to sleep. Instructions on appliance cleaning and maintenance were explained, and patients were given a log sheet to fill out the hours of sleep vs. hours of oral appliance wear per night to measure subjective compliance (see Annex – Material given to participant). Weight and any changes in medication or health status were also recorded.

For patients in the MAD group, the following was also given to the patient:

- Mandibular exercise sheet: upon waking up in the morning and removing the oral appliance, patients were advised to perform 3 sets of 5 repetitions of several jaw exercises (See Annex – Material given to participant). Stretching of the jaw muscles have been reported to help prevent jaw or TMJ pain and discomfort in the morning and hopefully prevent occlusal changes by "re-setting" the muscles in centric relation (49).
- An oral repositioning putty (Flexitime® VPS Impression Material – Easy Putty Refill, Handmix – Kulzer) made by the Orthodontic Resident is placed on the lower teeth and guides the patient to occlude in centric relation. Patients were instructed to use this every morning, after performing oral exercises, and could then examine if their teeth fit perfectly in the putty grooves (indicating no occlusal change) or if they did not (indicating likely occlusal changes)
- Participants were told to wait before activating their MAD until the next appointment.

1-week follow-up post appliance fitting: Patients were seen by the Orthodontic Resident 1 week after appliance delivery to ensure comfort and adjust appliance as necessary. Subjective compliance logs were reviewed to ensure that they were properly filled out, and the Dentitrac® microchip was downloaded to ensure that objective compliance was adequate. Weight and any changes in medication or health status were also recorded.

Patients in the MAD group were shown how to begin advancement of their device. One activation per side, per night was recommended, according to patient comfort. If patients began to feel excessive or lasting discomfort, they were instructed to turn back their activation level.

⇒ Beyond this point, weekly check-ins (via phone or e-mail) were performed by the Orthodontic Resident to ensure that patients were comfortable, still wearing their appliance and that there were no changes in health status or medication. If a patient had an issue with the appliance or experienced any lasting discomfort, the patient was seen between scheduled visits to manage the issue. Also, as previously described in the literature (57), an 8-week titration phase before moving on to the treatment phase serves to allow time for maximal possible activations and to avoid issues with compliance due to discomfort that may be associated with MADs while patients get used to the appliance.

Visit 3 (8 weeks after Visit 2) – End of titration period: Patient is seen by the Orthodontic Resident for compliance download and administration of a "Side-effects" questionnaire, performed to evaluate patient's overall experience with appliance (See Annex - Questionnaires). Weight and any changes in medication or health status were recorded. Patient was given instructions on how to perform portable sleep recording while wearing oral device (Medibyte® Braebon or Embletta® MPR – patient was assigned to the same machine as they were for initial screening sleep recording).

⇒ Sleep scores were then assessed by the same RPSGT:

- If AHI could continue to be improved and patients did not experience any TMJ discomfort, they were instructed to continue to advance their MAD.
- If AHI indicated very severe OSA (AHI≥50), patient was excluded from study and referred to seek CPAP treatment.

Visit 4 (4 weeks after Visit 3): Patient is seen by the Orthodontic Resident for compliance download and administration of the following questionnaires (ESS, HADS, FOSQ, PSQI). If patients showed moderate or severe signs of depression, patients would be referred to seek psychologic counselling. Weight and any changes in medication or health status were also recorded.

Visit 5 (4 weeks after Visit 4): Patient is seen by the Orthodontic Resident for compliance download. Weight and any changes in medication or health status were also recorded.

Visit 6 (4 weeks after Visit 5)– Post-treatment measurements: Patients were then seen at the MUHC by the research coordinator in order to obtain all the same data measured at Visit 1. Compliance chip was downloaded and subjective compliance diary was recuperated. Equipment for a final home sleep study was given to the patient.

"End of study" Visit: After all post-treatment data was obtained, patients met with the treating sleep physician (Dr Sushmita Pamidi) to go over their results and determine future course of action. Patients in the control group were informed of the inefficient nature of their treatment, and subsequently offered the MAD free of cost. All patients were also offered long-term follow-up at the MUHC Sleep Clinic and Orthodontic Clinc for further MAD follow-up.

An overview of all study visits is illustrated in Figure 6.

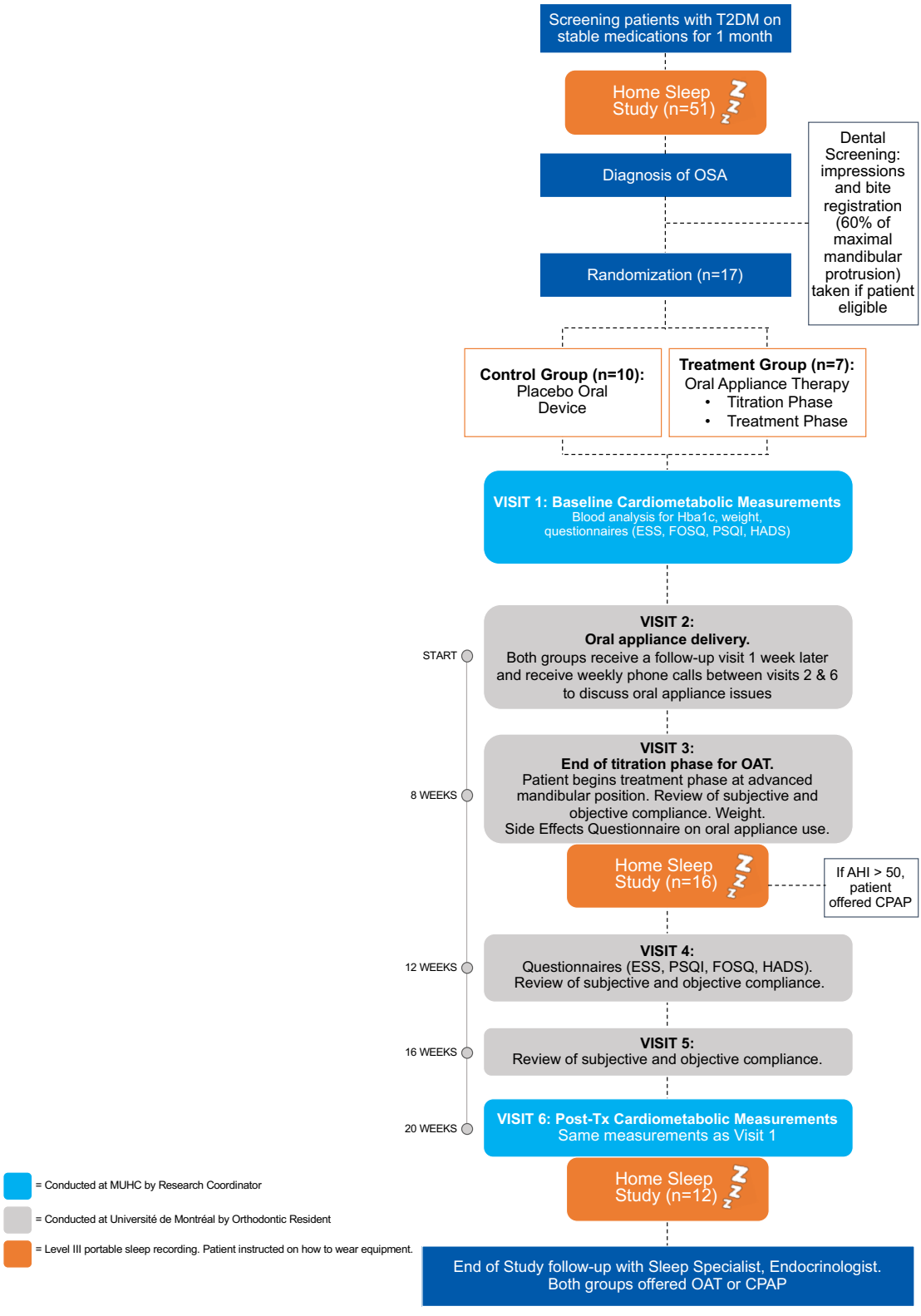

Figure 6. Overview of the study visits.

Statistical analysis

The Redcap program was used to record data entry; Redcap is a secure online system which allows access to its data by research members only. All patient information was coded numerically to prevent patient identification.

Data was analysed using SPSS and SAS by an experienced statistician. Normality of distribution was assessed by the Kolmogorov-Smirnov Test. T-tests and Fisher's exact tests were then used to compare baseline values for both groups. In order to evaluate the following questionnaires: PSQI, FOSQ ESS, HADS, polysomnographic data and Hba1c levels, Mixed Models using Type 3 Tests of Fixed Effects and Differences of Least Squares Means were used to compare the effect of time on appliance use in both placebo and MAD groups. Fisher's exact tests were used to compare Side Effects Questionnaires for both groups. T-tests and Fisher's exact tests were used to compare objective and subjective compliance.

Results

Patient description

17 patients were included in this sub-study; 10 were randomized to the placebo group, and 7 were randomized to the MAD group. All participants consented to participate in the study. Patient flowchart is illustrated in Figure 7.

Partial results are missing due to the following reasons:

- 1 MAD patient still in progress: results taken up to Visit 5
- 2 Placebo patients still in progress: results taken up to Visit 5 and Visit 3
- 1 Placebo patient drop out (no answer): results taken up to Visit 4
- 1 Placebo patient experienced a recoding error during sleep study at Visit 3. The patient refused to repeat this PSG, and also refused to do Visit 6 PSG.

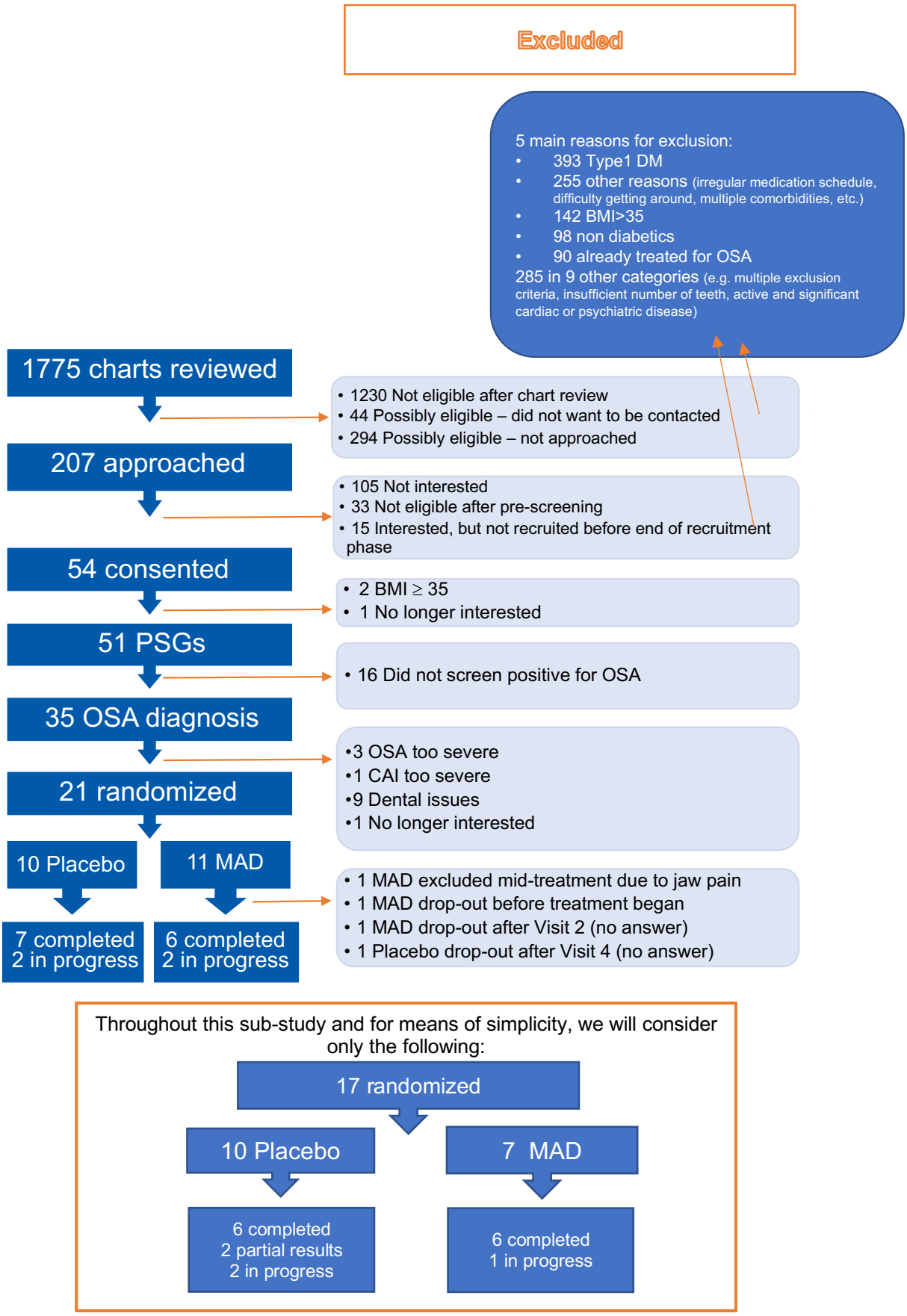

Figure 7. Patient flow chart.

Sociodemographic data

The placebo group (n=10) consisted of 7 males and 3 females; The MAD group (n=7) consisted of 5 males and 2 females. There was no significant sex difference between the groups (p=1.00, Fisher's exact test), see Table 6.

Mean age at the beginning of the study was 64.50 ± 9.70 years in the placebo group, ranging from 46.90 years to 77.80 years of age. In the MAD group, mean age at the beginning of the study was 62.27 ± 10.99 and ranged from 43.30 years to 76.50 years. There was no age difference between groups (p=0.66, t-test), see Table 6.

In the Placebo group, different ethnicities consisted of 5 Caucasians, 2 Asians, 1 African American, and 2 of other background (South Asian and Indian). In the MAD group, different ethnicities consisted of 6 Caucasians and 1 Asian. There was no significant ethnic difference between groups (p=0.66, Fisher's exact test), see Table 6.

BMI was calculated by dividing weight (measured in kilograms) by the height squared (measured in meters). Mean initial BMI was 29.37 ± 3.17 kg/m^2 in the Placebo group, ranging from 23.68 to 33.32 kg/m^2 and in the MAD group, mean initial BMI was 27.92 ± 3.75 kg/m^2 ranging from 22.78 to 33.57 kg/m^2. There was no difference between groups for BMI (p=0.40, t-test), see Table 6.

Mean initial AHI in the Placebo group was 21.00 ± 11.78 events/hour, ranging from 5.00 to 49.50. In the MAD group, mean initial AHI was 24.13 ± 11.97 events/hour, ranging from 11.10 to 43.60. There was no difference for initial AHI between groups (p=0.60, t-test), see Table 6.

Initial mean Hba1c in the Placebo group was 7.13 ± 0.96 %, ranging from 6.3 to 9.4% and in the MAD group, initial mean Hba1c was 7.33 ± 0.59 ranging from 6.7 to 8.3%. There was no difference between groups (p=0.64, t-test), see Table 6.

In the placebo group, mean number of medications was 5.30 ± 2.06, ranging from 2 to 9 per person. In the MAD group, mean number of medications was 7.29 ± 3.25 ranging from 4 to 12 per person. There was no difference between groups (p=0.14, t-test), see Table 6.

Comorbidities were classified and limited to the following categories: high blood pressure, high cholesterol, heart disease, and "other". The mean number of comorbidities in the Placebo group was 1.50 ± 1.18 ranging 0 to 3, and in the MAD group, 1.57 ± 0.79 ranging from 1 to 3. There was no difference between groups (p=0.89, t-test), see Table 6.

The number of years since Type II Diabetes Mellitus diagnosis was a mean of 12.25 ± 8.53 years, ranging from 2 to 26 years in the Placebo Group, and was 9.33 ± 5.01 years ranging from 3 to 15 years in the MAD group. There was no difference between groups (p=0.47, t-test), see Table 6.

	Placebo (n=10)	MAD (n=7)	p-value	Statistical test performed
Age (years)	64.56 ± 9.70	62.27 ± 10.99	0.66	T-test
Gender (n, %)				
Female	3, 30.00	2, 28.60	1.00	Fisher's exact test
Male	7, 70.00	5, 71.40	1.00	
Ethnicity (n, %)				
Caucasian	5, 50.00	6, 85.70	0.65	Fisher's exact test
Asian	2, 20.00	1, 14.30		
African American	1, 10.00	0, 0.00		
Other	2, 20.00	0, 0.00		
BMI (kg/m^2)	29.37 ± 3.17	27.92 ± 3.75	0.40	T-test
AHI (events/hour)	21.00 ± 11.78	24.13 ± 11.97	0.60	T-test
Hba1c ratio (%)	7.13 ± 0.96	7.33 ± 0.59	0.64	T-test
Number of medications	5.30 ± 2.06	7.29 ± 3.251	0.14	T-test
Number of comorbidities	1.50 ± 1.18	1.57 ± 0.79	0.89	T-test
Number of years since T2DM diagnosis	12.25 ± 8.53	9.33 ± 5.01	0.47	T-test

Table 6: Average initial study sample characteristics.

Legend: Mean ± SD

BMI: Body mass index

AHI: Apnea-hypopnea Index

Hba1c ratio: Glycated hemoglobin ratio, indicates glucose control over the past 2-3 months

Number of Comorbidities: limited to high blood pressure, high cholesterol, heart disease and "other"

Facial and intraoral characteristics:

Facial profiles, maxillary and mandibular characteristics, and modified Mallampati scores were assessed at baseline. Fisher's exact test found no significant difference between groups. See Table 7 for details.

	Placebo (n=10)	MAD (n=7)	p-value
Facial profile (n, %)			
Straight	4, 40.00	1, 14.30	0.34
Convex	6, 60.00	6, 85.70	
Concave	0, 0.00	0, 0.00	
Maxilla (n, %)			
Normal	7, 70.00	7, 100.00	0.23
Retrusive	3, 30.00	0, 0.00	
Protrusive	0, 0.00	0, 0.00	
Narrow	2, 20.00	2, 28.60	1.00
Mandible (n, %)			
Normal	4, 40.00	1, 14.30	0.42
Retrusive	5, 50.00	6, 85.70	
Protrusive	1, 10.00	0, 0.00	
Modified Mallampati (n, %)			
I	2, 20.00	2, 28.60	0.40
II	8, 80.00	4, 57.10	
III	0, 0.00	1, 14.30	

Table 7: Facial and oral characteristics.

Legend: n, % of patients

Statistical test performed was the Fisher's exact test

Polysomnographic data

The following table (Table 8) describes polysomnographic data recorded at Visits 1 (baseline), 3, and 6. Statistical tests were used to compare the effect of time in both groups. Significant decreases in AHI (p=0.002, Mixed Models of Type 3 Tests of Fixed Effects) and ODI (p=0.002, Mixed Models of Type 3 Tests of Fixed Effects) were found in the MAD group alone. No significant changes were found for the Placebo group, nor for CAI in both groups. No patients had sustained SpO_2 below 90% for over 10% of the night. See Figure 8 for illustrated changes in AHI and ODI comparing MAD and Placebo groups.

Appliance	Placebo			p-value	MAD			p-value
Visit	V1 (n=9)	V3 (n=9)	V6 (n=6)		V1 (n=7)	V3 (n=7)	V6 (n=6)	
AHI (events/hour)	21.66 ± 12.30	23.17 ± 15.03	23.50 ± 15.64	0.86	24.13 ± 11.97	13.87 ± 12.32	8.83 ± 5.93	**0.002**
ODI	19.29 ± 9.70	23.28 ± 15.07	20.13 ± 14.40	0.51	24.23 ± 12.57	13.67 ± 12.67	8.70 ± 6.41	**0.002**
CAI	1.09 ± 1.48	1.80 ± 2.58	0.50 ± 0.35	0.61	0.66 ± 0.57	0.61 ± 0.47	0.77 ± 0.73	0.61
Sustained SpO_2 below 90% for over 10% of night	0.00	0.00	0.00	1.00	0.00	0.00	0.00	1.00

Table 8A: Effects of appliance use on sleep variables.

Appliance	Placebo	MAD
AHI (events/hour)	1.84	-15.30

Table 8B: Difference in AHI pre- and post-appliance.

Legend: Mean ± SD
Placebo: Mandibular Essix device
MAD: Mandibular Advancement Device
AHI: Apnea-hypopnea Index
ODI: Oxygen desaturation Index
CAI: Central apnea Index
SpO_2: Peripheral oxygen saturation
Mixed Models of Type 3 Tests of Fixed Effects were used to compare the effect of time in each group
Statistically significant values are in bold
Table 8B: Positive value indicates an increase in AHI, negative value indicates a reduction in AHI

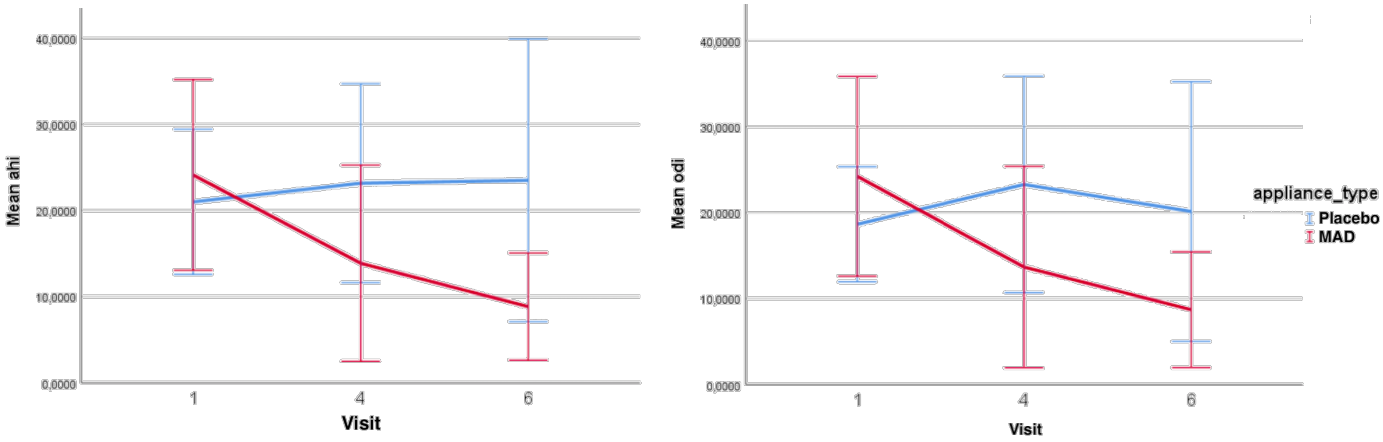

Figure 8. Changes in mean AHI and ODI throughout Visits 1, 4, 6.

Legend: Mean values depicted
AHI: Apnea-hypopnea Index
ODI: Oxygen desaturation Index
Placebo: Mandibular Essix device
MAD: Mandibular Advancement Device

Questionnaire data

The following tables summarize mean scores obtained in all sleep questionnaires (PSQI, ESS, FOSQ) and quality of life questionnaire (HADS) for Visits 1, 4, and 6 (access to complete questionnaires is available in section Annexe - Questionnaires).

The following table (Table 9) shows that when Type 3 Tests of Fixed Effects were performed, p-values generated from the interaction of time and appliance type did not show any significant differences for any of the questionnaires (PSQI p=0.48, ESS p=0.46, FOSQ p=0.62, Anxiety p=0.24, Depression p=0.80).

However, in Table 10, when Differences of Least Squares Means were performed to compare the effect of time on both appliance types between Visits 1 and 4, and Visits 1 and 6, **both groups** showed significant improvements in FOSQ scores (p=0.004 between V1-4, and p=0.026 between V1-6), significant decreases in ESS (p= 0.023 between V1-4), significant decreases in Anxiety scores (p=0.003 between V1-4, and p=0.041 between V1-6), as well as a significant decrease in Depression scores (p=0.025 between V1-6). No significant differences were found for PSQI scores.

Questionnaire	Placebo			MAD			p-value
	Visit 1 (n=9)	Visit 4 (n=9)	Visit 6 (n=7)	Visit 1 (n=7)	Visit 4 (n=7)	Visit 6 (n=6)	
PSQI	6.44 ± 3.28	5.44 ± 3.09	6.14 ± 3.53	5.86 ± 2.55	5.57 ± 1.27	4.83 ± 1.72	0.58♣ 0.54♠ 0.48♦
ESS	8.44 ± 4.45	5.44 ± 1.89	7.14 ± 3.24	6.86 ± 2.91	5.71 ± 2.50	5.17 ± 0.98	0.40♣ 0.06♠ 0.46♦
FOSQ	17.57 ± 1.94	19.00 ± 0.66	18.22 ± 1.74	17.79 ± 1.81	18.91 ± 0.79	19.11 ± 0.78	0.61♣ **0.01**♠ 0.62♦
HADS							
• Anxiety	7.00 ± 2.83	3.33 ± 2.74	5.14 ± 4.14	4.57 ± 2.70	3.29 ± 2.56	2.83 ± 2.93	0.21♣ **0.01**♠ 0.24♦
• Depression	4.33 ± 2.96	3.22 ± 3.03	3.29 ± 4.15	2.29 ± 1.50	1.86 ± 1.35	1.00 ± 1.27	0.19♣ 0.07♠ 0.80♦

Table 9: Effect of appliance use on sleep and quality of life questionnaires.

Legend: Mean score ± SD
Placebo: Mandibular Essix device
MAD: Mandibular Advancement Device
PSQI: Pittsburgh Sleep Quality Index
ESS: Epworth Sleepiness Scale
FOSQ: Functional Outcome of Sleep Questionnaire
HADS: Hospital Anxiety and Depression Scale
Statistical analysis was performed using Type 3 test of Fixed Effects
♣ p-value for the effect of appliance type
♠p-value for the effect of time
♦ p-value for the effect of appliance type * time
Statistically significant p-values are in bold

Questionnaire	Placebo		MAD		P Value
	Visit 1 (n=9)	Visit 4 (n=9)	Visit 1 (n=7)	Visit 4 (n=7)	
PSQI	6.44 ± 3.28	5.44 ± 3.09	5.86 ± 2.55	5.57 ± 1.27	0.33
ESS	8.44 ± 4.45	5.44 ± 1.89	6.86 ± 2.91	5.71 ± 2.50	**0.023**
FOSQ	17.57 ± 1.94	19.00 ± 0.66	17.79 ± 1.81	18.91 ± 0.79	**0.004**
HADS					
• Anxiety	7.00 ± 2.83	3.33 ± 2.74	4.57 ± 2.70	3.29 ± 2.56	**0.003**
• Depression	4.33 ± 2.96	3.22 ± 3.03	2.29 ± 1.50	1.86 ± 1.35	0.144
Questionnaire	Placebo		MAD		P Value
	Visit 1 (n=9)	Visit 6 (n=7)	Visit 1 (n=7)	Visit 6 (n=6)	
PSQI	6.44 ± 3.28	6.14 ± 3.53	5.86 ± 2.55	4.83 ± 1.72	0.37
ESS	8.44 ± 4.45	7.14 ± 3.24	6.86 ± 2.91	5.17 ± 0.98	0.078
FOSQ	17.57 ± 1.94	18.22 ± 1.74	17.79 ± 1.81	19.11 ± 0.78	**0.026**
HADS					
• Anxiety	7.00 ± 2.83	5.14 ± 4.14	4.57 ± 2.70	2.83 ± 2.93	**0.041**
• Depression	4.33 ± 2.96	3.29 ± 4.15	2.29 ± 1.50	1.00 ± 1.27	**0.025**

Table 10: Effect of appliance use on sleep and quality of life questionnaires.

Legend: Mean score ± SD
Placebo: Mandibular Essix device
MAD: Mandibular Advancement Device
PSQI: Pittsburgh Sleep Quality Index
ESS: Epworth Sleepiness Scale
FOSQ: Functional Outcome of Sleep Questionnaire
HADS: Hospital Anxiety and Depression Scale
Statistical analysis was performed using the Differences of Least Squares Means
Statistically significant values are in bold

Compliance data

The following table (Table 11) compares objective compliance which was recorded by the microchips embedded in each device and subjective compliance which was recorded by each patient in a daily log (Annex – Material given to participant). A significant difference was found when using paired T-tests between the following items in the MAD group: D) average use on treated days ($p=0.03$), E) average use on days worn (**(**$p=0.02$) and G) usual compliance (days worn ≥4 hours / days worn) ($p=0.005$), showing us that subjective compliance was over-reported within the MAD group. A tendency towards this same trend is also visible in the Placebo group, however not statistically significant.

Table 11 also compares objective compliance between MAD and Placebo devices. When comparing the number and percentage of people who were considered regular users described as an average of ≥4 hours use on the nights that the appliance was worn and for at least 70% of the treatment period (69), and patients who were described as frequent users and having an average use of ≥4 hours on total treated days being for at least 70% of the treatment period (70), Fisher's exact tests found no significant difference between groups ($p=0.59$ for both regular and frequent user classifications). Also, independent t-tests found no significant difference between any other objective compliance values, indicating similar patient compliance with both devices (see Table 11 for details).

	Placebo (n=10)		P-value	MAD (n=7)		P-value	Placebo (n=10)	MAD (n=7)	P-value
	Objective compliance	Subjective compliance		Objective compliance	Subjective compliance		Objective compliance	Objective compliance	
A) Regular user* (n, % yes)	8 (80.00)	8 (80.00)	1.00□	4 (57.10)	5 (71.40)	1.00□	8 (80.00)	4 (57.10)	0.59≈
B) Frequent user** (n, % yes)	8 (80.00)	8 (80.00)	1.00□	4 (57.10)	5 (71.40)	1.00□	8 (80.00)	4 (57.10)	0.59≈
C) % of days worn (days worn/days treated)	77.44 ± 24.94	82.11 ± 25.63	0.10•	77.69 ± 22.68	84.64 ± 17.76	0.14•	77.44 ± 24.94	77.69 ± 22.68	0.98◊
D) Average use on treated days (hours of use / days treated)	5.89 ± 2.43	6.51 ± 2.42	0.08•	5.56 ± 1.92	6.55 ± 1.77	**0.03**•	5.89 ± 2.43	5.56 ± 1.92	0.77◊
E) Average use on days worn (hours of use / days worn)	7.45 ± 1.36	7.95 ± 1.35	0.08•	7.04 ± 0.57	7.64 ± 0.63	**0.02**•	7.45 ± 1.36	7.04 ± 0.57	0.41◊
F) Everyday compliance, % (days worn ≥4 hours / days treated)	75.49 ± 25.88	81.39 ± 25.58	0.06•	74.14 ± 23.36	83.59 ± 18.56	0.06•	75.49 ± 25.88	74.14 ± 23.36	0.91◊
G) Usual compliance, % (days worn ≥4 hours / days worn)	96.31 ± 4.78	99.10 ± 1.33	0.10•	94.13 ± 3.93	98.50 ± 2.16	**0.005**•	96.31 ± 4.78	94.13 ± 3.93	0.34◊

Table 11: Comparison of objective and subjective compliance.

Legend: Mean ± SD
Placebo: Mandibular Essix device
MAD: Mandibular Advancement Device
□ McNemar test was performed
≈ Fisher's exact test was performed
• Paired t-test was performed
◊ Independent t-test was performed
***** Regular user: described as an average of ≥4 hours use on the nights that the appliance is worn and for at least 70% of the treatment period. (Kribbs 1993 Am Rev Resp Dis)
****** Frequent user: described as an average use of ≥4 hours on total treated days being for at least 70% of the treatment period (Pepin 1999 Am J Crit Care Med)

Patient satisfaction and frequency of complications

Patient satisfaction and frequency of complications were evaluated in the Side Effects questionnaire answered by all patients at Visit 3 (Annex - Questionnaires). The following table (Table 12) summarizes the descriptive data answered by patients in each group.

Variable	Placebo (n=10)	MAD (n=7)
Patient satisfaction (n, %)		
Very satisfied	3 (30.00)	4 (57.10)
Moderately satisfied	6 (60.00)	2 (28.60)
Moderately dissatisfied	0 (0.00)	1 (14.30)
Very dissatisfied	1 (10.00)	0 (0.00)
Frequency of complications (%)		
None	7 (70.00)	5 (71.40)
Less than once a month	2 (20.00)	0 (0.00)
Once a month	0 (0.00)	1 (14.30)
Every second week	0 (0.00)	1 (14.30)
1 to 3 times a week	1 (10.00)	0 (0.00)

Table 12: Descriptive data for patient satisfaction and frequency of complications.

Legend: n (%)
Placebo: Mandibular Essix device
MAD: Mandibular Advancement Device

In order to simplify statistical analysis, patients were divided amongst the following groups (see Figure 9 for illustrated results). Groups consisted of “satisfied” (including very and moderately satisfied) and “dissatisfied” (including moderately and very dissatisfied) to evaluate their satisfaction on a “yes” or “no” basis. The same was done in order to evaluate frequency of complications by categorizing patients into three groups: “none”, “infrequent” which included complications occurring once a month and less than once a month, and “frequent” including complications occurring every second week and one to three times a week. No significant differences were found between groups using Fisher’s exact tests (p=1.00 for both patient satisfaction and frequency of complications).

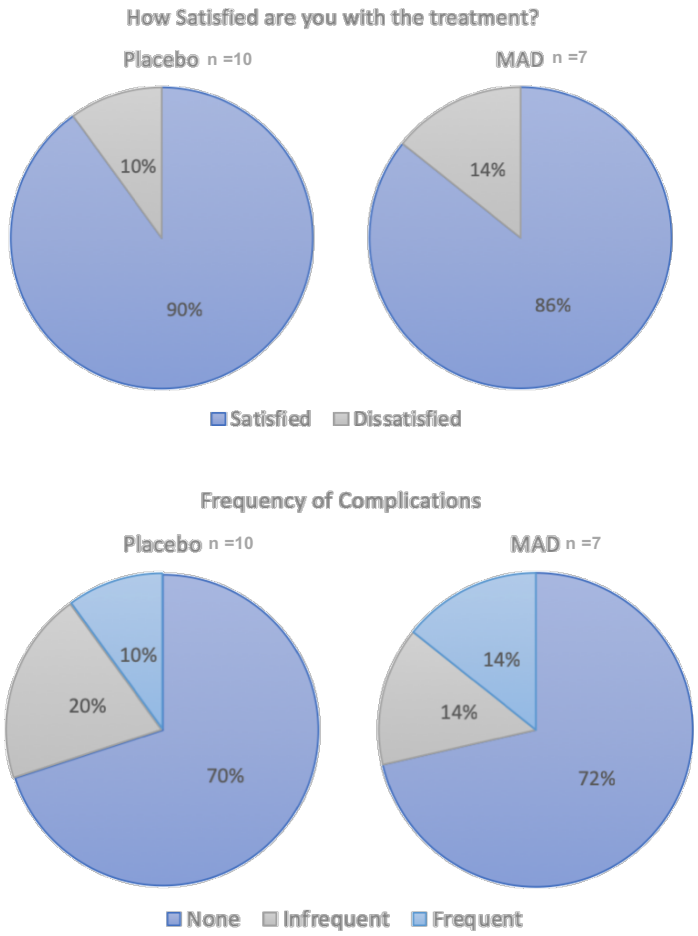

Figure 9. Patient satisfaction and frequency of complications for both groups.

Legend: Percentage of patients depicted
Placebo: Mandibular Essix device
MAD: Mandibular Advancement Device

Appliance side effects

Side effects felt by patients during appliance use were evaluated in the Side Effects questionnaire answered at Visit 3 (Annex – Questionnaires). The following table (Table 13) compares the number and percentage of patients who described the following effects as being present either: often but hardly disturbing, often and disturbing, and always strongly disturbing. Using Fisher's exact test, no significant differences were found between groups. The most frequently reported side effect was dryness of mouth by 40% of Placebo group patients and 57.1% of MAD group patients (p=0.64).

Treatment side effects (n, %)	Placebo (n=10)	MAD (n=7)	p-value
Dryness of mouth	4 (40.00)	4 (57.10)	0.64
Discomfort or pain in teeth	0 (0.00)	2 (28.60)	0.15
Discomfort or pain in jaws	0 (0.00)	2 (28.60)	0.15
Bite changes	0 (0.00)	1 (14.30)	0.41
Increased awakening with appliance	1 (10.00)	1 (14.30)	1.00
Discomfort caused by bulkiness of appliance	0 (0.00)	1 (14.30)	0.41

Table 13: Comparison of side effects felt with use of both devices.

Legend: n (%) of patients who described the listed side effects as being present: often but were hardly disturbing, often and disturbing, and always strongly disturbing.
Placebo: Mandibular Essix device
MAD: Mandibular Advancement Device
Statistical analysis was performed using Fisher's exact test.

Glycated hemoglobin

The following table (Table 14) shows the mean Hba1c Ratio for each group; Hba1c ratios were measured before and after treatment at Visits 1 and 6. Although Hba1c levels decreased by 0.09% for the MAD group and by only 0.03% in the Placebo group, no significant difference was found in either group (p=0.75) using Type 3 Tests of Fixed Effects evaluating the effect of appliance type * time.

If we were to assume a change in Hba1c levels of 0.1% for the MAD, and no change for the Placebo device, with standard deviations of 0.514 and 0.583 respectively, the study would

need 103 participants per group in order to have a power of 80% for an alpha of 0.05, using a t-test for two independent groups.

Appliance type	Visit 1 Hba1c	Visit 6 Hba1c	p-value
Placebo (n=7)	7.00 ± 0.59	6.97 ± 0.59	0.75
MAD (n=6)	7.17 ± 0.45	7.08 ± 0.62	

Table 14: Effect of appliance use on Hba1c Ratio.

Legend: Mean ± SD
Hba1c ratio: Glycated hemoglobin ratio, indicates glucose control over the past 2-3 months
Placebo : Mandibular Essix device
MAD: mandibular advancement device
Type 3 Tests of Fixed Effects evaluating the effect of appliance type * time

Discussion

Our study demonstrated that the use of MADs was able to significantly reduce OSA severity when compared to the Placebo device. Fifty percent of patients in the MAD group were considered complete responders after Visit 6 (achieved an AHI <5), and 33% of patients in the MAD group were considered partial responders (achieved an AHI <15 or >50% reduction of baseline AHI). For the MAD group, initial mean AHI was 24.13 events/hour, which was reduced to a mean of 8.83 events/hour, bringing OSA from the moderate category to the light category after three months of treatment. Overall, mean AHI was reduced about 63.41% or by 15.30 events/hour. Previous studies have shown MADs being able to reduce AHI anywhere between 30-72%, and successful treatment is usually described as reducing AHI to a target ≤5–10 events/hour or by 50% or more (71). Results from our study fall within this category and the treatment provided by MAD can therefore be considered a success.

Two patients in the MAD group were considered non-responders; the first patient had his AHI increase by 0.7 events/hour after Visit 3, and the second patient was considered a partial responder after Visit 3, however fell into the non-responder category after Visit 6 with an AHI slightly above the partial responder limit (15.4 events/hour). Non-response may be caused by certain anatomical factors in the airway that could not have been identified prior to beginning the study. No factors for predicting successful or unsuccessful treatment outcomes could be

identified after correlation tests were performed to evaluate changes in AHI after treatment and comparing them with initial OSA severity, modified Mallampati scores, BMI or amount of mandibular protrusion achieved by the end of the 3-month treatment period.

In terms of objective compliance for the MAD, we found that mean use on days worn was 7.04 ± 0.57 hours/day, and no significant difference was found when compared to the Placebo device (7.45 ± 1.36 hours/day). Our overall objective compliance is comparable to that of MADs used in a study by Vanderveken et al. (72), who also used a microchip to record compliance; they reported a mean use of 6.6 ± 1.3 hours/day. When evaluating if patients were both regular and frequent users, Vanderveken's study found that 82% of their patients were considered regular users and 79% were considered frequent users of the MAD; Our study found that only 57.10% of MAD patients vs. 80% of Placebo patients were both regular and frequent users. Although the percentage of frequent and regular uses in our MAD group is smaller than that found in Vanderveken's study, the majority of our MAD patients still fall within these categories and compliance on the nights when the device was worn was good.

When it comes to CPAP therapy, findings for objective compliance are so variable amongst studies, ranging from 46% to 80% of patients using it for a minimum of 4 hours per night (70); it is therefore difficult to accurately compare compliance rates to that of MADs. However, in a study reviewing CPAP compliance in the T2DM population, average CPAP use was only ∼5 hours/day (60); mean nightly compliance with MAD in our study was at least higher than that. Considering the significant and successful reduction in AHI that our MAD had after 3 months of treatment, as well as a good overall objective compliance, we consider the MAD to be a feasible treatment option for OSA in patients with T2DM.

Our Placebo device had an insignificant mean increase of 1.84 events/hour. This falls within the normal range of minor differences in PSG results which can be expected from night to night variations. Interestingly enough, results from placebo groups in other randomized and controlled trials using oral appliances to treat sleep apnea are inconsistent, and devices often vary in design. In a controlled study performed by Duran-Cantolla et al. (73), a mandibular occlusal splint was used as their placebo device, and a mean significant increase in AHI of 10.6 ±26.1 events/hour was discovered in this group. Also, in a study performed by Gagnon et al.

(74), it was found that a maxillary occlusal splint significantly increased AHI by over 50% in half of patients. On the other hand, another study by Aarab et al. (75) found a small yet significant decrease in AHI with their maxillary placebo device. In our study, only one patient in the Placebo group had an increase in AHI over 50% after Visit 3, however, her AHI was found to have decreased by 2 events/hour compared to initial AHI after Visit 6. While reviewing the literature on controlled studies using oral appliance therapy treating OSA, placebo devices are not always precisely described in terms of size or material; this information is important considering the different effects the placebo device may have on OSA. Considering the importance of having controlled studies, future research should be sure to include this information in their articles. Our Placebo device had minimal overall effects on PSG results, as well as minimal undesirable side effects and good compliance; it was also easy to integrate a compliance-monitoring microchip to it. We consider our Essix®-type appliance an acceptable Placebo device for future controlled studies.

Although undesirable side effects in our study were slightly more reported by participants in the MAD group, they were still minimal and not significantly different than those experienced with the Placebo device. A study by Fritsch et al. (76) found that side effects with MADs were frequent but only mildly disturbing when measured after 14 months of treatment: dryness of mouth was experienced in 86% of patients, discomfort in teeth by 59%, jaw pain in 40% and hypersalivation in 55% of patients. When compared to our MAD group, we found less dryness of mouth (57.1%), less discomfort in teeth (28.6%), less jaw pain (28.6%), and less hypersalivation (0%). This could be explained by the fact that our side-effects questionnaire was administered after only a 2-month titration period, however, the literature describes these "short-term" side effects as being most frequent during the first month of treatment and then tend to decrease with time (77). When looking at more "long-term" side effects which are possible with MAD use, such as occlusal changes, these were present in 32% of patients after 14 months of treatment in Fritsch's study (76), as opposed to only 14.3% of our patients after the 2-month titration period. Unfortunately, research has shown that subjective awareness of changes in occlusion is low and may not be the most accurate or reliable way to detect these issues (78). Monitoring changes in occlusion with model or intra-oral scanning would be a more precise

way of evaluating this side effect, and it would be interesting to perform a future long-term study evaluating potential changes in occlusion in the diabetic population.

In our study, patient satisfaction with both MAD and Placebo devices were high, being 86% and 90% respectively. Research by Ferguson et al. (77) compared treatment satisfaction rates for CPAP use and MAD use; after a 4-month treatment period, 80% of MAD patients were satisfied with treatment versus 70% of CPAP patients. Our satisfaction rate for MAD use was higher than both those found for MAD and CPAP in Ferguson's study. Patient satisfaction might be based on several different factors which differ from patient to patient. A qualitative study (54) showed that a patient's experience with OSA treatment is not only based on physical aspects of the device, but also depends on their lifestyle needs. Some of the most important factors that impact treatment preference are device effectiveness, its ability to be transported, potential embarrassment with device use, and cost. Physicians should be considerate of patient's preferences in order to select the most appropriate treatment option for them and hopefully increase their compliance and overall satisfaction.

When evaluating sleep and quality of life questionnaires, our study found that both appliances had significant improvements in ESS, FOSQ, Anxiety, and Depression questionnaires; no significant changes in PSQI were reported. A study by Godoy et al. (79) comparing 1.5 years of treatment with MAD and a Placebo device found similar results to our study, such as improvements in FOSQ for both devices and Beck's Depression scores for their MAD. However, they reported no significant changes in ESS for either device, nor changes in Beck's Anxiety scores; they also found that PSQI was improved in both groups.

When looking at our ESS scores, MAD had a mean reduction of 1.69, and 1.30 for the Placebo device after 3 months of treatment. In a study by Barnes et al. (80) comparing CPAP, MAD and a Placebo device, comparable results to our study were found: both MAD and CPAP significantly reduced mean ESS score by 1.5; however, the Placebo device insignificantly reduced mean scores by 0.5. Interestingly, our study demonstrates a "placebo effect" in terms of improving daytime sleepiness, anxiety and depression, an effect that is not consistently shown in other controlled studies ((71), (73)). On the other hand, a study performed by Aarab et al. (75) showed equal efficacy between CPAP, MAD and a Placebo device to reduce psychological distress, including depression and anxiety after 6 months of treatment. The "placebo effect" can

therefore not be neglected, and it is important for any larger scale research to consider incorporating control groups to their studies. It would also be interesting to evaluate the impact of sleep hygiene advice on patients' responses to these questionnaires by including a second control group which would only receive life style coaching for example, without use of a device.

No significant improvements in Hba1c were found with the MAD or Placebo device; In fact, mean reduction of Hba1c in the MAD group was 0.09%, and 0.03% in the Placebo group. Although insignificant, the slight decrease in both groups re-enforces the importance of randomized and controlled trials. A study analysing the effects of three months of using a MAD on glycemic control was recently published (81); it was a small non-controlled study with 24 subjects divided in to three groups of patients with: 1- light OSA (n=8), 2- moderate OSA (n=8), and 3- severe OSA (n=8). They found a significant decrease of 0.9% in Hba1c for patients with light OSA, a significant decrease of 0.7% in Hba1c in patients with moderate OSA, and no significant decrease of 0.05% in Hba1c in patients with severe OSA. Initial mean Hba1c levels in their study were slightly lower than those found in our study, and patients were limited to taking only oral anti-diabetic medication. This may be a potential indicator of better-controlled diabetes in their patient population, perhaps leading to better metabolic outcomes in response to OSA treatment. Their study also does not measure objective or subjective compliance, making it impossible to know if improvements in Hba1c are truly related to appliance use. Aside from lacking a control group, their study also fails to measure (or at least report) changes in BMI and lifestyle over the course of treatment, obvious and important influences on glycemic control. On the other hand, our study reported no significant changes in BMI between visits. Despite our results not showing any significant improvements in Hba1c, results from studies using CPAP treatment ((59), (61), (62)) still offer convincing evidence that MADs with adequate compliance can yield positive cardiometabolic outcomes in the T2DM population. A patient's metabolic phenotype and their medication regimen may affect the way they respond to OSA treatment and require further investigation as they may impact the success rate in improving glycemic control (60).

Our study also found a significant difference between several markers of objective and subjective compliance in the MAD group, as well as the tendency towards this same trend in the Placebo group. Fewer studies measuring objective compliance in MADs exist, as microchip

technology for compliance measurement is newer than it is for CPAP therapy. Contrary to our results, most current studies using microchips in MADs show a high agreement between subjective and objective compliance (82) (72), while other studies performed with CPAP show similar discrepancies to those found in our study (83). The difference between mean number of hours of objective (7.64 hours/day) and subjective compliance (7.04 hours/day) was 0.6 hours, or 36 minutes; although statistically significant, this may not seem like a very large difference. In CPAP studies finding a difference in objective and subjective compliance, difference in time reported was closer to an hour (83). In our opinion, the microchip however remains an accurate tool to record compliance and relieves the patient from having to keep a nightly log of their use. Also, when measuring specific health outcomes in a research or clinical setting, it is essential to closely monitor patient compliance to be able to evaluate the actual effect of treatment. Microchips are reliable, small additions to oral appliances with minimal risks to the patient, and also serve as a way for clinicians to investigate reasons for poor compliance if present (72). Furthermore, in our study, "bulkiness" of the appliance was only reported by one patient in the MAD group and by none in the Placebo group; whether this bulkiness was related or not to the microchip or the additional acrylic needed to embed it in the appliance seems to have a minimal impact on patient comfort and satisfaction.

A major limitation of this study is its small sample size due to the rigorous exclusion criteria that we had. Initially, we aimed to include patients who were on stable medication for three months prior to beginning the study, however, this was excessively difficult and hindered patient recruitment. We then decided to accept a one month period of stable medication prior to beginning the study; it still presented a challenge to have patients remain on their same medication throughout the next 5-6 months until completion of the project. The length and multiple visits of the study also seem to be discouraging factors for patients to want to participate. Also, dental issues in an aging diabetic population such as uncontrolled periodontitis, excessive tooth mobility, partial edentulism, active dental infections and the need for important tooth reconstruction were some of the main dental reasons contributing to patient exclusion. Another limitation of this study was objective compliance in the MAD group which could have been better; although it was good, only 57.1% were considered to be regular and frequent users of the appliance. Some of the main reasons for not wearing the MAD more

frequently were travelling, busy schedules, or having a cold for an extended period of time. Obviously, some of these issues are inevitable over a period of 5-6 months, and having a larger sample size would have helped minimize the impact of irregular MAD use in this group. As mentioned previously, another limitation of this project is the lack of objective evaluation of occlusal changes. Using an intraoral scanner to compare occlusion at three times (before, after two months of titration, and after three months of treatment) would have been interesting to see how early occlusal changes may begin to appear with MAD use in the diabetic population. It would also be interesting to have another control group of non-diabetic patients using the same MAD in order to assess any differences in rapidity or severity in occlusal changes between groups.

Conclusion

The results from this study indicate that the MAD is a feasible form of treatment for OSA in patients with T2DM patients, yielding significant reductions in polysomnographic readings and good compliance rates. This study also validated our Placebo device, which showed favorable responses to sleep questionnaires, had minimal overall effects on OSA, minimal undesirable side effects as well as good compliance; It was also easy to integrate a compliance-monitoring microchip to it. We consider our Essix®-type appliance an acceptable Placebo device for future controlled studies.

Although this study did not find any significant improvements in Hba1c levels, we cannot conclude that OSA treatment would have no impact on glycemic and other cardiometabolic outcomes in the T2DM population due to the very small size of this pilot study. Further large-scale, randomized controlled trials are required. Also, it is important to consider that a patient's metabolic phenotype and their medication regimen might affect the way they respond to OSA treatment; perhaps having less rigorous exclusion criteria and allowing a larger number of patients to be recruited would allow for different phenotype-categories or patient profiles to be analyzed and assess possible correlations with changes in glycemic control.

As the link between uncontrolled diabetes and periodontal disease is well established in the dental literature (84), it is important to thoroughly examine and ensure that patients' dentition and periodontium are in stable condition before beginning treatment. For this reason,

MADs are not suited for all T2DM patients with OSA; Clinicians must be especially careful when discussing OSA treatment options with their diabetic patients while ensuring they have the necessary access to a competent dental professional for both short and long term follow ups. Objective monitoring of occlusal changes with time in this population will be important and should be investigated in future large-scale studies.

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Annexe 1: Ethics Committee approvals

Université de Montréal

Comité d'éthique de la recherche en santé

30 janvier 2017

Objet: Approbation éthique – « L'effet des appareils d'avancé mandibulaire sur la santé métabolique chez les diabétiques de type II (The Effect of Oral Appliance Therapy on Cardiometabolic Outcomes in Patients with Type 2 Diabetes and Obstructive Sleep Apnea: A Multi-Centered Randomized Controlled Trial) »

Mme Nelly Huynh, Mme Émily Santini & Mme Andrée Montpetit,

Le Comité d'éthique de la recherche en santé (CERES) a étudié le projet de recherche susmentionné et a délivré le certificat d'éthique demandé suite à la satisfaction des exigences précédemment émises. Vous trouverez ci-joint une copie numérisée de votre certificat; copie également envoyée au Bureau Recherche-Développement-Valorisation.

Notez qu'il y apparaît une mention relative à un suivi annuel et que le certificat comporte une date de fin de validité. En effet, afin de répondre aux exigences éthiques en vigueur au Canada et à l'Université de Montréal, nous devons exercer un suivi annuel auprès des chercheurs et étudiants-chercheurs.

De manière à rendre ce processus le plus simple possible et afin d'en tirer pour tous le plus grand profit, nous avons élaboré un court questionnaire qui vous permettra à la fois de satisfaire aux exigences du suivi et de nous faire part de vos commentaires et de vos besoins en matière d'éthique en cours de recherche. Ce questionnaire de suivi devra être rempli annuellement jusqu'à la fin du projet et pourra nous être retourné par courriel. La validité de l'approbation éthique est conditionnelle à ce suivi. Sur réception du dernier rapport de suivi en fin de projet, votre dossier sera clos.

Il est entendu que cela ne modifie en rien l'obligation pour le chercheur, tel qu'indiqué sur le certificat d'éthique, de signaler au CERES tout incident grave dès qu'il survient ou de lui faire part de tout changement anticipé au protocole de recherche.

Nous vous prions d'agréer, Mesdames, l'expression de nos sentiments les meilleurs,

Dominique Langelier, présidente
Comité d'éthique de la recherche en santé (CERES)
Université de Montréal

DL/GP/gp
c.c. Gestion des certificats, BRDV
p.j. Certificat #17-003-CERES-P

adresse postale
C.P. 6128, succ. Centre-ville
Montréal QC H3C 3J7

3744 Jean-Brillant
4e étage, bur. 430-11
Montréal QC H3T 1P1

Téléphone : 514-343-6111 poste 2604
ceres@umontreal.ca
www.ceres.umontreal.ca

Centre universitaire de santé McGill | McGill University Health Centre

2016-12-22

Dr. Sushmita Pamidi
1001 Decarie Boulevard
Room B04.5243
Montreal, Quebec
H4A 3J1

c/o: Genevieve Tremblay

email: [redacted]

Re: REB Conditional Approval of a New Research Project **(OAT T2DM study / 2017-2769)**

"The Effect of Oral Appliance Therapy on Cardiometabolic Outcomes in Patients with Type 2 Diabetes and Obstructive Sleep Apnea: A Multi-Centered Randomized Controlled Trial"

Dear Dr. Pamidi,

Thank you for submitting your responses and corrections for the research project indicated above, as requested by the McGill University Health Centre (MUHC) Research Ethics Board (REB).

The MUHC REB, more precisely its Clinical Trials 2B Panel (CT2B) provided conditional approval for the research project at its full board meeting of 2016-10-19.

On 2016-12-21, Full Board review of your responses and corrections was provided by the MUHC REB. The research project was found to meet scientific and ethical standards for conduct at the MUHC.

The following documents were approved or acknowledged by the MUHC REB:

- Initial Submission Form (F11-6608)
- REB Conditions & PI Responses Form(s) (F20-9298)
-
    - Signed Commitment (2016-08-18)
    - Research Protocol (Version 2 2016-11-24)
    - Information and Consent Form (Version 2, 2016-12-07) in French and English
    - Study Flyer(Version 1 2016-09-28) in French and English
    - Study Timeline (Version 1 2016-09-29) in English
    - Continuous Glucose Monitor Picture
    - Continuous Glucose Measurement Instructions and Log(Version 1 2016-09-29) in English
    - Morning Survey Questionnaire (2008-06-03) in English
    - Functional Outcomes of Sleep Questionnaire (September 1996) in French and English
    - Pittsburgh Sleep Quality Questionnaire in French and English

- Epworth Sleepiness Scale (1990-97) in French and English
- Eating Well with Canada's Food Guide (Undated) in French and English
- Canadian Physical Activity Guidelines (Undated) in French and English
- Normal Sleep and Sleep Hygiene Guide (© 2004) in French and English
- Obstructive Sleep Apnea Guide (© 2004) in French and English)
- HO Timeline (Undated) in English
- Medtronic ipro2 Pictures (Undated)
- Pic Embletta (Undated)

This will be reported to the MUHC REB and will be entered accordingly into the minutes of the next CT2B meeting. Please be advised that you may only initiate the study after all required reviews and decisions are received and documented.

The approval of the research project is valid until 2017-12-21.

All research involving human subjects requires review at recurring intervals. To comply with the regulation for continuing review of at least once per year, it is the responsibility of the investigator to submit an *Annual Renewal Submission Form* (F9) to the REB prior to expiry. Please be advised that should be protocol reach its expiry before a Continuing review has been submitted, the data collected after the expiry date may not be considered valid. However, should the research conclude for any reason prior to approval expiry, you are required to submit a *Completion (End of Study) Report* (F10) to the board once the data analysis is complete to give an account of the study findings and publication status.

Furthermore, should any revision to the project or other development occur prior to the next continuing review, you must advise the REB without delay. Regulation does not permit initiation of a proposed study modification prior to its approval by the REB.

The MUHC REB is registered and works under the published guidelines of the *Tri-Council Policy Statement 2*, in compliance with the *Plan d'action ministériel en éthique de la recherche et en intégrité scientifique* (MSSS, 1998) and the *Food and Drugs Act* (2001.06.07), acting in conformity with standards set forth in the (US) *Code of Federal Regulations* governing human subjects research and functioning in a manner consistent with internationally accepted principles of good clinical practice.

We trust this will prove satisfactory to you. Thank you for your consideration in this matter.

Best Regards,

(s) Thomas Maniatis

Thomas Maniatis, **MD, CM, MSc (Bioethics), FACP, FRCPC**
Co-Chair MUHC-REB

Université de Montréal

N° de certificat
17-003-CERES-P

Comité d'éthique de la recherche en santé

CERTIFICAT D'APPROBATION ÉTHIQUE

Le Comité d'éthique de la recherche en santé (CERES), selon les procédures en vigueur, en vertu des documents qui lui ont été fournis, a examiné le projet de recherche suivant et conclu qu'il respecte les règles d'éthique énoncées dans la Politique sur la recherche avec des êtres humains *de l'Université de Montréal.*

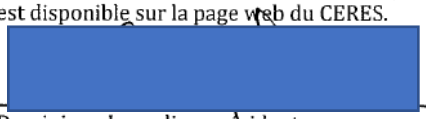
Projet	
Titre du projet	**L'effet des appareils d'avancé mandibulaire sur la santé métabolique chez les diabétiques de type II (The Effect of Oral Appliance Therapy on Cardiometabolic Outcomes in Patients with Type 2 Diabetes and Obstructive Sleep Apnea: A Multi-Centered Randomized Controlled Trial)**
Chercheuses requérantes	**Nelly Huynh** (92543), Professeure adjointe, Faculté de médecine dentaire - Département de santé buccale **Andrée Montpetit** (N.D.), Professeure adjointe, Faculté de médecine dentaire - Département de santé buccale **Émily Santini** (ND), Candidate à la M. Sc. en médecine dentaire, Faculté de médecine dentaire
Autres collaborateurs:	Sushmita Pamidi, John Kimoff & Mark Sherman (McGill), Fernanda Almeida, Najib Ayas & John Fleetham (UBC)
Financement	
Organisme	Non financé
Programme	
Titre de l'octroi si différent	
Numéro d'octroi	
Chercheur principal	
No de compte	

MODALITÉS D'APPLICATION

Tout changement anticipé au protocole de recherche doit être communiqué au CERES qui en évaluera l'impact au chapitre de l'éthique.

Toute interruption prématurée du projet ou tout incident grave doit être immédiatement signalé au CERES

Selon les règles universitaires en vigueur, un suivi annuel est minimalement exigé pour maintenir la validité de la présente approbation éthique, et ce, jusqu'à la fin du projet. Le questionnaire de suivi est disponible sur la page web du CERES.



Dominique Langelier, présidente
Comité d'éthique de la recherche en santé
Université de Montréal

30 janvier 2017
Date de délivrance

1er février 2018
Date de fin de validité

adresse postale
C.P. 6128, succ. Centre-ville
Montréal QC H3C 3J7

3744 Jean-Brillant
4e étage, bur. 430-11
Montréal QC H3T 1P1

Téléphone : 514-343-6111 poste 2604
ceres@umontreal.ca
www.ceres.umontreal.ca

Annexe 2: Information consent form

Centre universitaire de santé McGill

McGill University Health Centre

X HME MCH X HGM MGH X HRV RVH
X HNM MNH X ITM MCI X CL LC

INFORMATION AND CONSENT FORM

Research Study Title:	The Effect of Oral Appliance Therapy on Cardiometabolic Outcomes in Patients with Type 2 Diabetes and Obstructive Sleep Apnea: A Multi-Centered Randomized Controlled Trial
Researcher responsible for the research study:	Dr Sushmita Pamidi
Co-Investigator(s)/sites:	Montreal: Dr Nelly Huynh, Dr John Kimoff and Dr Mark Sherman Vancouver: Dr Fernanda Almeida, Dr Najib Ayas and Dr John Fleetham
Sponsor:	McGill University Health Centre – Research Institute Fonds de recherche du Québec – Santé (FRQS)

INTRODUCTION

We are inviting you to take part in this research study because you have been diagnosed with Type 2 diabetes (T2DM) and may be experiencing sleep apnea. Sleep apnea results in breathing pauses while you sleep and may result in a drop in blood oxygen levels and frequent awakenings during the night. Some studies show that sleep apnea may worsen diabetes. We want to test whether treatment of sleep apnea with an oral appliance improves blood glucose levels and overall health in patients with T2DM.

However, before you accept to take part in this study and sign this information and consent form, please take the time to read, understand and carefully examine the following information. You may also want to discuss this study with your family doctor, a family member or a close friend.

This form may contain words that you do not understand. We invite you to speak to the researcher responsible for this study (the "study doctor") or to other members of the research team, and ask them

to explain to you any word or information that is unclear to you before you sign this form.

BACKGROUND

Sleep apnea is quite common in individuals with T2DM, occurring in as many as eight out of ten people. The standard treatment for sleep apnea is with the use of a continuous positive airway pressure (CPAP) machine. The CPAP provides an air pressure to keep the airways opened during sleep so that a person with sleep apnea can breathe normally. When used appropriately, the CPAP improves sleepiness and quality of life. However, about half of the patients who receive a CPAP prescription cannot tolerate it and thus remain untreated and are potentially at increased risks of developing hypertension (high blood pressure) or diabetes or having a stroke. In light of this, this study aims to see if the use of an alternative treatment for sleep apnea, an oral appliance therapy, will improve blood sugar levels. An oral appliance is similar to a sports mouth guard or orthodontic retainer. Two different oral appliances will be used for this study: one that is made of two pieces that fit the top and bottom teeth (Figure 1) and one that is made of one piece that fits the upper teeth (Figure 2). Both are made by a dentist from a mold of the patients' dental impressions to specifically fit his mouth.

Figure 1

Figure 2

PURPOSE OF THE RESEARCH STUDY

The purpose of this study is to compare two different oral appliances to treat sleep apnea and see if they can help improve the levels of sugar in the blood and other aspects of diabetes health such as blood pressure, waist circumference and levels of fats in the blood.

For this research study, we will recruit a total of 120 participants; 60 at the McGill University Health Centre and 60 at the University of British Columbia Hospital, men and women, aged over 18 years old with T2DM.

DESCRIPTION OF THE RESEARCH PROCEDURES

This research study will take place at the Glen site of the McGill University Health Centre (MUHC) and at the Orthodontic Clinic of the Montreal University (3525 Queen-Mary Road, Montreal, QC, H3V 1H9).

1. Duration and number of visits (refer to the visit timeline you will be given)

Your participation in this research project will last approximately 26 weeks (6.5 months) and will include eight visits and two phone calls. The main visits will be planned as follows: a Screening visit, Visit 1 (Baseline: week -4, 1 to 2 weeks after screening), Visit 2-5 (Follow-ups: week 0, 8, 12, 16) and Visit 6 (End of study visit: week 20). Screening visit, Visit 1 and Visit 6 will take place at the Glen, follow-up visits will take place at the Orthodontic clinic. Following or on the day of Visit 1, dental impressions will have to be done at the Orthodontic clinic and an additional visit to the clinic might be needed after Visit 2. There will be one phone call between Visit 2 and 3 and between Visit 4 and 5. You will also have three overnight sleep studies at home. The Screening visit will last approximately 1 hour, Visit 1 and 6 will each last approximately 2.5 hours. Follow-up visits will last approximately 30 minutes. You will receive a weekly phone call once you start wearing your oral appliance to monitor adherence.

2. Study phase

Once you agree to participate, a sleep study will be done overnight at your house. If the sleep study reveals you do have sleep apnea, you will be assigned to one of the following groups:

Group 1: Two piece oral appliance therapy
Group 2: One piece oral appliance therapy

This study is randomized which means that you will be assigned randomly, like flipping a coin, to one of the groups. You may not choose the group to which you will be assigned. One person out of two (50%) will receive the two piece oral appliance (group 1) and one person out of two (50%) will receive the one piece appliance (group 2).

If the sleep study reveals no sleep apnea, you will not be included in the study. If the sleep study reveals that you have very severe sleep apnea that causes you to have very low oxygen levels at night, or if you have severe sleep apnea and are very sleepy during the day, you will not be able to participate in the study. Instead, we will inform you immediately and call your endocrinologist, in addition to starting you on CPAP and arranging for you to be seen in our sleep clinic.

As the oral appliance will be custom made for you, it will be yours to keep after you complete the study and your treatment continuation will be discussed with the study doctor.

Your endocrinologist will be notified of your participation and ask not to modify your medication for the duration of the study unless considered necessary. If your medication was to be modified, your participation would continue, but it would be important to inform us of any changes as soon as possible.

3. Tests and procedures

During your participation in this research study, the study doctor or a member of the research team will conduct the following tests and procedures:

DESCRIPTION OF STUDY PROCEDURES	
Procedure	**Description**
Blood draw	Blood (approximately 15 mL or 1 tablespoon) will be drawn from a vein in your arm with the use of a needle and analysed to measure the levels of inflammation, fats and sugars. If some of these analyses were done as part of your routine standard of care, we will simply obtain the values from your chart. You will need to fast for 12 hours prior to this test.
Blood pressure	Your blood pressure will be measured 3 times over a period 10 min by inflating a cuff around your arm. You will be asked to sit quietly with you legs uncrossed while the measurements are done. This procedure will be done once on each arm (left and right) at visit 1 and only on one arm at visit 6.
24 hours blood pressure measurement at home	Following Visit 1 and 6, you will be asked to wear a cuff around your non-dominant arm for a period of 24 hours. The cuff will be attached to a monitor worn on a waist belt. During the 24 hour period, the cuff will inflate every and deflate to measure your blood pressure every 20 minutes when you will be awake and every 30 minutes while you are asleep.
Waist circumference	Your waist circumference will be measured 2 to 3 times with a measuring tape.
Home sleep study	For the purpose of the study, Three home sleep studies will be performed. The material for the sleep studies will be given to you at your Screening visit, at Visit 3 and finally at Visit 6. The sleep study will include the following: a small nasal tube that will measure your breathing, a clip on your finger to monitor your oxygen levels, two belts (chest and belly) also to monitor your breathing and two adhesive electrodes placed on your chest to measure your heart rate. A member of the research team will explain to you how to install the 6 sensors and you will perform the installation on your own before you go to bed. You will be wearing the sensors throughout the night. On the day following the sleep study, you will return the sleep study monitoring equipment to us via a taxi cab driver (that we will arrange and pay for). If it happens that there is a technical problem with the recording and we do not get all the information needed, we may ask your permission to re-do the test (in the past, this has been necessary in less than 5% of participants.) Following analysis of the screening sleep study, the doctor will decide if you are eligible to participate in this study.
Urine sample	You will be asked to provide a urine sample at Visit 1 and 6.
Physical activity monitoring with Fitbit Flex	You will be asked to wear a Fitbit flex on your wrist for a period of 5 to 7 days. This device is worn on your wrist like a watch and measures things like the number of steps you take in a day and the intensity of your physical activity. The Fitbit flex will be returned by taxi following the recording period along with the CGM and the filled 3-day food record (paid and arranged by us).

DESCRIPTION OF STUDY PROCEDURES	
Procedure	**Description**
Continuous glucose measurement (CGM)	For the study, we will ask you to wear a continuous glucose monitor for 7 full days twice. The continuous glucose monitor is a small device (the size of a wrist watch) that measures glucose levels every 5 minutes and has a tiny sensor that is inserted just under your skin on the side of your lower abdomen. This will be inserted by a trained research staff and is generally not painful, although you may sense some initial small discomfort when the sensor is put in place. The sensor stays under the skin and the monitor is taped to your skin. After 7 days of wearing the monitor, you will remove the monitor yourself at home and send it back by taxi (also arranged and paid for by us). This is quite simple to do and the research staff will show you how to do this when the monitor is installed. During those 7 days, you will have to measure your glucose levels 4-6 times per day with a glucose monitor and note down the values on a log. The strips will be provided to you and if you do not have a glucose meter, it will also be provided.
Questionnaires	Your medical history, follow-up questions about your health as well as 4 questionnaires will be done: the Epworth sleepiness scale (ESS), the Pittsburgh sleep quality index (PSQI), the functional outcomes of sleep questionnaire (FOSQ) and the Hospital anxiety and depression scale (HADS). The ESS takes 2-3 minutes to complete, the PSQI 5-10 minutes, the FOSQ about 15 minutes and the HADS about 5 minutes. You will also have to fill a food questionnaire similar to the one you fill in the diabetes clinic for 3 days following Visit 1 and 6; two week days and one weekend day. It will take you approximately 15 minutes per day to fill this questionnaire. This questionnaire will be returned by taxi along with the CGM and the Fitbit. You will also fill a questionnaire to assess your comfort with the oral appliance. It will be completed at visit 3 and 6. This questionnaire takes about 10 minutes to fill out. After you receive you oral appliance, you will have to fill a daily diary to report for how long you wore the appliance during the night and if there was any discomfort, you will be asked to bring this diary to each follow-up visit.
Oral appliance therapy (OAT)	An oral appliance will be custom made for you by the study dentist, the model will depend on what group you have been assigned to (one or two pieces). The oral appliance fits in your mouth like a sports mouth guard or an orthodontic retainer. The dentist will first make an impression of your teeth to make your oral appliance and you will return to the dentist approximately 4 weeks later for fitting of the appliance. Over a period of 8 weeks acclimatization, you will wear the oral appliance and have one follow-up visit with the dentist one week after the fitting. This 8-week period is necessary for you to get comfortable with the appliance and for the dentist to do any adjustment that might be needed. Following these 8 weeks, you will have to wear the oral appliance for a period of 12 weeks. A sensor inside the oral appliance will record how long it is worn. We will ask you to bring the appliance to your follow-up visits so that we can assess how long you have worn it each night.

The schedule of procedures for each visit is listed below:

SCHEDULE OF STUDY PROCEDURES							
Procedure	**Screening**	**Visit 1** **Baseline** Week -4	**Visit 2** Week 0	**Visit 3** Week 8	**Visit 4** Week 12	**Visit 5** Week 16	**Visit 6** **End of study** Week 20
Blood draw		X					X
Urine sample		X					X
Home sleep study	X[1]			X[1]			X[1]
Blood pressure		X					X
24 hours blood pressure		X[1]					X[1]
Waist circumference		X					X
CGM (7 days)		X[1]					X[1]
Medical history	X						
Epworth sleepiness scale	X				X		X
PSQI, FOSQ and HADS		X			X		X
3-day food record		X[1]					X[1]
Fitbit for 5 to 7 days		X[1]					X[1]
Follow-up questionnaire			X	X	X	X	
Appliance comfort questionnaire				X			X
Daily appliance adherence diary			X[2]	X[2]	X[2]	X[2]	

1 – Done at home following the visit.
2 – Done at home once you start wearing the oral appliance until the end of the study.

PARTICIPANT'S RESPONSIBILITIES

- You will be expected to:
  - Come to all scheduled visits.
  - Have 3 home sleep studies
  - Fast 12 hours prior to Visit 1 and 6.
  - Wear the oral appliance every night during the 8-week acclimatization period and for another 12 weeks of treatment after that.
  - Follow the instructions to return the home sleep study material, blood pressure monitor, CGM monitor, Fitbit and 3-day food record.
  - Inform us of any change in medication or side effects you may experience.

BENEFITS ASSOCIATED WITH THE RESEARCH STUDY

You may or may not personally benefit from your participation in this research project. However, we hope that the study results will contribute to the advancement of scientific knowledge in this field and help us find better treatments for patients.

RISKS ASSOCIATED WITH THE RESEARCH STUDY

The study doctor and members of his or her team will answer any questions that you may have regarding the risks, discomforts and side effects associated with this study. Also, at each visit, the study doctor and members of his or her team will ask you questions about any side effects you may have experienced.

You will find below a list of the possible side effects related to the research procedures and the use of the oral appliance:

1. **Risks associated with research procedures**
   - Blood draw: You may experience:
     - Very commonly (>10% of people)
       - Temporary minor pain at site of puncture
       - Minor bruising or hematoma
     - Very rarely (less than 0.0001% of people)
       - Infection at the needle puncture site.
   - Home sleep study: There are no known or expected risks associated with the sleep test(s). Some individuals find the tube at the opening of the nostrils tickles them. However, most find that the test is just a little inconvenient.
   - CGM: The monitors have been used in research studies without reported difficulties. In rare case skin irritation or redness can occur. We will still monitor you closely should there be any problems. The monitor does not reveal the glucose values to you, and does not have any alarms. Most of the time, you will not even realize that it is there. You will be able to shower or take a bath with the monitor on.
   - 24 hour blood pressure monitoring: In rare cases, it is possible that the cuff will irritate the skin. If you notice any itchiness, redness or swelling, the cuff should be removed and the research team contacted.

2. **Risks associated with the use of the oral appliance**
   - Minor side effects such as:
     - Excessive salivation when starting to wear the appliance (common, 1 to 10% of people)
     - Gum irritation (uncommon, 0.1 to 1% of people)

   - Rarely (0.01 to 0.1% of people), some might have some complications such as:
     - Jaw pain
     - Movement of teeth

These can all be recognized and managed by the dentist.

Should you suffer harm of any kind following the use of the oral appliance, or following any other procedure related to the research study, you will receive the appropriate care and services required by your state of health.

OTHER POSSIBLE TREATMENTS

You do not have to take part in this study to receive medical care for sleep apnea. Other options exist such as the CPAP. However, you will only be included in this study if you have mild or moderate sleep apnea. Mild and moderate sleep apnea can remain untreated for the study period without it having a negative impact on your health. Following your participation, you will be referred to our sleep clinic for further management of your condition. We encourage you to discuss with the study doctor all available options.

VOLUNTARY PARTICIPATION AND THE RIGHT TO WITHDRAW

Your participation in this research project is voluntary. Therefore, you may refuse to participate. You may also withdraw from the project at any time, without giving any reason, by informing the study doctor or a member of the research team.

Your decision not to participate in the study, or to withdraw from it, will have no impact on the quality of care and services to which you are otherwise entitled, or on your relationship with the study doctor or clinical team.

The study doctor, the Research Ethics Board, the funding agency, or the Sponsor may put an end to your participation without your consent. This may happen if new findings or information indicate that participation is no longer in your interest, if you do not follow study instructions, or if there are administrative reasons to terminate the project.

If you withdraw or are withdrawn from the study, the information collected during the study will be stored as long as necessary to ensure your safety and the safety of the other participants, as well as to meet regulatory requirements. The Sponsor will continue to use any information collected from you prior to your withdrawal.

Any new findings that could influence your decision to stay in the research project will be shared with you as soon as possible.

CONFIDENTIALITY

During your participation in this study, the study doctor and their team will collect and record information about you in a study file. They will only collect information required to meet the scientific goals of the study.

The study file may include information from your medical chart, including your identity, concerning your past and present state of health, your lifestyle, as well as the results of the tests, exams, and procedures that you will undergo during this research project. Your research file could also contain other information, such as your name, sex, date of birth and ethnic origin.
The blood samples will be sent to the Royal Victoria central laboratory for analysis and will then be

destroyed.

All the information collected during the research project will remain strictly confidential to the extent provided by law. You will only be identified by a code number. The key to the code linking your name to your study file will be kept by the study doctor.

To ensure your safety, a copy of this information and consent form, sleep study and blood test results will be placed in your medical chart. As a result, any person or company to whom you give access to your medical chart will have access to this information.

The study doctor will forward your coded data to the sponsor or their representatives.
The Sponsor may share the coded study data with their commercial partners. However, the Sponsor will respect the confidentiality rules in effect in Quebec and Canada.

The study data will be stored for 7 years after publication of the results by the study doctor; Dr Sushmita Pamidi.

The data may be published or shared during scientific meetings; however it will not be possible to identify you.

For monitoring, control, safety, security, and marketing of a new study drug, your study file as well as your medical charts may be examined by a person mandated by Canadian or international regulatory authorities, such as Health Canada, as well as by representatives of the study sponsor, the institution, or the Research Ethics Board. All these individuals and organizations adhere to policies on confidentiality.

You have the right to consult your study file in order to verify the information gathered, and to have it corrected if necessary.

However, in order to protect the scientific integrity of the research project, accessing certain information before the project is ended may require that you be withdrawn from the study.

INCIDENTAL FINDINGS

Material incidental findings are findings made in the course of the study that may have significant impacts on your current or future wellbeing or that of your family members. A material incidental finding concerning you in the course of this research will be communicated to you and to a health professional of your choice.

FUNDING OF THE RESEARCH PROJECT

The study doctor has received funding from the Research Institute of the McGill University Health Centre for the completion of the research project.

COMPENSATION

You will receive 25$ per study visit at the Glen for costs and inconveniences incurred for those visits. At Visit 1 and 6, a snack will be served to you after the blood draw is completed. You will receive 10$ per visit to the Orthodontic Clinic for costs and inconveniences. If you withdraw from the study, or are withdrawn before it is completed, you will receive compensation proportional to the number of visits you have completed.

SHOULD YOU SUFFER ANY HARM

By agreeing to participate in this research project, you are not waiving any of your legal rights nor discharging the study doctor, the sponsor or the institution, of their civil and professional responsibilities.

CLINICAL TRIAL REGISTRATION

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at anytime.

CONTACT INFORMATION

If you have questions or if you have a problem you think may be related to your participation in this research study, or if you would like to withdraw, you may communicate with the study doctor or with someone on the research team at the following number:

- Geneviève Tremblay, Study Coordinator, 514-934-1934 ext.: 32354
- Lorraine Lavigne, Back-up Study Coordinator, 514-934-1934 ext.: 36479

For any question concerning your rights as a research participant taking part in this study or if you have comments, or wish to file a complaint, you may communicate with:

The Patient Ombudsman of the Glen / Royal Victoria Hospital at the following phone number:

514-934-1934 ext. 35655.

OVERVIEW OF ETHICAL ASPECTS OF THE RESEARCH

The McGill University Health Centre Research Ethics Board reviewed this research and is responsible for monitoring the study.

Research Study Title: The Effect of Oral Appliance Therapy on Cardiometabolic Outcomes in Patients with Type 2 Diabetes and Obstructive Sleep Apnea: A Multi-Centered Randomized Controlled Trial

SIGNATURES

Signature of the participant

I have reviewed the information and consent form. Both the research study and the information and consent form were explained to me. My questions were answered, and I was given sufficient time to make a decision. After reflection, I consent to participate in this research study in accordance with the conditions stated above.

I authorize the research study team to have access to my medical record for the purposes of this study.

I understand that to be included in this study the results of the first home sleep study must show the presence of sleep apnea.

I authorize the doctor in charge of this research study or a member of her research team to communicate with me directly to ask if I am interested in participating in other research.

Yes ☐ No ☐

I authorize the study doctor to inform my regular doctor(s) that I am taking part in this study:

Yes ☐ No ☐

Name of participant Signature Date

Signature of the person obtaining consent

I have explained the research study and the terms of this information and consent form to the research participant, and I answered all his/her questions.

Name of the person obtaining consent Signature Date

Annexe 3: Questionnaires

Si vous obtenez des scores indiquant des symptômes dépressifs d'intensité modérée ou sévère l'équipe de recherche vous le dira.

Si vous êtes un employé ou un étudiant de l'Université de Montréal, nous vous rappelons que le Centre de santé et de consultation psychologique (CSCP) peut être joint au (514) 343-6452 ou, pour les employés, au poste 1PSY (1779).

Si vous n'êtes pas un employé ou un étudiant de l'Université de Montréal, vous pouvez contacter la Clinique universitaire de psychologie de l'UdeM au (514) 343-7725. Les séances de consultation sont de septembre à avril.

Nous vous rappelons que vous pouvez aussi consulter le site Web de l'Ordre des psychologues du Québec pour trouver un psychologue près de chez-vous à l'adresse suivante : https://www.ordrepsy.qc.ca/

Hospital Anxiety and Depression Scale (HADS)

GL assessment
the measure of potential

Name: _____ Date: _____

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A	D			A	D
		I feel tense or 'wound up'	**I feel as if I am slowed down**		
3		Most of the time	Nearly all the time		3
2		A lot of the time	Very often		2
1		From time to time, occasionally	Sometimes		1
0		Not at all	Not at all		0
		I still enjoy the things I used to enjoy	**I get a sort of frightened feeling like 'butterflies' in the stomach**		
	0	Definitely as much	Not at all	0	
	1	Not quite so much	Occasionally	1	
	2	Only a little	Quite often	2	
	3	Hardly at all	Very often	3	
		I get a sort of frightened feeling as if something awful is about to happen	**I have lost interest in my appearance**		
3		Very definitely and quite badly	Definitely		3
2		Yes, but not too badly	I don't take as much care as I should		2
1		A little, but it doesn't worry me	I may not take quite as much care		1
0		Not at all	I take just as much care as ever		0
		I can laugh and see the funny side of things	**I feel restless as if I have to be on the move**		
	0	As much as I always could	Very much indeed	3	
	1	Not quite so much now	Quite a lot	2	
	2	Definitely not so much now	Not very much	1	
	3	Not at all	Not at all	0	
		Worrying thoughts go through my mind			
3		A great deal of the time	**I look forward with enjoyment to things**		
2		A lot of the time	As much as I ever did		0
1		Not too often	Rather less than I used to		1
0		Very little	Definitely less than I used to		2
		I feel cheerful	Hardly at all		3
	3	Never	**I get sudden feelings of panic**		
	2	Not often	Very often indeed	3	
	1	Sometimes	Quite often	2	
	0	Most of the time	Not very often	1	
		I can sit at ease and feel relaxed	Not at all	0	
0		Definitely	**I can enjoy a good book or radio or television programme**		
1		Usually			
2		Not often	Often		0
3		Not at all	Sometimes		1
			Not often		2
			Very seldom		3

Now check that you have answered all the questions

FOLD HERE

A	D
TOTAL	

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GL Assessment is part of the Granada Group

The Epworth Sleepiness Scale (ESS)

Your age (Yrs):_____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently, try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation listed below:

0 = would **never** doze off
1 = **slight chance** of dozing off
2 = **moderate chance** of dozing off
3 = **high chance** of dozing off

It is important that you answer each question as best you can.

Situation	**Chance of Dozing Off (0-3)**
Sitting and reading	___
Watching TV _____	___
Sitting, inactive in a public place (e.g. the theatre or in a meeting) _____	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone _____	___
Sitting quietly after a lunch without alcohol _____	___
In a car, while stopped for a few minutes in traffic	___

THANK YOU FOR YOUR COOPERATION

Functional Outcomes of Sleep Questionnaire
(Canadian English version of the FOSQ)

FUNCTIONAL OUTCOMES OF SLEEP QUESTIONNAIRE
(Canadian English version of the FOSQ)

Some people have difficulty performing everyday activities when they feel tired or sleepy. The purpose of this questionnaire is to find out if you generally have difficulty carrying out certain activities because you are too sleepy or tired. In this questionnaire, when the words "sleepy" or "tired" are used, it means the feeling that you can't keep your eyes open, your head is droopy, that you want to "nod off", or that you feel the urge to take a nap. These words do not refer to the tired or fatigued feeling you may have after you have exercised.

DIRECTIONS: Please put an (X) in the box for your answer to each question. Select only **one** answer for each question. Please try to be as accurate as possible. All information will be kept confidential.

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
1. Do you have difficulty concentrating on the things you do because you are sleepy or tired?		❒	❒	❒	❒
2. Do you generally have difficulty remembering things, because you are sleepy or tired?		❒	❒	❒	❒
3. Do you have difficulty finishing a meal because you become sleepy or tired?		❒	❒	❒	❒
4. Do you have difficulty working on a hobby (for example, sewing, collecting, gardening) because you are sleepy or tired?	❒	❒	❒	❒	❒

Functional Outcomes of Sleep Questionnaire (FOSQ)

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
5. Do you have difficulty doing work around the house (for example, cleaning house, doing laundry, taking out the trash, repair work) because you are sleepy or tired?	❒	❒	❒	❒	❒
6. Do you have difficulty operating a motor vehicle for a short time (less than 1 hour) because you become sleepy or tired?	❒	❒	❒	❒	❒
7. Do you have difficulty operating a motor vehicle for a long time (more than 1 hour) because you become sleepy or tired?	❒	❒	❒	❒	❒
8. Do you have difficulty getting things done because you are too sleepy or tired to drive or take public transportation?	❒	❒	❒	❒	❒
9. Do you have difficulty taking care of financial affairs and doing paperwork (for example, writing checks, paying bills, keeping financial records, filling out tax forms, etc.) because you are sleepy or tired?	❒	❒	❒	❒	❒

Functional Outcomes of Sleep Questionnaire (FOSQ)

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
10. Do you have difficulty performing employed or volunteer work because you are sleepy or tired?	❒	❒	❒	❒	❒
11. Do you have difficulty maintaining a telephone conversation, because you become sleepy or tired?	❒	❒	❒	❒	❒
12. Do you have difficulty visiting with your family or friends in <u>your</u> home because you become sleepy or tired?	❒	❒	❒	❒	❒
13. Do you have difficulty visiting with your family or friends in <u>their</u> home because you become sleepy or tired?	❒	❒	❒	❒	❒
14. Do you have difficulty doing things for your family or friends because you are too sleepy or tired?	❒	❒	❒	❒	❒

	(4) No	(3) Yes, a little	(2) Yes, moderately	(1) Yes, extremely
15. Has your relationship with family, friends or work colleagues been affected because you are sleepy or tired?	❒	❒	❒	❒

In what way has your relationship been affected? _____

_____

_____

Functional Outcomes of Sleep Questionnaire (FOSQ)

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
16. Do you have difficulty exercising or participating in a sporting activity because you are too sleepy or tired?	❒	❒	❒	❒	❒
17. Do you have difficulty watching a movie or videotape because you become sleepy or tired?	❒	❒	❒	❒	❒
18. Do you have difficulty enjoying the theater or a lecture because you become sleepy or tired?	❒	❒	❒	❒	❒
19. Do you have difficulty enjoying a concert because you become sleepy or tired?	❒	❒	❒	❒	❒
20. Do you have difficulty watching TV because you are sleepy or tired?	❒	❒	❒	❒	❒
21. Do you have difficulty participating in religious services, meetings or a group or club, because you are sleepy or tired?	❒	❒	❒	❒	❒
22. Do you have difficulty being as active as you want to be in the evening because you are sleepy or tired?		❒	❒	❒	❒
23. Do you have difficulty being as active as you want to be in the morning because you are sleepy or tired?		❒	❒	❒	❒

Functional Outcomes of Sleep Questionnaire (FOSQ)

	(0) I don't do this for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
24. Do you have difficulty being as active as you want to be in the afternoon because you are sleepy or tired?		❒	❒	❒	❒
25. Do you have difficulty keeping up with others your own age because you are sleepy or tired?		❒	❒	❒	❒

	(1) Very Low	(2) Low	(3) Medium	(4) High
26. How would you rate your general level of activity?	❒	❒	❒	❒

	(0) No intimate or sexual relationship	(4) No	(3) Yes, a little	(2) Yes, moderately	(1) Yes, extremely
27. Has your relationship with your intimate or sexual partner been overall affected because you are sleepy or tired?	❒	❒	❒	❒	❒

IF NO RELATIONSHIP STOP HERE!! **IF NO RELATIONSHIP STOP HERE!!**

	(0) No intimate or sexual relationship	(4) No	(3) Yes, a little	(2) Yes, moderately	(1) Yes, extremely
28. Has your desire for intimacy or sex been affected because you are sleepy or tired?		❒	❒	❒	❒

	(4) No	(3) Yes, a little	(2) Yes, moderately	(1) Yes extremely
29. Has your ability to become sexually aroused been affected because you are sleepy or tired?	❒	❒	❒	❒
30. Has your ability to "come" (have an orgasm) been affected because you are sleepy or tired?	❒	❒	❒	❒

Functional Outcomes of Sleep Questionnaire (FOSQ)

PITTSBURGH SLEEP QUALITY QUESTIONNAIRE
(Canadian English version of the Pittsburgh Sleep Quality Index - PSQI)

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month (past 30 days) only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time did you usually go to bed at night?

   BEDTIME _____

2. During the past month, how long (in minutes) did it usually take you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, what time did you usually get up in the morning?

   GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, checkmark the one best response. Please answer all questions.

5. During the past month, how often did you have trouble sleeping because you . . .

a) Could not get to sleep within 30 minutes

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Woke up in the middle of the night or early morning

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

c) Had to get up to use the washroom

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

d) Could not breathe comfortably

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

e) Coughed or snored loudly

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

f) Felt too cold

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

g) Felt too hot

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

h) Had bad dreams

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

i) Had pain

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

j) Other reason(s), please describe _____

_____

How often during the past month did you have trouble sleeping because of this?

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

6. During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

7. During the past month, how often did you take medicine to help you sleep (prescribed or "over the counter")?

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

8. During the past month, how often did you have trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

9. During the past month, how much of a problem was it for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

A moderate problem _____

A very big problem _____

10. Do you share your bed, room or home with someone?

Do not share a bed, room or home with someone

Someone in another room _____

Someone in same room, but not the same bed _____

Share a bed _____

If you share a bed, room or home with someone, ask him/her how often in the past month you have. . .

a) Snored loudly

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Had long pauses between breaths while asleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Had legs twitching or jerking while asleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Had episodes of disorientation or confusion when waking up at night

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

e) Had other restlessness while asleep, please describe_____

_____

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

OA Treatment Side Effects Questionnaire

Are you wearing your oral appliance? _____ No _____ Yes

How long did you wear your appliance for? _____ (months)

Reasons to stop wearing OA:
(you can select more than one)

_____ No/little effect
_____ Occlusion/jaw changes
_____ uncomfortable/cumbersome
_____ Painful
_____ Inconvenient to use
_____ Dental work changed
_____ Appliance doesn't fit any more
_____ Apnea worsened
_____ Lost weight, apnea lessened
_____ Started CPAP
_____ Lost the appliance
_____ Claustrophobic
_____ Could not swallow
_____ Mouth become too dry
_____ Other:

_____

Are you under other OSA treatment? _____ No _____ Yes

How many nights per week do you use your oral appliance? _____

How many hours per night do you use your oral appliance? _____

How satisfied are you with the treatment

_____ Very dissatisfied
_____ Moderately dissatisfied
_____ Moderately satisfied
_____ Very satisfied

Frequency of complications

_____ None
_____ Less than once a month
_____ Once a month
_____ Every second week
_____ 1 to 3 times a week
_____ 4 to 6 times a week
_____ Everyday

Treatment Side Effects:

Subjective Side- Effects:

For the following, Please tick the appropriate box ☑ :

	Not At all	Rare, but hardly disturbing	Rare, but disturbing	Often, but hardly disturbing	Often and disturbing	Always, strongly disturbing
Excessive salivation						
Dryness of mouth						
Bite changes						
Discomfort or pain in teeth						
Discomfort or pain in oral soft tissues						
Discomfort or pain in jaws						
Strong sensation in the tongue						
Tongue fatigue						

Do you have any side effects resulting from chewing?
_____ Never _____ Rarely _____ Sometimes _____ Often _____ Always

What is the severity of your chewing?
_____ Mild _____ Moderate _____ Severe

Do you use something to avoid side effects?
_____ No _____ Yes

What do you use to avoid side-effects?
_____ Exercises _____ Splint _____ Bite tab _____ Aliner-Morning repositioning appliance
_____ Other:
_____
_____

Device Related Side-Effects:

For the following, please tick the appropriate box ☑ :

	Not at all	Rarely and hardly disturbing	Rare, but disturbing	Often, but hardly disturbing	Often and disturbing	Always, strongly disturbing
Discomfort because the device does not stay in place						
Discomfort because of bulkiness of the appliance						
Claustrophobia-breathing difficulties with appliance in place						
Difficulties swallowing with appliance in place						
Device causes gagging						
Others: ***Please describe***						

Is the frequency of appliance breakage disturbing?
_____ No _____ Yes

Is the adjustment mechanism difficult to understand?
_____ No _____ Yes

Are there any appliance odors?
_____ No _____ Yes

Do you have any suspected allergic reaction to the appliance?
_____ No _____Yes

Describe suspected allergic reaction:
_____
_____

Sleep Related Side-Effects:

For the following, please tick the appropriate box ☑ :

	Not at all	Rarely and hardly disturbing	Rare, but disturbing	Often, but hardly disturbing	Often and disturbing	Always, strongly disturbing
Difficulties falling asleep with appliance						
Increased awakenings with appliance use						
More unrested sleep with appliance use						

Annexe 4: Flyers

Centre universitaire de santé McGill
Institut de recherche

McGill University Health Centre
Research Institute

Do you have type 2 diabetes? Do you have sleep problems?

Would you be interested in having a home sleep study as part of **research**?

You are NOT eligible if you:

- Are treated for sleep apnea
- Work night shifts
- Wear full lower denture

Investigators:
Dr Sushmita Pamidi
Dr John Kimoff
Dr Mark Sherman
Dr Nelly Huynh

Reason for the study

The purpose of this study is to see if the use of a dental device to treat sleep apnea or other sleep problems (e.g. teeth grinding) can help improve blood sugar, blood pressure and cholesterol.

What is sleep apnea?

Sleep apnea is when a person has breathing pauses while sleeping that may result in a drop in the blood oxygen levels. Some studies show that sleep apnea may worsen diabetes. A sleep test is done at home at the beginning of the study to find out if you have sleep apnea. It has been found that up to 80% of people with type 2 diabetes also have sleep apnea.

What dental device is used in this study?

The dental device fits in your mouth like a sports mouth guard or an orthodontic retainer. You wear it during the night. Either a one-piece or a two-piece dental device will be used.

Why participate?

For you and to contribute to knowledge about the treatment of sleep problems with a dental device and the effect on diabetes.

You may feel that your sleep is more restful while wearing a dental device. It is possible that, in your case, treating sleep problems may improve your diabetes control, but this is not certain as it is part of the questions we are trying to answer with this study.

What is involved?

1) **Screening:** 1 visit and 1 sleep test at home.

If you are found to have sleep apnea:

2) 6-7 visits over a 24 week period:

- A baseline visit, 4-5 follow-ups with the dentist and an end of study visit.
- The first and last visit include a blood draw as well as wearing an activity wrist band (5-7 days) and a small sensor to measure sugar levels (7 days).

3) Two more sleep studies at home in the middle and at the end of the study.

4) Treatment of sleep problems with a two-piece or one-piece dental device (20 weeks).

You will be compensated for your participation in the study.

Call for more information and to find out if you are eligible!

Study coordinator: **Geneviève Tremblay**
[redacted]

Study Sponsor: Research Institute of the McGill University Health Centre

Annexe 5: Material given to patient

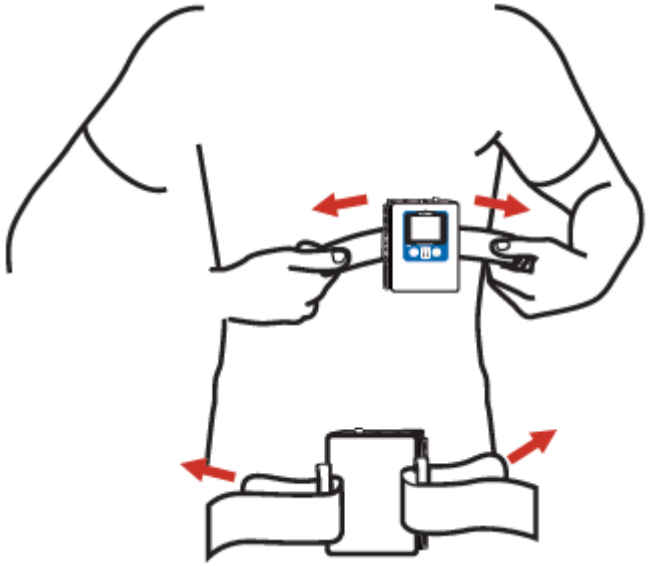
Instructions for home sleep study

- Recording will start automatically.
- Please wear a tank top or shirt.
- Use tape to secure wires to your shirt if needed.
- When you get up in the morning:
    - Remove equipment and fill the morning survey: put everything back in the travel case.
    - The equipment will be collected as arranged with the research team.

Here is how it will look after everything is set-up:

Step 1: Box/Recorder

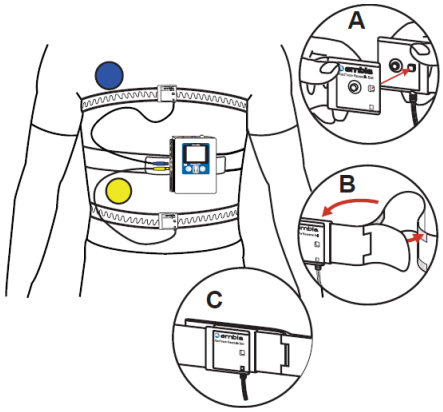
Use the black strap with 2 velcros to secure the pouch with the box inside around your torso.
It should be comfortable. You can use tape to secure if needed.



Step 2: Effort belts

Install the 2 belts to be comfortable; it should not be too tight, but not too loose either.

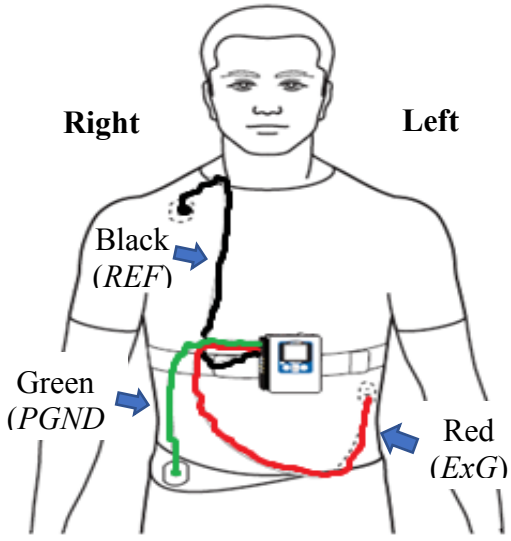
Plug each belt in the box: abdomen = yellow entry (*ABD*) and thorax = blue entry (*THO*).



Step 3: ECG

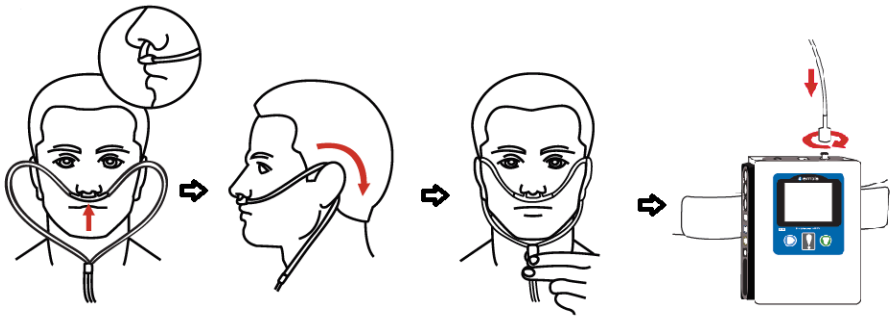
You will have to place 3 electrodes on your skin: one on your right shoulder, one on your right hip and one on your left rib cage.

1) Clean the areas where the electrodes will be with an alcohol wipe. Let dry.
2) Place an electrode at each site.
3) Plug the wires in the box and clip one on each electrode using the color code on the image.
4) Attach extra length of wire with velcro ties.



Step 4: Pressure cannula

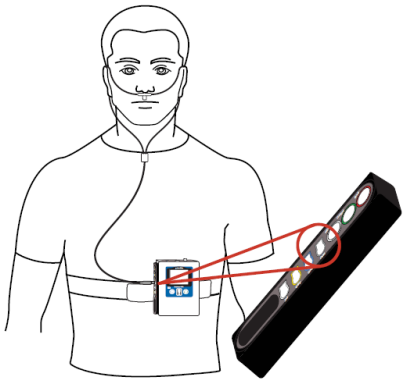
Follow the instructions below to put on the pressure cannula. The 2 prongs go inside the nostrils. The rest of the tube goes behind the ears then under the chin to be tightened.
Gently screw the tube on top of the box in the *PFlow* entry.

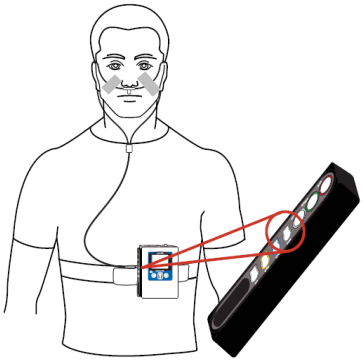


Step 5:

Thermistor

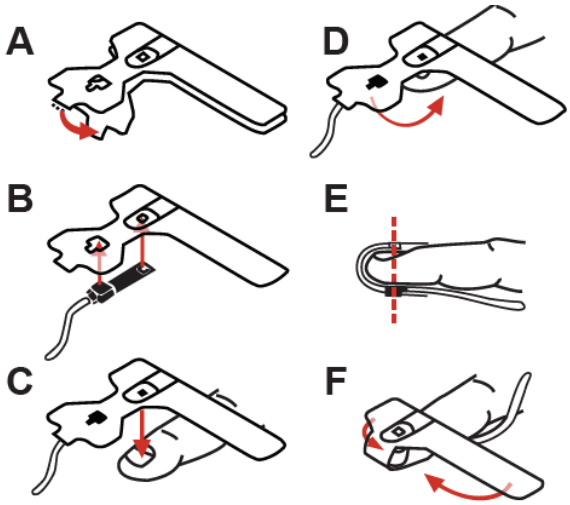
To put on the thermistor, follow the same steps as for the cannula.
The thermistor will sit on top of the cannula. Plug the wire in the *NAF* entry.
Secure the cannula and thermistor on the cheeks with tape.

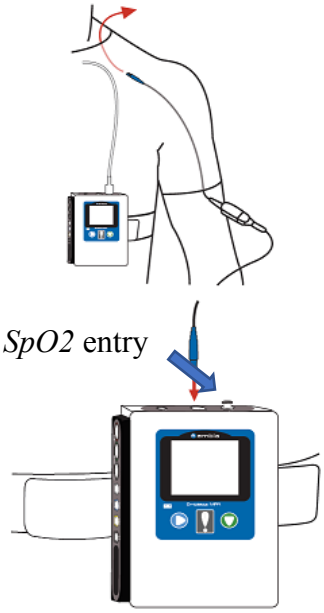




Step 6: SpO2 sensor

Follow the instructions below to put the sensor on your finger. Plug the wire into the box.





Example of daily journal:

The Effect of Oral Appliance Therapy on Cardiometabolic Outcomes in Patients with type 2 Diabetes and Obstructive Sleep Apnea

ORAL DEVICE DAILY DIARY

Participant ID: _____

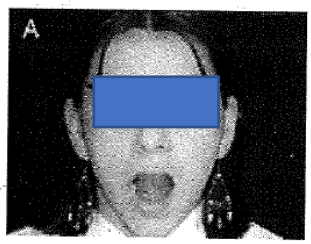
Week:		6pm	7pm	8pm	9pm	10pm	11pm	12am	1am	2am	3am	4am	5am	6am	7am	8am	9am	10am	11am	12pm	1pm	2pm	3pm	4pm	5pm
Date:	Sleep																								
Mon, Feb 25, 2019	Oral device																								
	Did you take any different medication?						No		Yes	if yes, which one and what dose:															
	Comments:																								
		6pm	7pm	8pm	9pm	10pm	11pm	12am	1am	2am	3am	4am	5am	6am	7am	8am	9am	10am	11am	12pm	1pm	2pm	3pm	4pm	5pm
Date:	Sleep																								
Tue, Feb 26, 2019	Oral device																								
	Did you take any different medication?						No		Yes	if yes, which one and what dose:															
	Comments:																								
		6pm	7pm	8pm	9pm	10pm	11pm	12am	1am	2am	3am	4am	5am	6am	7am	8am	9am	10am	11am	12pm	1pm	2pm	3pm	4pm	5pm
Date:	Sleep																								
Wed, Feb 27, 2019	Oral device																								
	Did you take any different medication?						No		Yes	if yes, which one and what dose:															
	Comments:																								
		6pm	7pm	8pm	9pm	10pm	11pm	12am	1am	2am	3am	4am	5am	6am	7am	8am	9am	10am	11am	12pm	1pm	2pm	3pm	4pm	5pm
Date:	Sleep																								
Thu, Feb 28, 2019	Oral device																								
	Did you take any different medication?						No		Yes	if yes, which one and what dose:															
	Comments:																								
		6pm	7pm	8pm	9pm	10pm	11pm	12am	1am	2am	3am	4am	5am	6am	7am	8am	9am	10am	11am	12pm	1pm	2pm	3pm	4pm	5pm
Date:	Sleep																								
Fri, Mar 01, 2019	Oral device																								
	Did you take any different medication?						No		Yes	if yes, which one and what dose:															
	Comments:																								
		6pm	7pm	8pm	9pm	10pm	11pm	12am	1am	2am	3am	4am	5am	6am	7am	8am	9am	10am	11am	12pm	1pm	2pm	3pm	4pm	5pm
Date:	Sleep																								
Sat, Mar 02, 2019	Oral device																								
	Did you take any different medication?						No		Yes	if yes, which one and what dose:															
	Comments:																								
		6pm	7pm	8pm	9pm	10pm	11pm	12am	1am	2am	3am	4am	5am	6am	7am	8am	9am	10am	11am	12pm	1pm	2pm	3pm	4pm	5pm
Date:	Sleep																								
Sun, Mar 03, 2019	Oral device																								
	Did you take any different medication?						No		Yes	if yes, which one and what dose:															
	Comments:																								
Week:		6pm	7pm	8pm	9pm	10pm	11pm	12am	1am	2am	3am	4am	5am	6am	7am	8am	9am	10am	11am	12pm	1pm	2pm	3pm	4pm	5pm
Date:	Sleep																								
Mon, Mar 04, 2019	Oral device																								
	Did you take any different medication?						No		Yes	if yes, which one and what dose:															

Exercise List provided to patients in MAD group:

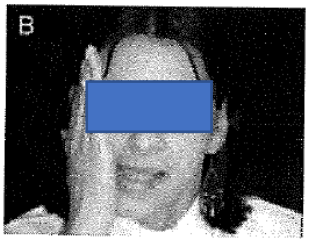
If I wake up with jaw and/or facial muscle discomfort, what should I do?
Some patients do experience jaw and/or facial muscle discomfort in the first few days of using oral appliances but the effects will dissipate over the course of a few weeks as your body adjusts to the appliance. With some basic stretching exercises, the immediate discomfort can be alleviated. Dr. Almeida has done considerable research in this area so she can confidently suggest a variety of techniques to restore movement and function to the jaw, and control and reduce any discomfort to the facial muscles.

While some patients do experience further discomfort beyond the adaptation period, this may be due to external life influences such as stress or worry. By faithfully continuing to perform the exercises, however, the discomfort can be reduced to a manageable level.

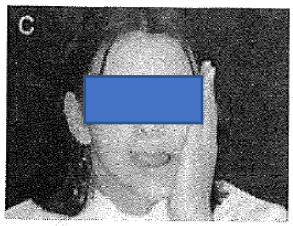
These exercises should be done in the morning after taking the appliance out of your mouth and in the evening before inserting the appliance into your mouth for the night. It is recommended that the sequence of exercises be done in 3 sets of 5 repetitions for each movement.



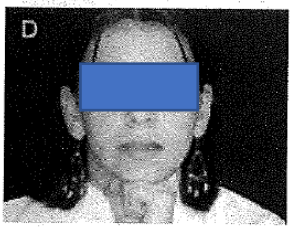
- Begin your sequence of exercises by controlling your mouth opening: Open your mouth (as in Image A) touching your tongue to your upper palate and keep contact there firmly.



- Keeping your mouth slightly open :
  Place your right palm against your right jaw and cheek.
  Move your mandible (lower jaw) to the right while applying light hand resistance (as in Image B).



- Repeat the same movement but reverse the side of your jaw:
  Place your left palm against your left jaw and cheek.
  Move your mandible (lower jaw) to the left while applying light hand resistance (as in Image C).



- Next, stretch the jaw and muscles vertically:
  Place your fist under your chin (as in Image D).
  Provide light resistance while opening your mouth.

- Finally, stretch your mouth open as wide as possible using your fingers
  (as in Image E).

Rest briefly before repeating the sequence of exercises.

Annexe 6: Oral Exam

Dental / Oral Exam

Study ID: _____ Date Completed: _____

Extra Oral Exam

Profile
STRAIGHT ☐ CONVEX ☐ CONCAVE ☐

Maxilla
NORMAL ☐ PROTRUSIVE ☐ RETRUSIVE ☐

Mandible
NORMAL ☐ PROTRUSIVE ☐ RETRUSIVE ☐

Intra Oral Exam

Overjet: _____ *(mm)* Overbite: _____ *(%)*

Canine Relationship R
CLI ☐ CLII ☐ CLIII ☐

Molar Relationship R
CLI ☐ CLII ☐ CLIII ☐

Canine Relationship L
CLI ☐ CLII ☐ CLIII ☐

Molar Relationship L
CLI ☐ CLII ☐ CLIII ☐

Protrusion Range: _____
(mm (ideally with George Gauge or similar at smallest thickness))

Maximum Opening _____
(mm (edge to edge))

Does the patient have frontal teeth (from canine to canine) in the upper jaw?
YES ☐ NO ☐

Does the patient have frontal teeth (from canine to canine) in the lower jaw?
YES ☐ NO ☐

Does the patient have bridges or implants in the upper jaw?
YES ☐ NO ☐

Does the patient have bridges or implants in the lower jaw?
YES ☐ NO ☐

Crossbite (you can select more than 1 answer)

NO ☐ ANTERIOR ☐ (LEFT ☐ RIGHT ☐) POSTERIOR ☐ (LEFT ☐ RIGHT ☐)

Crowning Mandible (you can select more than 1 answer)

SPACING ☐ NORMAL ☐ CROWDING ☐

Crowning Maxilla (you can select more than 1 answer)

SPACING ☐ NORMAL ☐ CROWDING ☐

Presence of Tori Mandible

YES ☐ NO ☐

Presence of Tori Maxilla

YES ☐ NO ☐

Lateral Open Bite

YES ☐ NO ☐ (anterior or posterior open bite)

Anterior and/or Posterior Open Bite (you can select more than 1 answer)

ANTERIOR OPEN BITE ☐ (LEFT ☐ RIGHT ☐) POSTERIOR OPEN BITE ☐ (LEFT ☐ RIGHT ☐)

Contact in the Frontal Area?

YES ☐ NO ☐

Visible or Disturbing Space in the Frontal Area?

YES ☐ NO ☐

Visible or Disturbing Space in the Molar / Premolar Region?

YES ☐ NO ☐

Narrow Maxilla?

YES ☐ NO ☐

Palatal Height is Higher Than Usual?

YES ☐ NO ☐

Previous Temporomandibular Joint Dysfunction?

YES ☐ NO ☐

Current Temporomandibular Joint Dysfunction?

YES ☐ NO ☐

Asymptomatic or Symptomatic TMJ Dysfunction?

SYMPTOMATIC ☐ ASYMPTOMATIC ☐ (click sounds without pain or limitation of jaw movement)

Does the patient report teeth grinding (bruxism) during sleep?
YES ☐ NO ☐

Does the patient report teeth grinding (bruxism) during sleep?
0 ☐ 1 ☐ 2 ☐ 3 ☐

Current Discomfort or Pain in Jaws?
YES ☐ NO ☐

Current Discomfort or Pain in Teeth?
YES ☐ NO ☐

Current Discomfort or Pain in Oral Soft Tissue?
YES ☐ NO ☐

Oral Hygiene
Good ☐ Fair ☐ Poor ☐

Periodontal Disease?
None ☐ Mild ☐ Moderate ☐ Severe ☐

Previous Orthodontic Treatment?
YES ☐ NO ☐

Enough Teeth or Structure for Mandibular Advancement?
NO ☐ YES ☐ MAYBE ☐

Does the patient report teeth grinding in the past history during sleep?
YES ☐ NO ☐

Periodontal Disease (PSR code)?
0 ☐ I ☐ II ☐ III ☐ IV ☐

Modified Mallampati

Modified Mallampati?
0 ☐ I ☐ II ☐ III ☐ IV ☐