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MARCELA LIMA GURGEL

AVALIAÇÃO TRIDIMENSIONAL DA VIA AÉREA SUPERIOR NA APNEIA OBSTRUTIVA DO SONO: REVISÃO SISTEMÁTICA DA LITERATURA E ESTUDOS TOMOGRÁFICOS EM PACIENTES TRATADOS COM APARELHO DE AVANÇO MANDIBULAR E CIRURGIA ORTOGNÁTICA BIMAXILAR

FORTALEZA
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Área de Concentração: Clínica Odontológica com ênfase em Radiologia.

Orientador: Prof. Dr. Fábio Wildson Gurgel Costa.

Co-orientadores: Prof. Dr. Cauby Maia Chaves Júnior e Profa. Dra. Lucia Helena Soares Cevidanes.

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Filipenses 4:4-10;13.

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RESUMO

O objetivo deste estudo foi buscar na literatura parâmetros metodológicos evolvendo tomografia computadorizada de feixe cônico (TCFC) para análise da via aére superior (VAS), avaliar seus aspectos craniofaciais em pacientes com apneia obstrutiva do sono (AOS), bem como comparar a influência do aparelho de avanço mandibular (AAM) e da cirurgia ortognática bimaxilar (COB) sobre as dimensões da VAS. Para tal, foram delineados três estudos: revisão sistemática (capítulo 1), estudo coorte prospectivo (capítulo 2) e estudo coorte retrospectivo comparativo (capítulo 3). No estudo 1, foram incluídos 29 estudos, que em sua maioria relataram a posição durante a TCFC (vertical ou supina) e tecidos duros como referências para avaliação da VAS . Os autores divergiram na delimitação e terminologias da VAS. Risco de viés moderado e alto foram encontrados. A meta-análise utilizou dois subgrupos (vertical e supino). Não foi identificada diferença estatística entre grupo controle e grupo AOS (p=0,18) considerando a área da VAS. O volume no grupo AOS foi estatisticamente menor que o controle (p <0,003 e d de Cohen = -0,81) na posição vertical, mas não na posição supina. Pacientes com AOS demonstraram dimensões anteroposteriores menores (p=0,02; d de Cohen = -0,52) que o grupo controle sem diferenças entre os subgrupos. As medidas laterais foram menores no grupo AOS posição supina, mas não na posição vertical (p=0,002; d de Cohen = -0,6). No estudo 2, a largura transversal medida na sutura frontomaxilar (p<0,01) e o ângulo entre o ramo mandibular e a horizontal de Frankfurt (p=0,03) foram inversamente correlacionados com o índice de apneia e hipopneia (IAH), enquanto o ângulo goníaco (p=0,04) foi diretamente correlacionado com a protrusão terapêutica. Os volumes totais da VAS (p=0,01), orofaringe superior (p=0,04) e inferior (p=0,09) foram também foram diretamente correlacionados com a protrusão terapêutica mandibular. A área superficial total das vias aéreas superiores apresentou correlação estatística inversa com a melhora do IAH (p=0,01). O estudo 3 comparou um grupo AOS com AAM, o qual gerou aumento estatístico no volume (p=0,003) e área superficial (p=0,003) superior da orofaringe, com um grupo de COB sem AOS, o qual mostrou melhora significativa em todas as regiões da VAS após a cirurgia. O aumento na orofaringe superior foi significativamente maior (p=0,001) no grupo cirúrgico que no grupo com aparelho. Os movimentos rotacionais mandibulares diferiram significativamente (p<0,001), os grupos com aparelho e cirúrgico apresentaram respectivamente rotação mandibular no sentido horário e anti-horário. Como conclusão, foi possível constatar a escassez de parâmetros metodológicos que avaliem a VAS de modo padronizado. A meta-análise demonstrou que diferenças nos métodos podem interferir nos resultados, diminuindo a

qualidade da evidência dos estudos. Ademais, foi constatado que a anatomia craniofacial influencia no volume da VAS, bem como na determinação de um avanço mandibular adequado para o sucesso no tratamento. No estudo envolvendo o AAM e COB, ambos os métodos de tratamento foram eficazes, sendo o aparelho mais eficiente na região da orofaringe superior, e as cirurgia em todas a regiões da VAS através de rotações mandibulares, retrospectivamente nos sentidos horário e anti-horário.

Descritores: Tomografia Computadorizada de Feixe Cônico; Apneia Obstrutiva do Sono; Anatomia; Dispositivos de Avanço Mandibular; Cirurgia Ortognática.

ABSTRACT

The aim of this study was to search the literature for methodological parameters involving cone beam computed tomography (CBCT) for the analysis of the upper airway (UA), to evaluate its craniofacial aspects in patients with obstructive sleep apnea (OSA), as well as to compare the influence of mandibular advancement device (MAD) and bimaxillary orthognathic surgery (BOS) on the UA dimensions. Three studies were designed: systematic review (chapter 1), prospective cohort study (chapter 2) and comparative retrospective cohort study (chapter 3). In study 1, 29 articles were included, most of which reported position during CBCT (vertical or supine) and hard tissues as references for assessing UA. The authors differed in the delineation and terminology of the UA. Risk of bias moderate and high were found. The meta-analysis evaluated two subgroups (vertical and supine). No statistical difference was identified between the control group and the OSA group ($p = 0.18$) considering the area of the upper airway. The volume in the OSA group was statistically lower than the control ($p < 0.003$ and Cohen's $d = -0.81$) in the vertical position, but not in the supine position. OSA patients demonstrated smaller anteroposterior dimensions ($p = 0.02$; Cohen's $d = -0.52$) than the control group without differences between subgroups. The lateral measurements were lower in the AOS group in the supine position, but not in the vertical position ($p = 0.002$; Cohen's $d = -0.6$).In study 2, the transverse width measured in the frontomaxillary suture ($p < 0.01$) and the angle between the mandibular ramus and the Frankfurt horizontal ($p = 0.03$) were inversely correlated with the apnea and hypopnea index (AHI) , while the goniac angle ($p = 0.04$) was directly correlated with therapeutic protrusion. The total volumes of the UA ($p = 0.01$), upper oropharynx ($p = 0.04$) and lower ($p = 0.09$) were also directly correlated with the mandibular therapeutic protrusion. The total surface area of the upper airways showed an inverse statistical correlation with the improvement in AHI ($p = 0.01$). Study 3 compared an OSA group with MAD, which generated a statistical increase in volume ($p = 0.003$) and upper surface area ($p = 0.003$) of the oropharynx, with a COB group without OSA, which showed significant improvement in all UA regions after surgery. The increase in the upper oropharynx was significantly greater ($p = 0.001$) in the surgical group than in the group with braces. The mandibular rotational movements differed significantly ($p < 0.001$), the groups with MAD and BOS had respectively clockwise and counterclockwise mandibular rotation. As a conclusion, it was possible to verify that the methodological parameters to evaluate the UA were not standardized. The meta-analysis demonstrated that differences in methods can interfere with the results, decreasing the quality of the evidence from the studies. In addition, it was found that the craniofacial anatomy

influences the volume of the upper airway, as well as the determination of an adequate mandibular advancement for successful treatment. In the study involving MAD and BOS, both methods of treatment were effective, being the most efficient device in the upper oropharynx region, and surgery in all regions of the upper airways through mandibular rotations, retrospectively in the clockwise and counterclockwise directions.

Keywords: Cone-Beam Computed Tomography; Obstructive Sleep Apnea; Anatomy; Mandibular Advancement Devices; Orthognathic Surgery.

SUMÁRIO

I. INTRODUÇÃO GERAL

I. INTRODUÇÃO GERAL

A apneia obstrutiva do sono (AOS) representa, dentre os distúrbios respiratórios do sono, a desordem mais prevalente, acometendo em torno de 14,3% da população mundial e mais da metade dos indivíduos em alguns países. O Brasil apresenta uma população de 49 milhões de indivíduos com AOS, estando entre os 10 países com maior prevalência desse distúrbio, o qual é mais comum em idades mais avançadas e em indivíduos do sexo masculino A AOS é um distúrbio complexo e crônico representado por repetidos episódios de obstrução do fluxo de ar através do colapso parcial ou total da via área superior (VAS), gerando despertares abruptos durante o sono, além gerar um desequilíbrio na saturação do oxigênio (DAL FABBRO, 2010; NEELAPU *et al.*, 2017; BENJAFIELD *et al.*, 2019).

As interrupções recorrentes no fluxo aéreo geram um padrão de sono não reparador, culminando em importantes sinais clínicos como presença de sonolência diurna excessiva, falta de atenção em situações importantes, perda do estado de vigília, dificuldade no aprendizado, alterações neurocognitivas, ansiedade, depressão e isolamento social. Além dos sintomas psicossomáticos, o constante estresse oxidativo gerada por abrutas variações da saturação da oxi-hemoglobina tornam a AOS um fator de risco para o desenvolvimento de doenças cardiovasculares graves como arritmias, aumento na pressão arterial e acidente vascular cerebral. Devido ao aspecto crônico da AOS, bem como seu impacto nas taxas de mortalidade, doenças cardiovasculares e qualidade de vida, os estudos diagnósticos da AOS são de extrema relevância (DAL FABBRO, 2010; BENJAFIELD *et al.*, 2019).

O diagnostico da AOS é obtido através da polissonografia (PSG), a qual representa um exame validado, sendo considerada padrão ouro na identificação dessa desordem. A PGS identifica diversos parâmetros musculares, sanguíneos, estágios do sono, atividade cerebral e ocular. Além disso, esse exame quantifica o número de apneias por hora de sono através do índice de apneia e hipopneia (IAH). O IAH e a saturação mínima e média da oxi-hemoglobina (SpO_2) são considerados os principais padrões de escolha para diagnóstico e classificação da desordem. O diagnóstico da AOS é caracterizado por valores de IAH ≥ 5; a partir disso, pode ser classificada em leve (IAH = 5-15), moderada (IAH = 15-30) e severa (IAH ≥ 30) (KAPUR *et al.*, 2017).

Apesar de o diagnóstico da AOS através da PSG ser consolidado e seguro, os mecanismos evolvendo a etiologia da AOS ainda não são completamente elucidados, uma vez que múltiplos fatores neurológicos, genéticos, físicos, musculares e anatômicos podem estar evolvidos. Estruturas anatômicas como VAS e esqueleto craniofacial podem apresentar grande

influência no desenvolvimento da doença. A VAS é uma estrutura composta por tecidos moles, sendo fluida e maleável, alterando sua conformação facilmente de acordo com movimentos de postura, deglutição e respiração. Embora toda essa dinâmica e complexidade façam com que a estrutura da VAS desempenhe um importante papel no desenvolvimento da AOS, os mecanismos envolvendo sua patência, permeabilidade e colapsabilidade ainda não são bem elucidados (BROWN *et al.*, 2009; CHENG *et al.*, 2014). Ademais, o esqueleto craniofacial, através de seus diferentes padrões de crescimento, pode influenciar no tamanho da VAS. Entretanto, a literatura científica ainda falha no esclarecimento acerca do uso desses fatores como preditores do colapso da VAS e do desenvolvimento da AOS (SONNESEN, 2010).

O tratamento padrão-ouro para AOS é o *continuous positive airway pressure* (CPAP), o qual constitui-se de um aparelho eletrônico associado a uma máscara de adaptação facial que fornece ar pressurizado para a VAS a fim de manter sua patência e passagem de ar. Apesar de o CPAP representar o padrão ouro, alternativas como cirurgia ortognática de avanço bimaxilar e o uso do aparelho de avanço mandibular são consideradas eficazes em manter a patência da VAS e melhorar os sintomas da AOS. Entretanto, as técnicas diferem em muitos aspectos, que vão desde os custos até as técnicas de procedimento, sendo importante o conhecimento de como essas terapias agem diretamente na anatomia craniofacial e da VAS para um planejamento e tratamento de sucesso (HOLTY; GUILLEMINAULT, 2010; ALCALDE *et al.*, 2019; SISTLA; PARAMASIVAN; AGRAWAL, 2019).

Ademais, tecnologias como a tomografia computadorizada de feixe cônico (TCFC) e os *software* tomográficos têm sido uma essencial ferramenta para uma avaliação tridimensional (3D) do esqueleto craniofacial e VAS. Comparado com as tomografias computadorizadas (TC) convencionais, a TCFC gera imagens com melhor resolução e menor tempo de exposição aos raios X durante a aquisição. Além disso, a imagem por TCFC possibilita a realização de diversas avaliações e medidas, que vão desde o volume até a área mínima da VAS. Vale ressaltar que apesar das vantagens de difusão desses avanços tecnológicos, o grande número de possibilidades e variedades entre equipamentos, aplicativos e medidas de avaliação levantam um questionamento na comunidade científica acerca dos métodos de estudo para aplicar metodologias de avaliação da VAS com precisão (HUANG; BUMANN; MAH, 2005).

Diante das lacunas ainda existentes na literatura acerca das variáveis anatômicas da VAS envolvidas na AOS, da influência de características craniofaciais e possíveis tratamentos para AOS, os estudos evolvendo essa temática são de suma importância e ainda são bastante explorados. Entretanto, metodologias bem delineadas devem ser aplicadas para tal.

II. PROPOSIÇÃO

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Geral

Avaliar aspectos tomográficos craniofaciais e da VAS, correlacioná-los com desfechos terapêuticos em pacientes com AOS tratados com AAM, bem como comparar o movimento mandibular e as dimensões da VAS entre tratamentos com AAM e COB

Específicos

1. Sumarizar a evidência da literatura acerca dos parâmetros metodológicos de avaliação da VAS em TCFC de adultos com AOS.
2. Avaliar características craniofaciais (dimensões lineares e angulares) e de VAS (área e volume) em TCFC de pacientes com AOS tratados com aparelho de avanço mandibular, bem como determinar se essas variáveis podem influenciar a severidade da AOS e os desfechos dessa intervenção.
3. Comparar alterações tridimensionais da VAS e rotação mandibular entre pacientes com AOS submetidos a tratamento com aparelho de avanço mandibular e indivíduos sem AOS submetidos a cirurgia ortognática bimaxilar para correção de Classe II.

III. CAPÍTULOS

III. CAPÍTULOS

A presente tese foi baseada no Artigo 46 do Regimento Interno do Programa de Pós-Graduação em Odontologia da Universidade Federal do Ceará, que regulamenta o formato alternativo para dissertações de Mestrado e teses de Doutorado, permitindo a inserção de artigos científicos de autoria ou coautoria do candidato (ANEXOS 1 e 2). Dessa forma, a presente tese de doutorado é composta por três capítulos. Por se tratar de pesquisas envolvendo seres humanos, os estudos referentes aos capítulos 2 e 3 utilizaram-se de dados secundários de projetos de pesquisa previamente submetidos e aprovados, respectivamente, pelos Comitês de Ética em Pesquisa da Universidade Federal de São Paulo (ANEXO 3) e Universidade Estadual de São Paulo – Faculdade de Odontologia Campus Araraquara (ANEXO 4)

Capítulo 1: PARÂMETROS METODOLÓGICOS PARA AVALIAÇÃO DAS VIAS AÉREAS SUPERIORES POR TOMOGRAFIA COMPUTADORIZADA DE FEIXE CÔNICO EM ADULTOS COM APNEIA DO SONO OBSTRUTIVA: REVISÃO SISTEMÁTICA DA LITERATURA E META-ANÁLISE

Artigo será submetido para publicação na revista:

"*Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*"

ISSN 2212-4403; Qualis CAPES A2; fator de impacto 1.6 – 1.8 (5 anos) (ANEXO 5).

Capítulo 2: CARACTERÍSTICAS CRANIOFACIAIS TRIDIMENSIONAIS ASSOCIADAS À SEVERIDADE DA APNEIA DO SONO OBSTRUTIVA E RESULTADOS DE TRATAMENTO

Artigo foi submetido para publicação na revista:

"*Clinical Oral Investigations*"

ISSN 1436-3771; Qualis CAPES A1; 2.8 - 2.7 (5 anos) (ANEXO 6).

Capítulo 3: COMPARAÇÃO TRIDIMENSIONAL ENTRE OS EFEITOS DO APARELHO DE AVANÇO MANDIBULAR E DA CIRURGIA ORTOGNÁTICA BIMAXILAR NA VIA AÉREA SUPERIOR

Artigo será submetido para publicação na revista:

"*PLOS ONE*"

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III. CAPÍTULO 1

"*Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*"

METHODOLOGICAL PARAMETERS FOR UPPER AIRWAY ASSESSMENT BY CONE-BEAM COMPUTED TOMOGRAPHY IN ADULTS WITH OBSTRUCTIVE SLEEP APNEA: A SYSTEMATIC REVIEW OF THE LITERATURE AND META-ANALYSIS

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Declarations of interest:
The authors declare no conflict of interest.

ABSTRACT

Objective. To summarize and meta-analyze the literature regarding cone-beam computed tomography (CBCT) related to methodological parameters for upper airway (UA) assessment in adults with obstructive sleep apnea (OSA).

Study design. This is a systematic review registered on PROSPERO (CRD42021237490) and based on PRISMA checklist. The search strategy was applied to 7 databases and grey literature. The Risk of Bias (RoB) and meta-analysis were performed.

Results. Twenty-nine studies were included. The authors mostly reported the position during CBCT (upright or supine) and hard tissue references. The authors diverged in UA delimitation and terminologies. Moderate and high RoB were found. The meta-analysis showed two subgroups (upright and supine). No statistical differences were identified ($p=0.18$) considering the UA area. The volume in OSA was statistically smaller than the control ($p<0.003$ and Cohen's $d = -0.81$) in upright position. OSA patients demonstrated smaller anteroposterior dimensions ($p = 0.02$; Cohen's $d = -0.52$). The lateral measurements were lower in OSA (supine) ($p = 0.002$; Cohen's $d = -0.6$).

Conclusions. The CBCT position and hard tissue references for UA delimitations were the most reported. No standardized methodological parameter was identified, and the metanalysis showed that it seems to interfere in the study outcomes.

Keywords: Cone-Beam Computed Tomography (CBCT); Anatomy; Sleep Apnea, Obstructive; Airway Management.

INTRODUCTION

Sleep breathing disorders are a complex of abnormal respiratory conditions that currently affect the population's quality of life. Obstructive sleep apnea (OSA) is the most prevalent disturbance in the spectrum of sleep breathing diseases, being diagnosed in approximately 936 million individuals worldwide. The partial or total airflow obstruction in the upper airway (UA), which is characteristic of this disorder, may lead to recurrent and abrupt awakes during the night and oxygen desaturation.[1-3]

On account of the constant sleep interruption, OSA patients may show non-reparative sleep, demonstrating symptoms such as excessive daytime sleepiness, neurocognitive and social interaction alterations, irritability, anxiety, and depression. Moreover, the oxy-hemoglobin saturation variations may lead to strokes, coronary artery diseases, alterations in blood pressure and arrhythmias, being associated with high mortality and risk of developing cardiovascular diseases.[2, 4]

Due to the important OSA clinical manifestations, an appropriate diagnosis is required using the polysomnographic exam (PSG) as a validated gold-standard method. This exam evaluates several parameters considering the brain activity (electroencephalogram); muscles activity (electromyogram and periodic limb movements); sleep pattern (sleep efficiency, total sleep, wake after sleep onset; sleep onset and latency time); the rapid eye movements (REM and electrooculogram); the sleep stages (N1, N2, N3, REM); the arousal index (AI); respiratory disturbance index (RDI); Oxygen desaturation index (ODI); mean and minimum oxyhemoglobin pulse saturation (SpO_2) and AHI (frequency of apnea / hypopnea events per hour of sleep). Regarding these last parameters, SpO_2 and AHI are mainly used to confirm OSA diagnosis. The AHI cutoff references and threshold classify OSA diagnostic (AHI $\geq$ 5) in three levels: mild (AHI = 5-15 events / hour), moderate (AHI = 15-30 events / hour) and severe (AHI $\geq$30 events / hour).[4, 5]

The UA collapse and patency are essential keys in the OSA etiology, being influenced by the neurologic system, sex, weight, muscle activity, craniofacial anatomy, and genetic factors. Despite UA role in OSA development, the dynamic mechanisms involving the airflow and UA permeability are unclear and importantly in need of being studied. Thus, the UA, OSA and the several possible associated anatomic factors are still explored by the scientific community.[6-8]

Cone-beam computed tomography (CBCT) is a three-dimensional (3D) image exam used to evaluate craniofacial aspects and UA anatomy with great precision. Despite the helicoidal computed tomography (CT) being still widely adopted, the CBCT acquisition

presents less x-ray exposure and more accurate images. Although OSA may not be diagnosed by CBCT, this exam is important in studying several anatomic factors that plays essential role for the clinicians and researches in evaluating the etiology, severity and prognosis of the disorder. Furthermore, image technology advancements have provided different software for image analysis, showing tools that may study the UA in all the dimensional axes by different measurements such as volume, surface area, cross-sectional area, angles, and shape. The anatomic variations and image technology developments produce several possibilities for UA evaluation.[6-8]

Therefore, it is a challenge for the researchers to choose a consolidated method to analyze the UA of OSA patients and compare results with other authors in a reliable approach, especially considering the patient's position, software for image analysis, UA measurements, terminology, references, and subdivisions. Moreover, this fact may impact in the studies credibility, confounding the applicability of the scientific outcomes in the clinical practice. In this context, the present study aims to report, with a systematic review and meta-analysis, the methodological parameters for upper airway assessment by CBCT in adults with obstructive sleep apnea.

MATERIALS AND METHODS

Protocol and registration

The present study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[9] The abstract was based on PRISMA 2020's abstract and search checklist extensions. This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number: CRD42021237490. The database search strategy was applied on February 17th, 2021, after the submission on PROSPERO.

Eligibility criteria

The inclusion criteria adopted in this systematic review were clinical trials or observational studies that evaluated the upper airway of adults with OSA using CBCT. Reviews, letters to the editor, personal opinions of authors, book chapters, abstracts from scientific events, studies conducted in children and adolescents, computed tomographic image modalities other than CBCT, studies without a polysomnographic and/or OSA diagnosis, animal studies, studies without upper air evaluation, studies not written in Latin (Roman)

alphabet, studies on cadavers, case reports, and studies with syndromes associated with OSA were excluded.

Information sources and methods

Different virtual health databases and grey literature were searched and accessed as follows:

1. PubMed - (https://pubmed.ncbi.nlm.nih.gov/ - supported by the National Center for Biotechnology Information - NCBI).
2. Scopus - (https://www.scopus.com/ - provided by Elsevier and accessed by the Federal University of Ceará Library).
3. Web of Science - (www.webofknowledge.com - maintained by Clarivate Analytics).
4. COCHRANE - (www.cochrane.org).
5. LILACS - (https://lilacs.bvsalud.org/en/ - Latin American and Caribbean Health Science Literature).
6. DOSS - (https://www.ebsco.com/ - Dentistry & Oral Sciences Source from EBSCO Information Services).
7. EMBASE (http://www.elsevier.com/online-tools/embase/ - Excerpta Medica dataBASE produced by Elsevier, Netherlands).
8. Google scholar - (https://scholar.google.com/).
9. ProQuest Dissertations & Theses Global - (https://about.proquest.com).
10. OpenGrey (http://www.opengrey.eu/ - System for Information on Grey Literature in Europe).

After identification and screening, the references of the included articles were searched to identify more studies to this systematic review.

Search strategy

In order to better delimitate the study keywords, the clearly framed question "What are the methodological parameters for upper airway assessment by CBCT in adults with OSA?" was elaborated, guiding the definition of the Population, Exposure, Comparison, Outcomes, and Studies (PECOS). Thus, this review considered the following characterization to perform the search strategy:

- Population (P): adults with OSA;
- Exposure (E): upper airway data assessed by CBCT;

- Control (C): comparison group;
- Outcomes (O): methodological parameters of image assessment and secondary data of the studies;
- Studies (S): clinical trials or observational studies.

PubMed database was first accessed to identify the Medical Subject Heading Terms (Mesh Terms) and develop the algorithm for all database searches. The Mesh Terms "Sleep Apnea, Obstructive", "Tomography, X-Ray Computed" and "Tomography" were selected and combined using the Boolean operators "OR" and "AND". Filters were applied only in the ProQuest search.

The algorithm was adapted for each platform and it was applied simultaneously in all databases, without date limitation (Table 1).

Selection process

Peer review

The selection of potential studies was performed independently by two authors (M.L.G. and F.S.R.C.). A third author (F.W.G.C.) supervised the process and had the final decision regarding possible divergences.

Managing records

The data initially included was automatically deduplicated with the Endnote® software, using the "Find duplicates" tool (EndNote®, Thomson Reuters, Philadelphia, PA, USA). After the automatic removal of duplicates, all the remain titles and abstracts were independently evaluated and classified using the tools "include" and "exclude" from the software Rayyan® (Rayyan® Qatar Computing Research Institute, Doha, Qatar).[10] The studies included after the Rayyan classification were independently fully read by the same reviewers, and the inclusion criteria were also applied in the full texts.

Data collection process

All descriptive and quantitative data from the selected studies were manually extracted and categorized in spreadsheets by a single author (M.L.G.) using Microsoft Excel. The quantitative analysis was obtained as mean and standard deviation, and the data expressed in box plots were extracted using the WebPlotDigitazer – Copyright 2010/2020 (https://apps.automeris.io/wpd/). The metric measurements, such as linear distance, area, and

volume, were expressed in millimeters (mm), square millimeters (mm2) and cubic millimeters (mm3), respectively. All numeric values given by the studies in centimeters, square or cubic, were transformed in mm, mm^2 or mm^3. The velocity reports were expressed in meters per second (m/s). The resistance was given by Pascal per cubic centimeter per second ($Pa/cm^3/s$), while tension and pressure were given by Pa.

Data items

The relevant data items to be exported were delimitated by two authors (F.W.G.C. and C.M.C.J.) with expertise in this study subject. The following variables were considered: study design, sample, type of intervention, sex, age, body mass index (BMI), CBCT acquisition set, upper airway delimitations, upper airway measurements, examiners, reliability, polysomnographic data, and main outcomes.

Study risk of bias assessment

To assess the risk of bias (RoB) of the included studies, the Mixed Methods Appraisal Tool MMAT – version 2018 (http://mixedmethodsappraisaltoolpublic.pbworks.com/) – was adapted for the present study and used as the Meta-Analysis of Assessment and Review Instrument.[10-12] The RoB judgment was based on the MMAT screen questions from item 3:

3. Quantitative non-randomized studies: case-control and cohort studies.

3.1. Are the participants representative of the target population?

3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?

3.3. Are there complete outcome data?

3.4. Are the confounders accounted for in the design and analysis?

3.5. During the study period, is the intervention administered (or exposure occurred) as intended?

The MMAT responses were categorized in yes, no, or cannot tell and were quantified in four levels of evidence according to the percentage of meeting MMAT criteria (25%, 50%, 75%, and 100%). In order to generate a visual graphic of the risk of bias, the RevMan software (Review Manager, software version 5.4.1, Cochrane Collaboration, Copenhagen, Denmark) was used with an adaptation to MMAT – version 2018 questions. The MMAT responses yes, no, or cannot tell were interpreted as low, high, and unclear risk, respectively, in the RevMan RoB table evaluation.

Effect Measures

Since different measures were evaluated, quantitative data were analyzed by standardized mean difference (SMD) ± standard deviation (SD).

Synthesis methods

A meta-analysis was performed using RevMan software (Review Manager, software version 5.4.1, Cochrane Collaboration, Copenhagen, Denmark), adopting a confidence level of 95% and a random model. I-squared (I2) and Tau² statistics were used to evaluate the heterogeneity. The meta-analysis included case-control studies with the same variables in the case and control groups. These studies were analyzed in subgroups with forest plots expressing SMD, random effect, and 95% of confidence interval (95% CI). The funnel plot assessed publication bias considering the significance level ($p<0.05$). A sensitivity analysis was performed by remotion of studies one-to-one to verify individual interference of each research in the final result of the meta-analysis.

Reporting bias assessment

The quality of evidence was evaluated regarding the study design, sample size, calculation risk of bias, consistency, objectivity, population heterogeneity, precision, reliability, study power, statistical analysis, conflict of interest, and other relevant aspects.

RESULTS

Study selection

The initial search in the electronic databases identified 5844 studies, while the search in the grey literature found 143 articles. After removing the duplicated data, two reviewers independently screened 3038 titles and abstracts from the main databases and 137 from grey literature, remaining 196 studies to be fully read by the authors. The critical analysis in this phase excluded 166 studies. Therefore, 29 studies were included for data synthesis (Figure1).

Study characteristics

Sample

All included records were observational studies (13 [44.8%] case-control/comparative studies and 16 [55.1%] cohort studies). This subject area was most published by the scientific community of the United States of America (10 [34.4%]) (Figure 2). A total of 1201 OSA and

control patients had the UA three-dimensionally evaluated by the authors. Bimaxillary orthognathic advancement surgery, distraction osteogenesis maxillary expansion, mandibular advancement devices, and titration of adjustable mandibular positioning gauge represented the main interventions applied by the authors. Seven hundred and fifty-six adults composed the OSA population, showing a mean age of 53±5 years, ranging from 19 to 80 years, with BMI of 29.5± 0.7. There were 506 (67%) males, 197 (26,1%) females and 50 (6.6%) individuals without this information. Moreover, the PSG data reported was AHI, RDI, ODI, AI, REM sleep, NREM sleep, Min SpO_2, Mean SpO_2; and 8 (27.5%) studies did not report PSG parameters, although it has been mentioned as the OSA diagnosis method. Only 3 (10.3%) articles described the sample size calculation (Table 2).

CBCT evaluation

Among the studies, 17 (58.6%) fully described the image acquisition process. The mostly reported patient's position was upright 14 (48.2%), followed by supine 8 (27.5%). Other 6 (20.0%) studies did not report the position during the image acquisition, being the data imputed after searching for the characteristics informed by the equipment platforms. Thus, other 2 (6.8%) supine and 4 (13.7%) upright positions required to the acquisition were identified. The most reported reference planes to perform the CBCT were the Frankfurt plane (FP), perpendicular to the floor in the supine position, and parallel to the floor in upright CBCT. In addition, the natural head position was also used as a reference to upright tomographic acquisition. Seven (24.1%) studies did not report this information. Twenty software were used for image analysis: Amira, Torrance, Dolphin, Vworks, 3dMDVultus, MIMICS-Materialise Interactive, Invivo5, Analyse, Dental Slice®, CS 3D Imaging Software, OnDemand3DApp, Romexis, ANSYS ICEM CFD 17.0, ANSYS Fluent, Maxilim, InVivoDental, 3D Slicer, INTAGE Volume Editor, ITK-Snap, CS 3D Imaging Software (Figure 3). The Dolphin software was the most reported (n = 20.6%). The reliability and ICC of CBCT measurements were described by 14 (48.2%) and 11 (37.9%) studies, respectively (Table 3).

Upper airway evaluation

The CBCT instructions regarding the UA anatomy stability were found in 14 (48.2%) of the studies, while the image orientation and registration (for cohort studies) were reported, respectively, by 8 (27.5%) and 2 (12.5%) articles. The UA evaluation methods diverged among the studies. The UA and subdivisions were denominated by 14 different terms: superior UA,

inferior UA, upper airway, nasopharynx, oropharynx, hypopharynx, retropalatal space, retroglossal space, superior oropharynx, inferior oropharynx, velopharynx, glossopharynx, laryngopharynx, intraoral airway, and pharyngeal airway. Twelve studies (41.7%) used only hard tissue references for UA delimitation, while 9 (31%) used hard and soft tissue delimitation. Nine different hard tissue structures were described: hard palate, posterior nasal spine (PNS), basion (Ba), most anterior and/or inferior portion of second cervical vertebra (AIC2), most anterior and/or inferior portion of third cervical vertebra (AIC3), hyoid bone, retrognathion point (RGn), B point (B) and mentual point (Me). The soft tissue references were composed by tip of the uvula, tip of the epiglottis, base of the epiglottis, and base of the tongue. The authors also reported the Frankfurt plane, palatal plane, and occlusal plane as references to UA delimitation. Volumetric, linear (axial, sagittal, and coronal), angular, shape, and uniformity measurements were described. The area was reported as UA axial, sagittal, minimum, maximum, or mean cross-sectional area in different UA subregions. By using computational simulations, 2 authors reported UA velocity, and 1 study evaluated resistance, pressure, and UA wall stress (Table 4).

Risk of bias in studies

The RoB assessment by the RevMan software evaluation is shown in Figure 4 by a graph expressing each risk of bias item presented as percentages across all included studies. Moreover, the RoB according to MMAT is expressed in Table 5. These analyzes identified 8 studies with high risk (*25%/**50%), 17 with moderate risk (***75%), and 4 with low risk (****100%).

Results of individual studies

Each study was analyzed considering simple size calculation, the description of the method, confounding factors such as reliability, patient positions during CBCT acquisition, instructions, image orientation, registration, matched samples, and standardization. The individual RoB of the included studies is reported in Table 5 and summarized in Figure 5.

Results of syntheses

UA area did not differ between OSA and control group

The meta-analysis of area measurements evaluated 322 cases and 190 controls, and it did not show a statistically significant difference between the two groups (p=0.18). The effect size was medium (Cohen's d = -0.6 [CI95% = -1.47 to 0.27]). There was significant

heterogeneity (Tau^2 = 1.47, I^2 = 94%, p <0.001). The sensitivity analysis showed that the individual removal of the study by Bruiwer et al. (2016)[11] significantly interfered in these results, leading to a smaller area in OSA group with a large size effect (p = 0.05, Cohen's d = -0.89 [CI95% = -1.62 to -0.16])

According to the CBCT acquisition positions, 2 patient's subgroups were evaluated: upright and supine position. In patients in an upright position, no differences were identified between OSA and control groups (p = 0.14) and a significant large effect size was found (Cohen's d = -0.96 [CI95% = -2.22 to 0.30]. There was no heterogeneity between these studies (Tau^2 = 1.11, I^2 = 89%, p <0.001), and the sensitivity analysis showed that the individual removal of the studies did not significantly change this outcome (p <0.05). In the supine position, there was no significant difference between the OSA and control groups (p = 0.52). The heterogeneity between the studies (Tau^2 = 1.77, I^2 = 96%, p <0.001) was considerably high. The sensitivity analysis demonstrated that individual removal from studies did not significantly change this outcome (p> 0.05) (Figure 6).

OSA patients showed smaller UA volume compared with control group in upright position, but not in the supine position compared to the control group

The meta-analysis of UA volume evaluated 214 OSA cases and 195 controls, showing a statistically significant difference between the groups (p=0.005). The effect size was medium, with Cohen's d = -0.53 (CI95% -0.91 to -0.16). There was moderate heterogeneity between the studies (Tau^2 = 0.22, I^2 = 69%, p <0.001), and the sensitivity analysis demonstrated that the individual removal of the studies did not significantly change this outcome (p <0.05).

Regarding the position during CBCT acquisition in patients positioned upright, the OSA group showed a significant smaller volume (p<0.003) and a Cohen's d = -0.81 [CI95% = -1.25 to -0.36] with a large effect size. The heterogeneity between these studies was moderate (Tau^2 = 0.19, I^2 = 63%, p = 0.02), and the sensitivity analysis showed that the individual removal of the studies did not significantly change this outcome (p <0.05). In the supine position, there was no significant difference between the OSA and control groups (p = 0.51) and there was no significant heterogeneity between the studies (Tau^2 = 0.00, I^2 = 0%, p = 0.51). The sensitivity analysis demonstrated that the individual removal of the studies did not significantly change this outcome (p > 0.05) (Figure 6).

OSA patients showed smaller AP dimension than the control group not interfered by position

The meta-analysis of anteroposterior (AP) linear measurements evaluated a total of 216 case samples and 117 control samples, showing a significant difference between the two groups ($p = 0.02$). The effect size was medium (Cohen's d = -0.52 [CI95% = -0.95 to -0.10], and there was a significant moderate heterogeneity between the studies ($Tau^2 = 0.17$, $I^2 = 63\%$, $p = 0.02$). The sensitivity analysis demonstrated that the individual removal of the studies significantly changed this outcome, after removing the Ogawa et al. (2007)[12] study, no differences were identified between the groups ($p = 0.05$). Comparing the upright and supine subgroups, no difference in the AP axial linear measurements was identified ($p > 0.05$) (Figure 7).

OSA patients showed smaller LAT dimension in the supine position, but not in the upright position compared to the control group

Analyzing the lateral (LAT) linear measurements, 216 OSA and 117 control patients did not show a statistic difference ($p = 0.39$). There was significant heterogeneity between the groups ($Tau^2 = 0.93$, $I^2 = 90\%$, ($p < 0.001$) with a small effect size (Cohen's d = - 0.36 [CI95% -1.18 to -0.46]). In the upright subgroup, similar results were found, while in the supine group a significant difference was found ($p=0.002$) associated with a significant moderate heterogeneity ($Tau^2 = 0.00$, $I^2 = 69\%$, $p = 0.69$) and with a medium effect size (Cohen's d = - 0.60 [CI95% -0.98 to -0.21]). In the sensitivity analysis, the individual removal of studies did not significantly change this outcome ($p > 0.05$) (Figure 7).

Publication bias

According to the funnel plot analysis, no publication bias was identified in the studies included in the syntheses for area, volume and AP and LAT linear measurements (Figures 6 and 7).

Reporting biases

Among the 13 case-control studies, 4 papers had to be excluded from the meta-analysis due to the absence of all measurements in OSA and control groups, considerable differences in measurements or unhealthy control group. From the 9 remain studies evaluated by meta-analysis, 4 did not present an equal sample in the OSA and control groups.

DISCUSSION

In this systematic review, the scientific databases were searched to access tomographic three-dimensional upper airway evaluation methods in adult patients with obstructive sleep apnea polysomnographic diagnosis. Once the upper airway anatomy is a complex soft tissue structure influenced by multiple factors such as muscle activity, gravity, weight, posture, breath, and swallowing movements, the evaluation of methods that minimize the external influence in upper airway patency is essential to accurate analysis, diagnosis, treatment, and prognosis.[7, 8, 13] Although this dynamic characteristic represents an important aspect of the upper airway assessment, this systematic review found that the literature is still unclear in reporting standardized airway assessment methods.[7, 8] The present study identified 29 observational papers which applied different upper airway evaluations regarding several aspects such as CBCT equipment, CBCT acquisition, patient position, and instructions. Furthermore, the image software, processing, reliability, delimitation, nomenclature, and three-dimensional evaluations also diverged among the authors, evidencing that there is no agreement and standardization for an accurate study of obstructive sleep apnea adult patients' upper airway.

Among the studies included in this synthesis of results, the United States of America (USA) showed most of the publications, which may be justified by the OSA prevalence in the country. According to Benjafiled et al. (2019)[1], the USA is in the top ten countries with the higher numbers of OSA individuals, showing an OSA prevalence (AHI ≥ 5) of 33.2%. Although Brazil, Germany, Japan, China, and India are also in the top ten OSA ranking, the publications from these countries only represented 3.4% to 10.3% of the studies included in this systematic review. The sex predominance found in this screening was in agreement with the literature, being more prevalent in males (66.9%) than in females (26%). The BMI (29.5± 0.7) in OSA patients were not in accordance with previous studies that identified higher BMI values in OSA population.[1, 13, 14] However, this report may be explained by the studies eligibility criteria, which mostly excluded overweight patients to minimize this risk factor as a bias. Most studies included in this paper did not report the sample size calculation or the ethnicity, which are essential information to a proper statistical power and to validate the proposed hypotheses. Thus, the population reported by 89.6% of the studies may not accurately represent the OSA population.[15]

Only 58.6% of the studies fully described the complete position method during the CBCT acquisition, and the authors reported these steps differently. The upright position was

found in 51.7% of the studies, while the supine in 24.1%. Reference planes to perform the CBCT were also reported. For supine position, the Frankfurt plane (FP) perpendicular to the floor was described as a reference. Frankfurt plane parallel to the floor and head natural position were described for upright position. Once the UA may dynamically be deformed with position changes, all these steps during CBCT acquisition are important to achieve a three-dimensional image with maximum accuracy, representing as much as possible the real UA characteristics of OSA patients.[7, 8] However, 24.1% of the studies included did not report all the steps for the CBCT acquisition. According to Sousa et al., (2016)[16], comparing computed tomography (CT) images obtained in supine (Frankfurt plane perpendicular to the floor) and supine (44° of upward inclination) positions, the UA volume were different, being greater with the head inclination.[16] Hsu et al., (2019)[17] analyzed sagittal UP dimensions in the supine and upright positions. The authors identified that body position changes could influence the anterior-posterior distance of most constricted areas in UA and hyoid bone. Due to patient position and posture relevance, applying and reporting these details during the CBCT acquisition is extremely important for an adequate UA analysis, study reproducibility, and evidence quality.

Despite the most common reported software being represented by Dolphin image, with accuracy and validation well elucidated, several authors diverged among the image software analysis. A total of 19 other systems were mentioned, being 62% commercial and 31% of free access.[6, 18] The Romexis (free access and semi-automated) and Invivo5 (commercial and automated) are software with accuracy demonstrated by Kamaruddin et al., (2019)[18], which showed precision in reproducing UA volume and minimum cross-sectional area. Amira and OnDemand3D also performed reliable UA volumetric, linear, and area measurements.[19] ITK Snap and 3D slicer are free access programs and were considered as accurate software, especially for anatomic irregular volume and area measurements. Moreover, Gomes et al., (2019)[20], after analyzing a mathematical model, demonstrated that semi-automatic segmentations by ITK Snap showed great accuracy for irregular structures.[21] Although the software commonly reported in the included studies demonstrated acceptable accuracy, more studies comparing different image applications are still unclear and need to be critically considered when determining the software of choice for UA evaluations. The development of precise free applications is an important step for more studies to elucidate the complexity of UA patency in OSA.

The UA assessment differed among the articles regarding image acquisition instructions, image orientation, registration, UA denomination, and measurements. Only 48.2% of the studies considered instructions during the CBCT to maintain the UA as stable as possible.

Considering that the airflow is dynamic, with muscle action during inspiratory, expiratory and swallow movements, and that CBTC is a static image exam, the instruction to avoid profound respiratory movements, to not move, to not swallow, and to keep the gaze fixed in a static point during the image acquisition is essential. However, it was not described by several authors (51.8%).[7, 8] Another relevant image factor is the head orientation and the registration, only reported by 27.5% and 12.5% of the analyzed papers.

The 3D image evaluations express different anterior, posterior, superior and lateral measurements depending on the space axes (x, y, and z). In the head orientation, these space planes are quantified, placed, and standardized in the same coordinate arrangement for all the images using craniofacial structures as anatomic reference, minimizing possible inconstancies during the image analysis from different individuals. Moreover, images from cohort studies are obtained with more than one CBCT acquisition in different follow-up times. Due to the possible variances among head positions in this step, the baseline image from longitudinal designs should be oriented according to coordinate planes, and the follow-up 3D images should ideally be registered according to the oriented baseline image. The registration process for cohort studies is paramount in comparing anatomy variables in more than one-time point. The head orientation and registration are critical processes to obtain dimensional outcomes with accuracy, precision, and reproducibility.[22]

This systematic review showed no agreement among the authors regarding the UA terminology and subdivision references, identifying 14 UA terms and different soft and hard tissue references. The same airway region, from hard palate to epiglottis, was reported by the authors with 4 nomenclatures: upper airway, oropharynx, pharyngeal airway, and velopharynx. The nasopharynx and oropharynx were described with 3 and 8 different delimitations, respectively. Furthermore, the inferior UA limit was reported by several structures such as tip of epiglottis, base of epiglottis, Me, C2, C3, Hyoid bone and RGn, and may be justified by the FOV size of the CBCT equipment used. Standardized UA terminology and delimitation are essential for a better anatomic understanding in the medicine scenario, being a factor to be considered in UA evaluations in OSA patients by CBTC. In addition, the UA patency and OSA severity may be influenced not only by age, sex, or BMI. The tongue, soft palate, uvula and epiglottis may also change the UA morphology during the physiologic neuromuscular activity, leading to a hard tissue choice for most accurate evaluations.[23] UA denomination, delimitations, and subdivisions have been suggested according to the following description: nasopharynx (the posterior nasal cavity between the cranial base and hard palate), oropharynx (the region between the hard palate and hyoid bone), and hypopharynx (region above the hyoid bone).[24]

This study showed a moderate RoB in most of the articles (56.6%). This finding reflected the lack of information about sample size calculation, matched sample, CBCT instructions, image orientation/registration, and examiner reliability. Only 1 study, Rodrigues et al. (2017)[25], met 100% of MMAT criteria. A high RoB was shown in 30% of the studies representing UA 3D evaluation methods with low confidence in their results. These articles failed in several aspects such as sample size calculation, divergences between the OSA and control patients, reproducible measurements reports, clear definition of the evaluations, all the CBCT parameters for images standardization, examiner's reliability tests, and statistic outcomes. Importantly, only 2 articles were designed considering the minimization of confound factors as CBCT image acquisition posture and instructions for UA maintenance, image orientation and registration, and the measurements' reliability (ICC). All the described methodologic parameters are essential to achieve an accurate, precise, reliable, and consistent outcome for UA analyses in OSA patients by CBCT.[15, 17, 22, 24, 26] Based on the studies with low RoB, this systematic review suggests steps for a precise UA with CBCT in OSA individuals (Figure 8).

Regarding the PSG data, the AHI, AI, RDI, ODI, Min SpO_2, Mean SpO_2 were the parameters reported. Ten authors did not mention the PSG data for OSA diagnosis. Among the 20 studies that reported the PSG, 4 did not mention the AHI; however, it is important to quantify the numbers of apnea and hypopnea obstructive events, diagnose and classify the disease. This outcome may reflect in a non-standardized OSA sample reported by the authors. The SpO_2 is also a relevant parameter for OSA diagnosis; however, the case-control studies did not report the oxygen saturation.[2, 4]

The meta-analysis syntheses performed in the case-control studies identified that OSA patients showed a smaller volume than the control patients, while the upper airway area measurements did not differ between them. Interestingly, the subgroup analysis based on CBCT positions during image acquisition (supine and upright) showed that the volume measurements in the supine position did not differ comparing the groups. In contrast, these dimensions in the upright OSA group were significantly reduced. These findings highlight the role of the position during the CBCT acquisition in the UA measurements. Comparing OSA patients with the comparative group, the supine position in healthy patients may influence the UA dimensions due to the gravity forces in the pharyngeal muscles. Moreover, AP linear dimensions did not show differences between the groups, while the LAT dimensions were smaller only in OSA individuals evaluated in supine position, evidencing once more the effects of posture, position, and gravity in the UA anatomy. These outcomes may suggest to the researchers that the CBCT

equipment choice depends on the study to be performed. Case-control studies may show more bias by images acquired in the supine position, once control and OSA patients may demonstrates a different muscle response with gravity. On the other hand, cohort studies should preferably be performed in a position as similar as possible to the situation during sleep in which obstructive events occur, emphasizing the importance of CBCT scans performed not only in the supine position, but also in the presence of sedation. The meta-analyses limitations by analyzing the groups and subgroups may be justified by the differences in the sample size and references for linear evaluations.[8, 13, 23]

The current findings identified relevant aspects for a proper UA evaluation protocol, impacting the clinician's decisions regarding CBTC upper airway analysis methods in adult patients diagnosed with OSA. Furthermore, the studies' divergences and the application of non-standardized methods reported in this paper highlight the lack of studies with evidence power quality. Methodologically, the imbalance regarding OSA and comparative groups' sample size and different methods used for CBCT assessment and PSG reports were potential limitations in this systematic review. However, a sensitivity analysis was performed to minimize the meta-analysis bias.

Hence, the present systematic review identified that most of the methods to analyze CBCT UA characteristics of OSA adults were reported, predominantly considering the CBCT patient position during the image acquisition and hard tissue references for upper airway delimitations. However, no standardized and consolidated methodological parameters were found. The meta-analysis indicates that the divergences showed may interfere in the study outcomes, evidencing the necessity of future well-designed investigations to provide a better accuracy and reproducibility of CBCT measurements in UA of OSA patients.

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FIGURES AND CAPTIONS

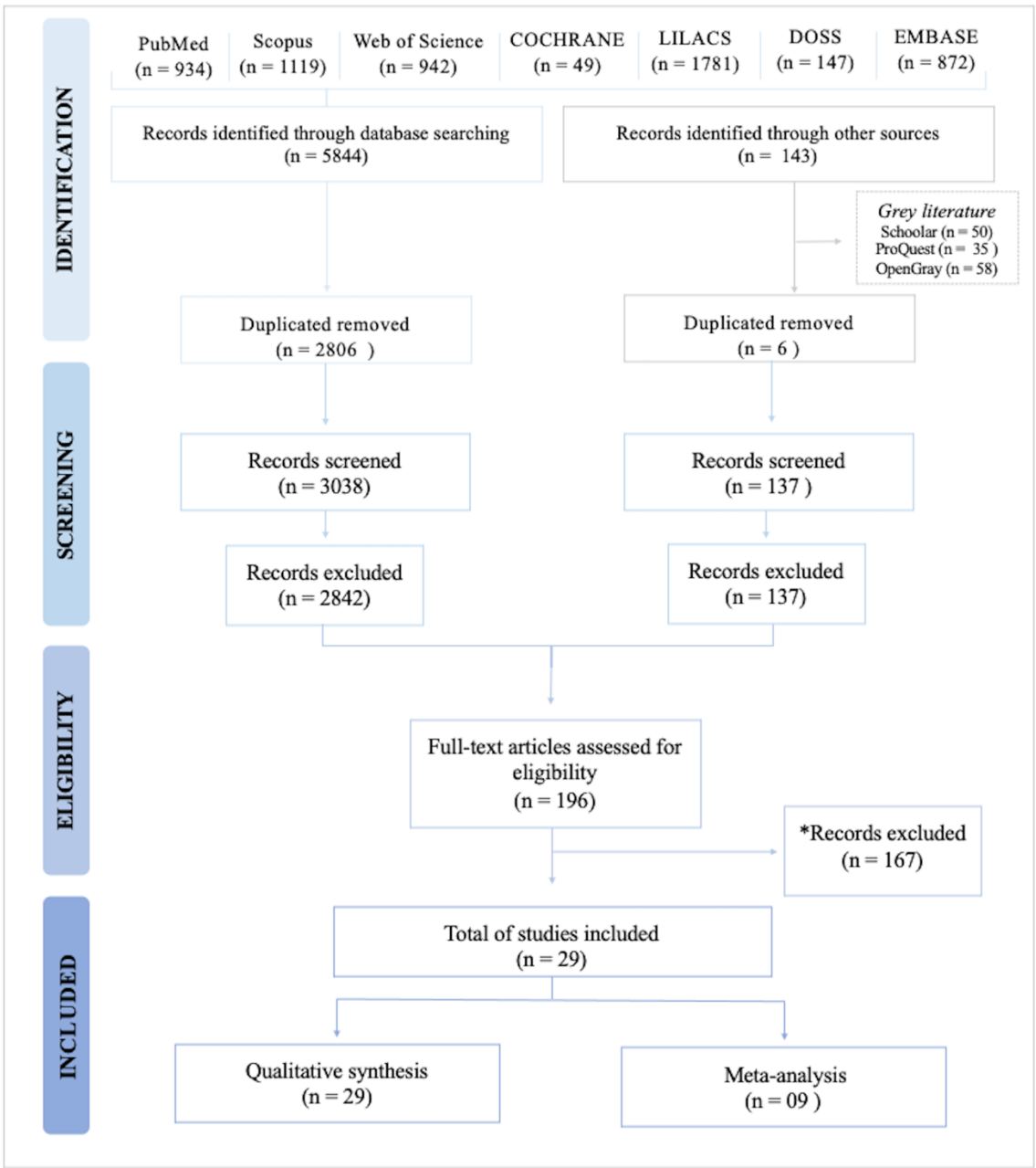

Figure 1. Study selection according to PRISMA flowchart. *Reviews (n = 31), letters to the editor (n = 13), abstracts from scientific events (n = 9), studies conducted in children or adolescents (n = 6), studies without CBCT studies with magnetic resonance imaging without CBCT scans (n = 1), studies without a polysomnographic and/or OSA diagnosis (n = 11), studies without upper airway evaluation (n = 9), studies not written in Latin (Roman) alphabet (n = 50), case reports (n = 25), studies with OSA with other associated syndromes (n = 12).

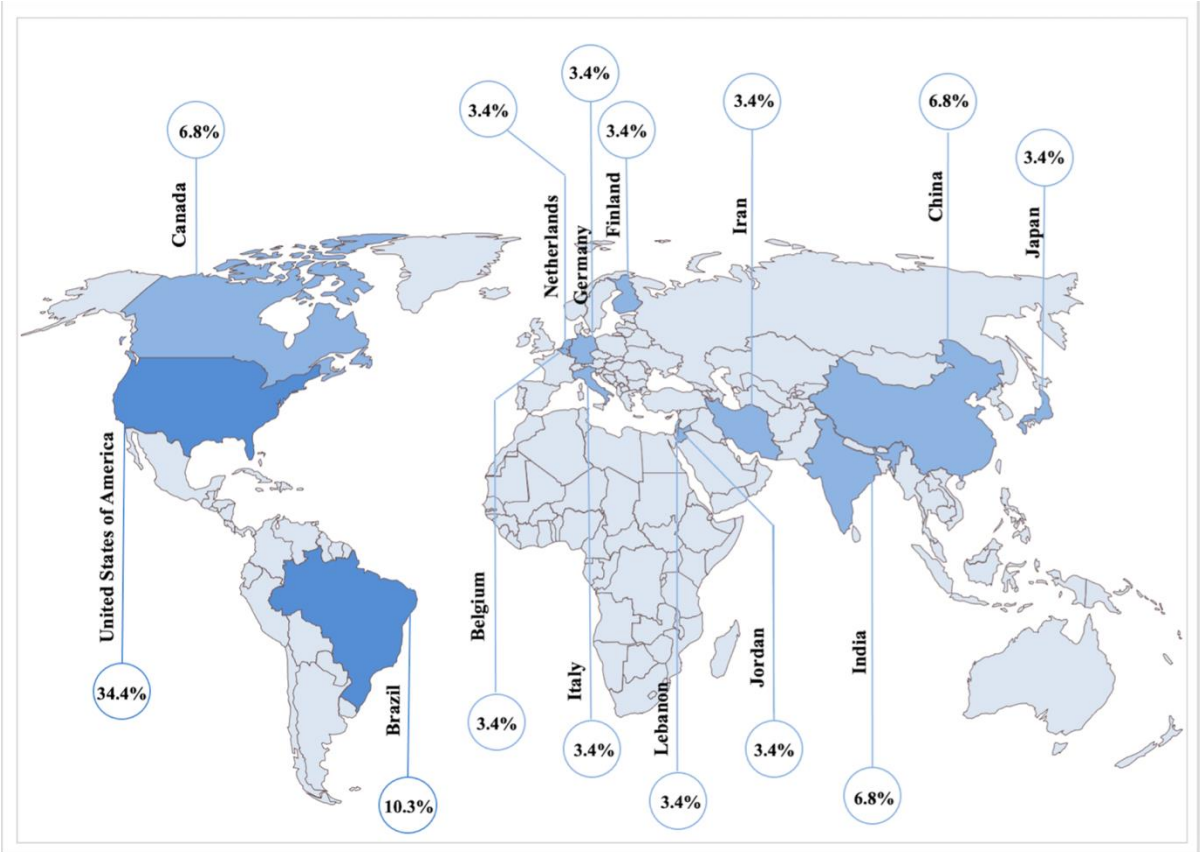

Figure 2. World map with the percentage of the studies, according to the country of the included articles.

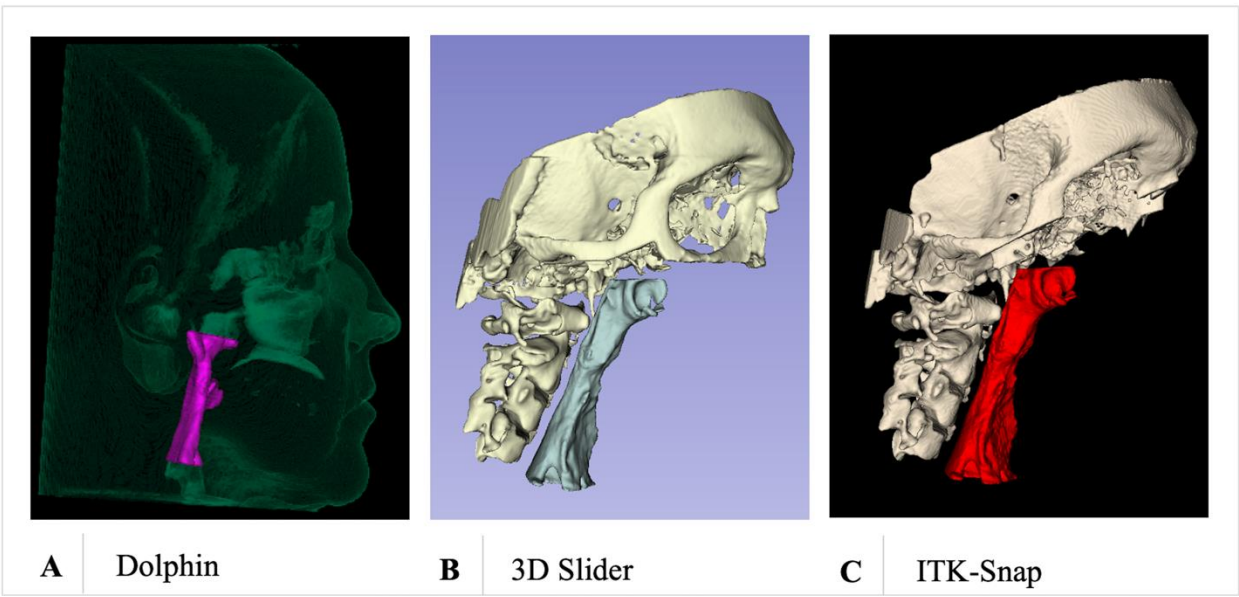

Figure 3. Three-dimensional reconstructions in CBCT different software. (A) Dolphin. (B) IKT-Snap. (C) 3D Slicer.

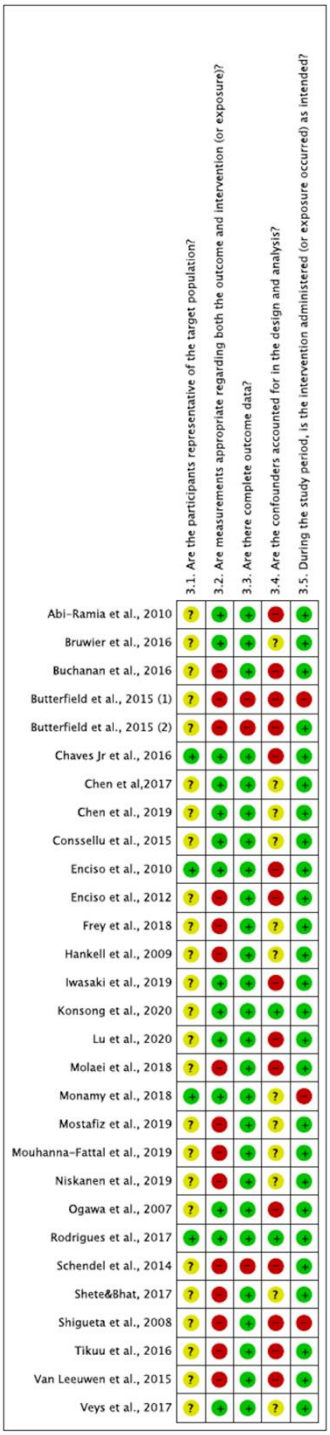

Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

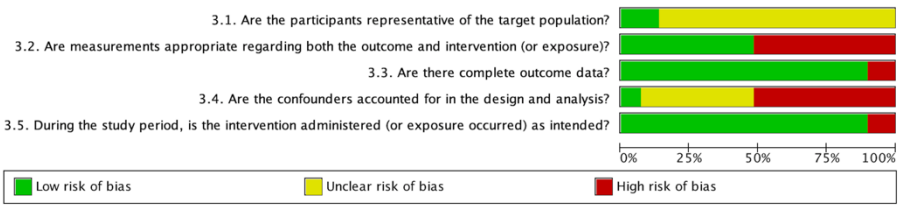

Figure 5. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

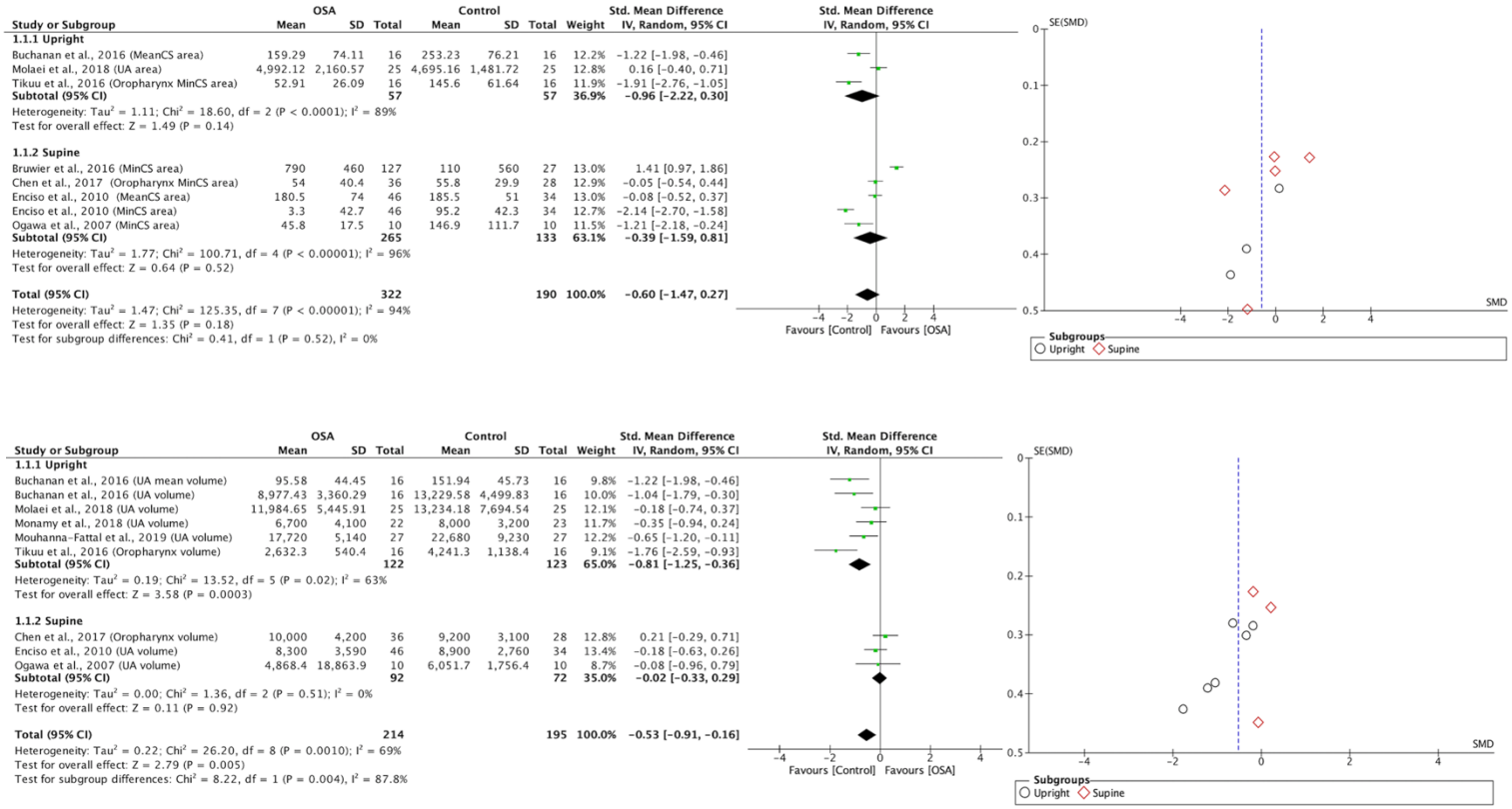

Figure 6. Meta-analysis of upper airway area and volume. CS = Cross sectional.

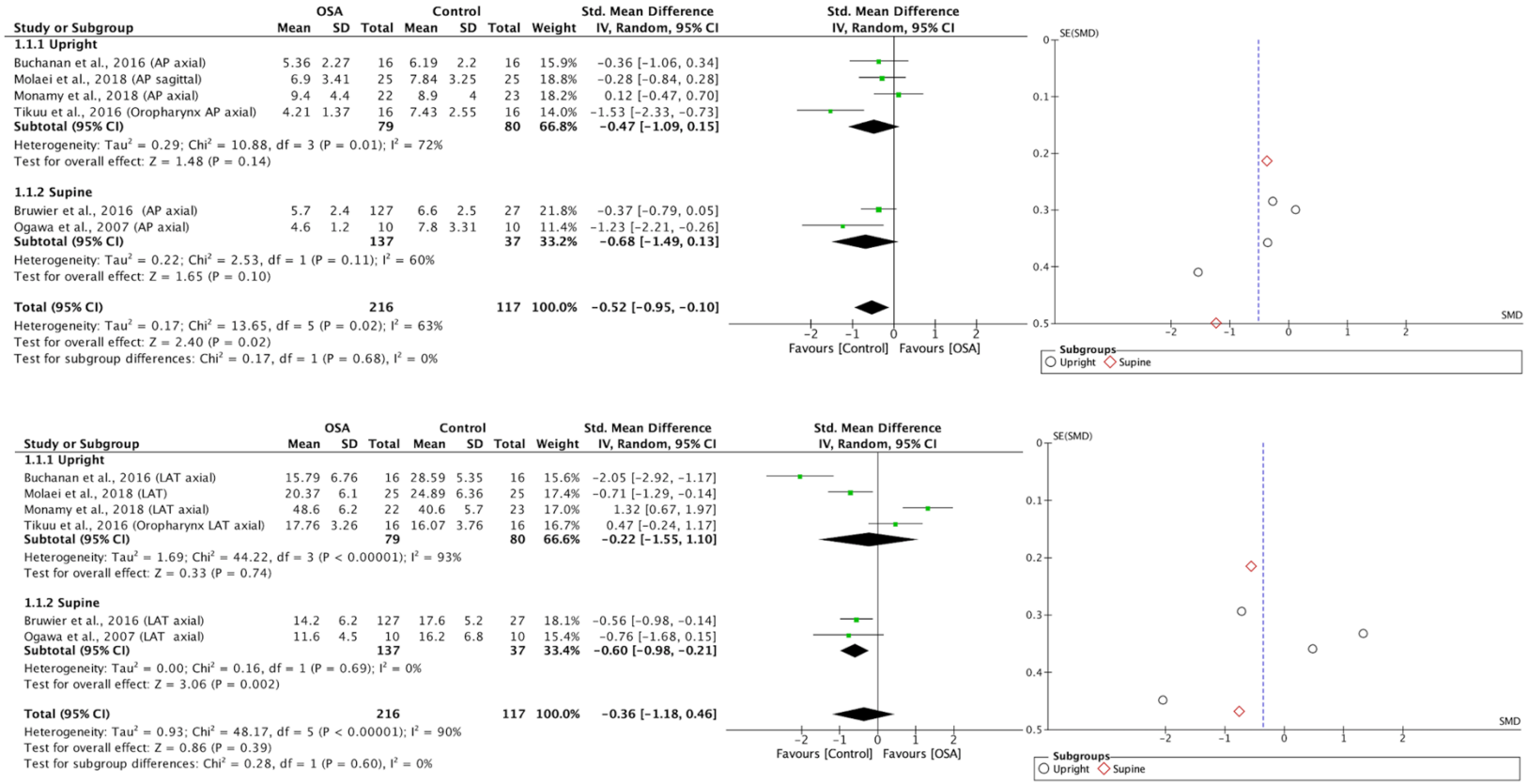

Figure 7: Meta-analysis of upper airway anteroposterior (AP) and lateral (LAT) linear dimensions.

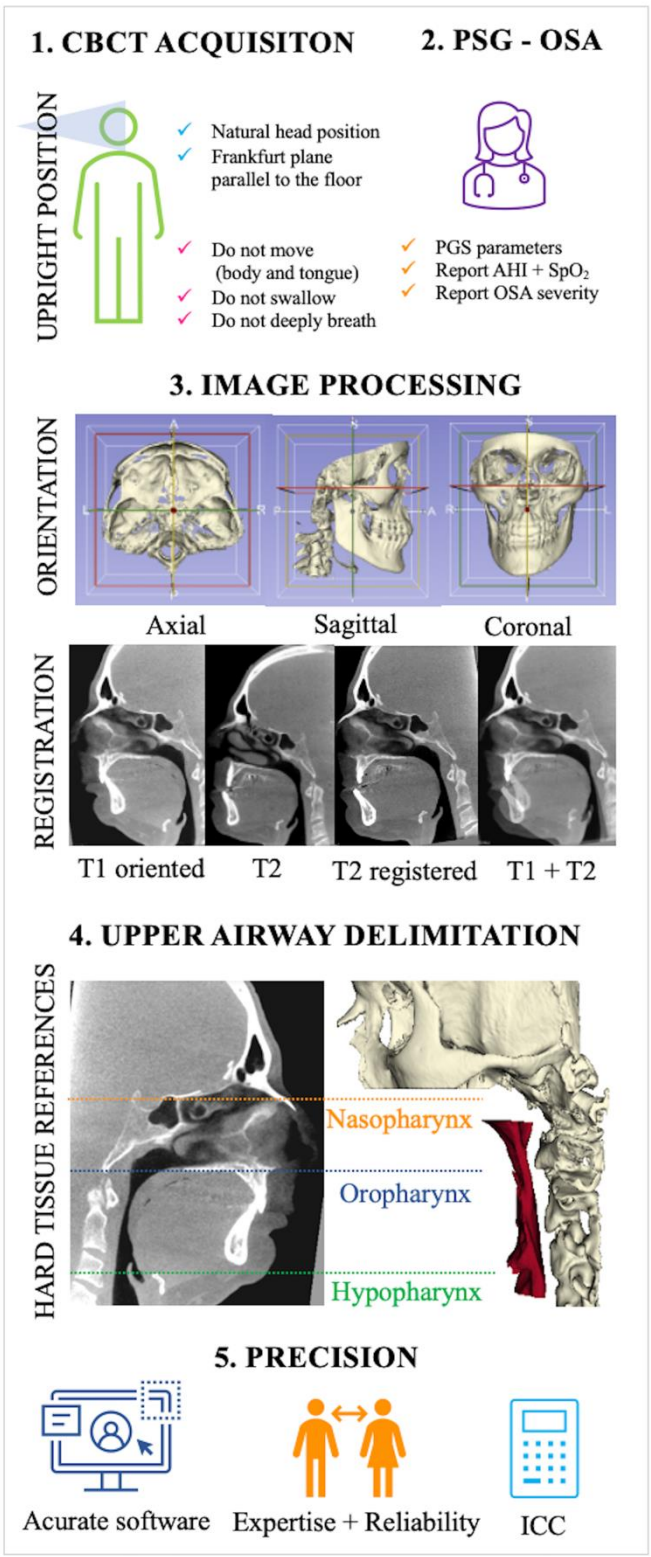

Figure 8. Suggested steps for outcomes with good quality evidence.

Table 1: Study search strategy.

Databases/ Date	Search strategy	Studies (N)
PubMed	**#1** ("sleep apnea, obstructive"[MeSH Terms] OR "sleep apnea obstructive"[All Fields] OR "Obstructive Sleep Apneas"[All Fields] OR "Obstructive Sleep Apnea Syndrome"[All Fields] OR "Obstructive Sleep Apnea"[All Fields] OR "OSAHS"[All Fields] OR "Sleep Apnea Hypopnea Syndrome"[All Fields] OR "Upper Airway Resistance Sleep Apnea Syndrome"[All Fields]) **#2** ("tomography, x ray computed"[MeSH Terms] OR "x-ray computed tomography"[All Fields] OR "computed x ray tomography"[All Fields] OR "x ray computer assisted tomography"[All Fields] OR "x ray computer assisted tomography"[All Fields] OR "x ray computerized tomography"[All Fields] OR "CT X Ray"[All Fields] OR "CT X Rays"[All Fields] OR "Tomodensitometry"[All Fields] OR "computed x ray tomography"[All Fields] OR "Xray Computed Tomography"[All Fields] OR "X-Ray CAT Scan"[All Fields] OR ("tomography, x ray computed"[MeSH Terms] OR ("Tomography"[All Fields] AND "x ray"[All Fields] AND "computed"[All Fields]) OR "x-ray computed tomography"[All Fields]) OR "Transmission Computed Tomography"[All Fields] OR "X-Ray CT Scan"[All Fields] OR "X-Ray CT Scans"[All Fields] OR "x ray computerized tomography"[All Fields] OR "cine ct"[All Fields] OR "cine ct"[All Fields] OR "Electron Beam Computed Tomography"[All Fields] OR "Electron Beam Tomography"[All Fields] OR "x ray computerized axial tomography"[All Fields] OR "x ray computerized axial tomography"[All Fields] OR "Tomographies"[All Fields] OR "Tomography"[All Fields]) **Algorithm** #1 AND #2	934
Scopus	**#1** TITLE-ABS-KEY ("Obstructive Sleep Apneas" OR "Obstructive Sleep Apnea Syndrome" OR "Obstructive Sleep Apnea" OR "OSAHS" OR "Sleep Apnea Hypopnea Syndrome" OR "Upper Airway Resistance Sleep Apnea Syndrome") **#2** TITLE-ABS-KEY ("X-Ray Computed Tomography" OR "Computed X Ray Tomography" OR "X-Ray Computer Assisted Tomography" OR "X Ray Computer Assisted Tomography" OR "X-Ray Computerized Tomography" OR "CT X Ray" OR "CT X Rays" OR "Tomodensitometry" OR "Computed X-Ray Tomography" OR "Xray Computed Tomography" OR "X-Ray CAT Scan" OR "X-Ray CAT	1119

	Scans" OR "Transmission Computed Tomography" OR "X-Ray CT Scan" OR "X-Ray CT Scans" OR "X Ray Computerized Tomography" OR "Cine-CT" OR "Cine CT" OR "Electron Beam Computed Tomography" OR "Electron Beam Tomography" OR "X-Ray Computerized Axial Tomography" OR "X Ray Computerized Axial Tomography" OR "Tomographies" OR "Tomography") **Algorithm** #1 AND #2	
Web of Science	**#1** TS = ("Obstructive Sleep Apneas" OR "Obstructive Sleep Apnea Syndrome" OR "Obstructive Sleep Apnea" OR "OSAHS" OR "Sleep Apnea Hypopnea Syndrome" OR "Upper Airway Resistance Sleep Apnea Syndrome") Índice = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Tempo estipulado=Todos os anos **#2** TS = ("X-Ray Computed Tomography" OR "Computed X Ray Tomography" OR "X-Ray Computer Assisted Tomography" OR "X Ray Computer Assisted Tomography" OR "X-Ray Computerized Tomography" OR "CT X Ray" OR "CT X Rays" OR "Tomodensitometry" OR "Computed X-Ray Tomography" OR "Xray Computed Tomography" OR "X-Ray CAT Scan" OR "X-Ray CAT Scans" OR "Transmission Computed Tomography" OR "X-Ray CT Scan" OR "X-Ray CT Scans" OR "X Ray Computerized Tomography" OR "Cine-CT" OR "Cine CT" OR "Electron Beam Computed Tomography" OR "Electron Beam Tomography" OR "X-Ray Computerized Axial Tomography" OR "X Ray Computerized Axial Tomography" OR "Tomographies" OR "Tomography") Índice = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Tempo estipulado=Todos os anos **Algorithm** #1 AND #2	942

COCHRANE	**#1** "Obstructive Sleep Apneas" OR "Obstructive Sleep Apnea Syndrome" OR "Obstructive Sleep Apnea" OR "OSAHS" OR "Sleep Apnea Hypopnea Syndrome" OR "Upper Airway Resistance Sleep Apnea Syndrome" in Title Abstract Keyword - (Word variations have been searched) **#2** "X-Ray Computed Tomography" OR "Computed X Ray Tomography" OR "X-Ray Computer Assisted Tomography" OR "X Ray Computer Assisted Tomography" OR "X-Ray Computerized Tomography" OR "CT X Ray" OR "CT X Rays" OR "Tomodensitometry" OR "Computed X-Ray Tomography" OR "Xray Computed Tomography" OR "X-Ray CAT Scan" OR "X-Ray CAT Scans" OR "Transmission Computed Tomography" OR "X-Ray CT Scan" OR "X-Ray CT Scans" OR "X Ray Computerized Tomography" OR "Cine-CT" OR "Cine CT" OR "Electron Beam Computed Tomography" OR "Electron Beam Tomography" OR "X-Ray Computerized Axial Tomography" OR "X Ray Computerized Axial Tomography" OR "Tomographies" OR "Tomography" in Title Abstract Keyword - (Word variations have been searched) **Algorithm** #1 AND #2	49
LILACS	**#1** ("Obstructive Sleep Apneas" OR "Obstructive Sleep Apnea Syndrome" OR "Obstructive Sleep Apnea" OR "OSAHS" OR "Sleep Apnea Hypopnea Syndrome" OR "Upper Airway Resistance Sleep Apnea Syndrome") **#2** ("X-Ray Computed Tomography" OR "Computed X Ray Tomography" OR "X-Ray Computer Assisted Tomography" OR "X Ray Computer Assisted Tomography" OR "X-Ray Computerized Tomography" OR "CT X Ray" OR "CT X Rays" OR "Tomodensitometry" OR "Computed X-Ray Tomography" OR "Xray Computed Tomography" OR "X-Ray CAT Scan" OR "X-Ray CAT Scans" OR "Transmission Computed Tomography" OR "X-Ray CT Scan" OR "X-Ray CT Scans" OR "X Ray Computerized Tomography" OR "Cine-CT" OR "Cine CT" OR "Electron Beam Computed Tomography" OR "Electron Beam Tomography" OR "X-Ray Computerized Axial Tomography" OR "X Ray Computerized Axial Tomography" OR "Tomographies" OR "Tomography") **Algorithm** #1 AND #2	1781

DOSS	**#1** ("Obstructive Sleep Apneas" OR "Obstructive Sleep Apnea Syndrome" OR "Obstructive Sleep Apnea" OR "OSAHS" OR "Sleep Apnea Hypopnea Syndrome" OR "Upper Airway Resistance Sleep Apnea Syndrome") **#2** ("X-Ray Computed Tomography" OR "Computed X Ray Tomography" OR "X-Ray Computer Assisted Tomography" OR "X Ray Computer Assisted Tomography" OR "X-Ray Computerized Tomography" OR "CT X Ray" OR "CT X Rays" OR "Tomodensitometry" OR "Computed X-Ray Tomography" OR "Xray Computed Tomography" OR "X-Ray CAT Scan" OR "X-Ray CAT Scans" OR "Transmission Computed Tomography" OR "X-Ray CT Scan" OR "X-Ray CT Scans" OR "X Ray Computerized Tomography" OR "Cine-CT" OR "Cine CT" OR "Electron Beam Computed Tomography" OR "Electron Beam Tomography" OR "X-Ray Computerized Axial Tomography" OR "X Ray Computerized Axial Tomography" OR "Tomographies" OR "Tomography") **Algorithm** #1 AND #2	147
EMBASE	**#1** ('obstructive sleep apneas':ti,ab,kw OR 'obstructive sleep apnea syndrome':ti,ab,kw OR 'obstructive sleep apnea':ti,ab,kw OR 'osahs':ti,ab,kw OR 'sleep apnea hypopnea syndrome':ti,ab,kw OR 'upper airway resistance sleep apnea syndrome':ti,ab,kw) **#2** ('x-ray computed tomography':ti,ab,kw OR 'computed x ray tomography':ti,ab,kw OR 'x-ray computer assisted tomography':ti,ab,kw OR 'x ray computer assisted tomography':ti,ab,kw OR 'x-ray computerized tomography':ti,ab,kw OR 'ct x ray':ti,ab,kw OR 'ct x rays':ti,ab,kw OR 'tomodensitometry':ti,ab,kw OR 'computed x-ray tomography':ti,ab,kw OR 'xray computed tomography':ti,ab,kw OR 'x-ray cat scan':ti,ab,kw OR 'x-ray cat scans':ti,ab,kw OR 'transmission computed tomography':ti,ab,kw OR 'x-ray ct scan':ti,ab,kw OR 'x-ray ct scans':ti,ab,kw OR 'x ray computerized tomography':ti,ab,kw OR 'cine-ct':ti,ab,kw OR 'cine ct':ti,ab,kw OR 'electron beam computed tomography':ti,ab,kw OR 'electron beam tomography':ti,ab,kw OR 'x-ray computerized axial tomography':ti,ab,kw OR 'x ray computerized axial tomography':ti,ab,kw OR 'tomographies':ti,ab,kw OR 'tomography':ti,ab,kw)**Algorithm** #1 AND #2	871

Grey Literature

Google Schoolar	**Algorithm** Allintitle: "Obstructive Sleep Apnea" AND “Tomography"	50
ProQuest	**#1** ("Obstructive Sleep Apneas" OR "Obstructive Sleep Apnea Syndrome" OR "Obstructive Sleep Apnea" OR "OSAHS" OR "Sleep Apnea Hypopnea Syndrome" OR "Upper Airway Resistance Sleep Apnea Syndrome") **#2** ("X-Ray Computed Tomography" OR "Computed X Ray Tomography" OR "X-Ray Computer Assisted Tomography" OR "X Ray Computer Assisted Tomography" OR "X-Ray Computerized Tomography" OR "CT X Ray" OR "CT X Rays" OR "Tomodensitometry" OR "Computed X-Ray Tomography" OR "Xray Computed Tomography" OR "X-Ray CAT Scan" OR "X-Ray CAT Scans" OR "Transmission Computed Tomography" OR "X-Ray CT Scan" OR "X-Ray CT Scans" OR "X Ray Computerized Tomography" OR "Cine-CT" OR "Cine CT" OR "Electron Beam Computed Tomography" OR "Electron Beam Tomography" OR "X-Ray Computerized Axial Tomography" OR "X Ray Computerized Axial Tomography" OR "Tomographies" OR "Tomography") Filter: Dissertaions e Thesis **Algorithm** #1 AND #2	35
OpenGrey	**#1** "Obstructive Sleep Apneas" OR "Obstructive Sleep Apnea Syndrome" OR "Obstructive Sleep Apnea" OR "OSAHS" OR "Sleep Apnea Hypopnea Syndrome" OR "Upper Airway Resistance Sleep Apnea Syndrome" **#2** "X-Ray Computed Tomography" OR "Computed X Ray Tomography" OR "X-Ray Computer Assisted Tomography" OR "X Ray Computer Assisted Tomography" OR "X-Ray Computerized Tomography" OR "CT X Ray" OR "CT X Rays" OR "Tomodensitometry" OR "Computed X-Ray Tomography" OR "Xray Computed Tomography" OR "X-Ray CAT Scan" OR "X-Ray CAT Scans" OR "Transmission Computed Tomography" OR "X-Ray CT Scan" OR "X-Ray CT Scans" OR "X Ray Computerized Tomography" OR "Cine-CT" OR "Cine CT" OR "Electron Beam Computed Tomography" OR "Electron Beam Tomography" OR "X-Ray Computerized Axial Tomography" OR "X Ray Computerized Axial Tomography" OR "Tomographies" OR "Tomography" **Algorithm** #1 AND #2	58

Table 2: Design characteristic descriptions of the included studies.

Author/ Year	Country/ Continent	Study design/ Follow-up	Sample (n)/ Sex (M/F)	Age Range/ (Mean±SD)	BMI Mean±SD	Sample size Calculation	Sample Ethnicity	Intervention	PSG data Reported
Ogawa et al., 2007[12]	United States of America/ North America	Retrospective cross-sectional case-control/ NA	Total (n): 20 (14M/6F) OSA (n): 10 (6M/4F) Control (n): 10 (8M/2F)	Total: NR OSA: NR (5.29±14.7) Control: NR (45.4±19.5)	Total: NR OSA: 29.5±9.05 Control: 23.1±3.05	NO	NR	NO	NR
Shigueta et al., 2008[27]	United States of America/ North America	Prospective cross-sectional case-control/ NA	Total (n): 29 (19M/10F) OSA (n): 15 (NR) Control (n): 14 (NR)	Total: 25-64 (NR) OSA: 38-64 (51.8.±7.67) Control: 25-63 (44.4±13.01)	Total: NR OSA: 25.5±3.23 Control: 23.5±3.52	NO	NR	NO	AHI
Hankell et al., 2009[28]	United States of America/ North America	Prospective cohort/ NR	OSA (n): 26 (17M/9F)	NR	NR	NO	NR	MAD	NR
Enciso et al., 2010[29]	United States of America/ North America	Prospective cross-sectional comparative/ NA	Total (n): 80 (63M/17F) OSA (n): 46 (42M/4F)) Snore (n): 34 (21M/13F)	Total: NR OSA: NR (57.5.±10.25) Snore: NR (50.8±13.46)	Total: NR OSA: 27.7±3.83 Snore: 25.131±3.33	YES	YES	NO	AHI RDI
Abi-Ramia et al., 2010[30]	Brazil/ South America	Prospective cohort/ 7 months	OSA (n): 16 (6M/10F)	OSA: NR (47.6±NR)	NR	NO	NR	MAD Twin-Block	NR
Enciso et al., 2012[31]	United States of America/ North America	Prospective cross-sectional comparative/ NA	Total (n): 86 (66M/20F) AHI > 15 (n): 53 (45M/8F) AHI < 15(n): 33 (21M/12F)	Total: 24 – 80 (NR) AHI > 15: 29-80 (58.4.±10.35) AHI < 15: 24-68 (47.6±12.74)	Total: NR AHI ≥ 15: 27.6±3.74 AHI < 15: 25.01±3.65	NO	NR	NO	RDI AI
Schendel et al., 2014[32]	United States of America/ North America	Prospective cohort/ 6 months	OSA (n): 10 (8M/2F)	OSA: 35-62 (46.4.±9.7)	OSA: 28.55.±5.05	NO	NR	Bimaxillary Orthognathic Advancement Surgery	NR
Butterfield et al., 2015[33]	Canada/ North America	Retrospective cohort/ 1-49 months	OSA (n): 10 (13M/12F)	OSA: 19-61 (42.4.±11.7)	OSA: 30.33±4.18	NO	NR	Bimaxillary Orthognathic Advancement Surgery associated or not with Septoplasty or Tonsillectomy or Genioplasty or Uvulopalatopharyngoplasty or Uvulopalatoplasty	AHI Min SpO_2 Mean SpO_2
Butterfield et al., 2015[34]	Canada/ North America	Retrospective longitudinal case-control/ 3-12 months	Total (n): 24 (16M/8F) OSA (n): 12 (10M/2F) Control (n): 12 (6M/6F)	Total: NR OSA: NR (42.75.±13.03) Control: NR (43.17±7.72)	Total: NR OSA: 30.5±4.1 Control: 29.211±3.41	NO	NR	Bimaxillary Orthognathic Advancement Surgery	AHI

Conssellu et al., 2015[35]	Italy/ Europe	Prospective cohort/ 6 months	OSA (n): 10 (3M/7F)	OSA: NR (53.4±11.3)	OSA: 24.5±2.7	NO	NR	MAD	AHI
Van Leeuwen et al., 2015[36]	United States of America/ North America	Prospective cohort/ 1 day	OSA (n): 9 (NR)	NR	NR	NO	NR	Titration of a Gauge	NR
Bruwier et al., 2016[11]	Belgium/ Europe	Prospective cross-sectional case-control/ NA	Total (n): 154 (97M/57F) OSA (n): 127 (85M/42F) Control (n): 27 (12M/15F)	Total: NR OSA: NR (53.±11) Control: NR (45±17)	Total: NR OSA: 31.35±5.3 Control: 27.1±5.7	NO	NR	NO	AHI RDI
Buchanan et al., 2016[37]	United States of America/ North America	Retrospective cross-sectional case-control/ NA	Total (n): 32 (23M/9F) OSA (n): 16 (13M/6F) Control (n): 16 (10M/6F)	Total: 21-72 OSA: 21-68 (43.3.±11.25) Control:28-72 (44.6±12.96)	Total: NR OSA: NR Control:NR	NO	NR	NO	NR
Chaves Jr et al., 2016[38]	Brazil/ South America	Pilot prospective cohort/ 8 months	OSA (n): 10 (NR)	NR	NR	NO	NR	MAD	AHI Min SpO_2 Mean SpO_2
Tikuu et al., 2016[39]	India/ Asia	Prospective cross-sectional case-control/ NA	Total (n): 32 (NR) OSA (n): 16 (NR) Control (n): 16 (NR)	Total: 31-72 OSA: 34-72 (52.94.±13.09) Control:31-65 (44.75±11.73)	Total: NR OSA: 33.1±4.2 Control: 29.3±3.6	NO	NR	NO	NR
Shete&Bhad, 2017[40]	India/ Asia	Prospective cohort/ 6 months	OSA (n): 37 (28M/9F)	NR	NR	NO	NR	MAD Modified Twin-block	SpO_2
Chen et al, 2017[41]	Netherlands/ Europe	Prospective logitutidnal case-control/ NR	Total (n): 44 (25M/19F) OSA (n): 31 (21M/10F) Control (n): 13 (4M/9F)	Total: NR OSA: NR (43.5±9.7) Control: NR (24.7±2.1)	NR	NO	NR	MAD	AHI
Rodrigues et al., 2017[25]	Brazil/ South America	Retrospective cross-sectional/ NA	OSA (n): 33 (13M/16F)	OSA: NR (46.1±NR)	OSA: 29.72±NR	YES	NR	NO	AHI
Veys et al., 2017[42]	Belgium/ Europe	Prospective cohort/ 4-6 months	OSA (n): 11 (9M/3F)	OSA: 36-57 (44.7.±9.5)	OSA: 26.5±3.5	NR	NR	Bimaxillary Orthognathic Advancement Surgery	NR
Monamy et al., 2018[43]	Jordan/ Asia	Prospective cross-sectional case-control/ NA	Total (n): 45 (40M/5F) OSA (n): 22 (19M/3F) Control (n): 23 (21M/2F)	Total: NR OSA: NR (54.2±10.6) Control: NR (50.3±10.6)	Total: NR OSA: 37.8±6.6 Control: 29.1±4.2	YES	NR	NO	AHI
Frey et al., 2018[44]	Germany/ Europe	Prospective cohort/ 14-28 months	OSA(n): 10 (4M/6F)	OSA: NR (46.1.±NR)	OSA: 29.72±NR	NO	NR	Bimaxillary Orthognathic Advancement Surgery	AHI

Molaei et al., 2018[45]	Iran/ Asia	Prospective cross-sectional case-control/ NA	Total (n): 50 (28M/22F) OSA (n): 25 (16M/9F) Control (n): 25 (12M/13F)	Total: NR OSA: NR (49.33±15.12) Control: NR (38.9±10.59)	Total: NR OSA: NR Control: NR	NO	NR	NO	AI
Chen et al., 2019[46]	China/ Asia	Retrospective cohort comparative/ 1.5 months	Total (n): 64 (41M/19F) OSA responders (n): 36 (21M/15F) OSA non-responders (n): 28 (20M/8F)	Total: NR OSA responders: NR (58±4.3) OSA non-responders NR (59±4.3)	Total: NR OSA responders: 27.37±3.62 OSA non-responders: 30.4±5.64	NO	NR	MAD Mandibular Advancement Splint	AHI
Mostafiz et al., 2019[47]	United States of America/ North America	Retrospective cross-sectional/ NA	OSA(n): 33(23M/10F)	OSA: 28-67 (51.11.±9.89)	OSA: 27.98±4.54	NO	NR	NO	Min SpO_2 RDI REM sleep NREM sleep
Mouhanna-Fattal et al., 2019[48]	Lebanon/ Asia	Prospective cross-sectional case-control/ NA	Total (n): 54 (54M/02F) OSA (n): 27 (27M/0F) Control (n): 27 (27M/0F)	Total: NR OSA: NR (49.4±NR) Control: NR (44.4±NR)	Total: NR OSA: 32.83±NR Control: 28.2±NR	NO	NR	NO	NR
Niskanen et al., 2019[49]	Finland/ Europe	Retrospective cohort/ 12 moths	OSA (n): 20 (19M/1F)	OSA: 32-59 (48±NR)	NR	NO	YES	Bimaxillary Orthognathic Advancement Surgery	AHI ODI
Iwasaki et al., 2019[50]	Japan/ Asia	Retrospective cohort/ NR	OSA (n): 20 (15M/5F)	OSA: NR (29.6±8.3)	OSA: 25.8±6.2	NO	NR	Distraction osteogenesis maxillary expansion	AHI ODI AI Min SpO_2 Mean SpO_2
Konsong et al., 2020[51]	United States of America/ North America	Retrospective cohort/ 2-24 months	OSA (n): 30 (19M/11F)	OSA: 22-68 (47.4±11.2)	OSA: 30±5.1	NO	NR	Bimaxillary Orthognathic Advancement Surgery	AHI
Lu et al., 2020[52]	China/ Asia	Prospective cohort/ 6 months	OSA (n): 30 (22M/8F)	OSA: 60-70 (NR)	OSA: 27.2±3.8	NO	NR	MAD Adjustable Oral Appliance	AHI Min SpO_2 Mean SpO_2

NR = not report; NA = applied; OSA = obstructive sleep apnea; M = male; F = female; BMI = body mass index; MAD = mandibular advancement device; PSG = polysomnography; AHI = apnea and hypopnea index; AI = apnea index; ODI = oxygen desaturation index; RDI = respiratory disturbance index; REM = rapid eye movement; NREM = non rapid eye movement; Min SpO_2 = minimum oxygen saturation; Mean SpO_2 = mean oxygen saturation

Table 3: Characteristic description considering important aspects for CBCT evaluation.

Author/ Year	CBCT Unit	Voxel Size (mm)	FOV (cm)	Position during CBCT	Reference plane during CBCT acquisition	Image format	Software for image analysis	Examiners/ Blind	Expertise	Reliability/ Type	ICC
Ogawa et al., 2007[12]	Newtom QR-DVT 9000	0.25	NR	Supine	FP perpendicular to the floor	NR	Amira	NR	NR	NR	NR
Shigueta et al., 2008[27]	Newtom QR-DVT 9000	NR	NR	*Supine	NR	NR	Torrance 4.0	1 (Blind)	NR	YES/Intra-examiner	0.994-0.998
Hankell et al., 2009[28]	iCAT Classic	0.4	22	Upright	NR	DICOM	Dolphin 11.0	NR	NR	YES/NR	0.946-0.999
Enciso et al., 2010[29]	Newtom QR 3G	NR	NR	*Supine	NR	DICOM	Vworks 5.0	1 (Blind)	NR	YES/Intra-examiner	0.965-0.979
Abi-Ramia et al., 2010[30]	NewTom 3G	NR	22.86	Supine	FP perpendicular to the floor	DICOM	ITK-Snap1.8.0	2 (NR)	NR	YES/Inter-examiner	NR
Enciso et al., 2012[31]	NewTom 3G	0.33	30.48	Supine	NR	DICOM	Vworks 5.0	1 (Blind)	YES	NR	NR
Schendel et al., 2014[32]	iCAT	NR	NR	Upright	Natural head position	DICOM	3dMDVultus	NR	NR	NR	NR
Butterfield et al., 2015[33]	Planmeca Promax 3-D Mid	NR	NR	Upright	Natural head position	DICOM	Dolphin 11.7	NR	NR	NR	NR
Butterfield et al., 2015[34]	Planmeca Promax 3-D Mid	NR	NR	*Upright	NR	DICOM	Dolphin 11.7	NR	NR	NR	NR
Conssellu et al., 2015[35]	NR	NR	NR	NR	Natural head position	DICOM	MIMICS—Materialise Interactive	NR	NR	NR	NR
Van Leeuwen et al., 2015[36]	Kodak Model 9500 Cone Beam CT	NR	NR	Upright	NR	NR	Invivo5	NR	NR	NR	NR
Bruwier et al., 2016[11]	New Tom 5G	NR	16x21	Supine	FP perpendicular to the floor	NR	Dolphin 11.7	NR (Blind)	NR	NR	NR

Buchanan et al., 2016[37]	iCAT Next Generation unit	NR	NR	Upright	NR	DICOM	Analyse 10.0	1 (Blind)	NR	NR	NR
Chaves Jr et al., 2016[38]	iCATTM	0.4	NR	*Upright	NR	BPT	Dental Slice®	1 (NR)	NR	YES/Intra-examiner	NR
Tikuu et al., 2016[39]	NR	NR	NR	Upright	Natural head position	NR	CS 3D Imaging Software 3.2.9 OnDemand3DApp 1.0	NR	NR	YES/NR	NR
Shete & Bhad, 2017[40]	Promax 3D Mid	0.25	13x3x17	Upright	Natural head position	DICOM	Romexis	3 (NR)	NR	YES/Intra-examiner	>0.9
Chen et al, 2017[41]	NewTom 5G CBCT system	0.3	NR	Supine	FP perpendicular to the floor	DICOM	Amira 4.1 ANSYS ICEM CFD 17.0 ANSYS Fluent	2 (NR)	YES	NR	NR
Rodrigues et al., 2017[25]	i-CAT	0.25	16x22	Upright	Natural head position	DICOM	Dolphin	1 (Blind)	NR	YES/Intra-examiner	0.988-0.999
Veys et al., 2017[42]	i-CAT	0.4	22x17	Upright	Natural head position	DICOM	Maxilim 2.2.2	1 (NR)	NR	NR	NR
Monamy et al., 2018[43]	Kodak Dental Systems	0.3	18x20	Upright	FP parallel to the floor	DICOM	InVivoDental 5.2	NR	NR	YES/NR	0.930-0.999
Frey et al., 2018[44]	Newtom 5G scanner	0.3	NR	Supine	FP perpendicular to the floor	DICOM	Artec Studio 0.7.4.2 Amira 4.1	NR	NR	NR	NR
Molaei et al., 2018[45]	Newtom VGi cone-beam	NR	NR	*Upright	NR	DICOM	AnalyzeDirect	NR	NR	NR	NR
Chen et al., 2019[46]	NewTom 3G CBCT san	NR	30.48	Supine	FP perpendicular to the floor	DICOM	Amira 4.1	1 (NR)	NR	YES/Intra-examiner	0.878 - 1
Mostafiz et al., 2019[47]	Newtom 3G-QR	NR	NR	Supine	NR	NR	Dolphin 3D Sinus/Airway Analysis	2 (Blind)	NR	YES/Intra and inter-examiner	0.959-0.963
Mouhanna-Fattal et al., 2019[48]	Kodak 9500 Cone Beam 3D System	NR	NR	Upright	Natural head position	DICOM	Amira 5.0	1 (Blind)	NR	YES/Intra-examiner	0.704-0.996
Niskanen et al., 2019[49]	Scanora 3D or ProMax 3D Max CBCT machine	0.4	NR	*Upright	NR	NR	Romexis 4.4.1	1 (Blind)	NR	YES/Intra-examiner	0.988-0.998
Iwasaki et al., 2019[50]	i-CAT	NR	NR	Upright	FP parallel to the floor	NR	INTAGE Volume Editor	NR	NR	NR	NR

Konsong et al., 2020[51]	Carestream CS 9300	0.3	NR	Upright	Natural head position	DICOM	3D Slicer	1 (NR)	NR	YES/Intra-examiner	>0.95
Lu et al., 2020[52]	KaVo 3DXam	NR	NR	Upright	FP parallel to the floor	NR	NR	NR	NR	NR	NR

* Data imputed after searching for the characteristics informed by the equipment platform. CBCT = cone-beam computed tomography; FOV = field of view; NR = not report; NA = not applied; FP = Frankfurt plane; ICC = intraclass correlation coefficient.

Table 4: Characteristic description considering important aspects for upper airway evaluation.

Authors/ Year	Instructions during CBCT	Head orientation	Registration	Upper airway delimitation	Upper airway references	Evaluations	Main Outcomes
Ogawa et al., 2007[12]	NR	NR	NA	Superior UA Inferior UA	Hard palate – Occlusal plane (PFP) Occlusal plane – AIC2 (PFP)	1. UA volume 2. MinCS area 3. AP axial distance (MinCS area) 4. LAT axial distance (MinCS area) 5. Shape (AP/LAT) 6. MinCS area Location	Upper airway 3D characteristics are significantly different between OSA and control group, being important to the disease identification.
Shigueta et al., 2008[27]	NR	NR	NA	Upper airway	AIC2	1. AP axial distance (AIC2 level) 2.LAT axial distance (AIC2 level) 3. AP x LAT 4. CS area (AIC2 level) 5. Ratio item 3/item 4	AP, LAT distance and ratio (APxLAT/CS area) values were statistically lower in OSA group.

Hankell et al., 2009[28]	NR	YES	NR	Oropharynx	C2	1. UA volume 2. MinCS area 3. AP axial distance (MinCS area) 4. LAT axial distance (MinCS area) 5. Shape – LAT/AP (MinCS area) 6. MaxCS area 7. AP axial distance (MaxCS area) 8. LAT axial distance (MaxCS area) 9. Shape – LAT/AP (MaxCS area) 10. CS area (C2 level) 11. AP axial distance (C2 level) 12. LAT axial distance (C2 level) 13. Shape – LAT/AP (C2 level)	LAT dimensions (C2 level), total volume, and cross-sectional area gained in the oropharynx may be predicted from the amount of mandibular forward movement. The saddle angle was a predictor of the AP dimension. The facial axis predicted the airway shape at C2.
Enciso et al., 2010[29]	NR	NR	NR	Upper airway	PNS – AIC2 (PFP)	1. UA volume 2. MinCS area 3. MeanCS area 4. AP axial distance (MinCS area) 5. LAT axial distance (MinCS area) 6. UA height 7. Soft palate height 8. Soft palate sagittal width 9. Uniformity (MinCS area/MeanCS area)	3D upper airway analysis by CBCT is useful to evaluate OSA severity, being associated with RDI.
Abi-Ramia et al., 2010[30]	NR	NR	NA	Upper airway	ROI placed between PNS – AIC3	1. UA volume	Mandibulae advancement with Twin-block appliance increased the upper airway.
Enciso et al., 2012[31]	NR	NR	NR	Upper airway	NR	1. Presence or not of an narrow Upper airway	No significant difference was identified in the presence of an narrow upper airway comparing the groups with moderate/severe OSA and the group with no or mild OSA.
Schendel et al., 2014[32]	NR	NR	NR	Retropalatal space Retroglossal space	PNS – Tip of soft palate Tip of soft palate – Hyoid bone	1. Retropalatal and Retroglossal volume 2. Retropalatal and Retroglossal MinCS area 3. Retropalatal and Retroglossal AP axial distance (MinCS area) 4. Retropalatal and Retroglossal LAT axial distance (MinCS area)	Bimaxillary Orthognathic Advancement Surgery significantly reducing the

						5. UA, Retropalatal and Retroglossal height 6. Soft palate height 7. Soft palate sagittal width 8. Location of MinCS area	collapsibility of upper airway space and improving OSA symptoms.
Butterfield et al., 2015[33]	Avoid swallowing during image acquisition	NR	NA	Nasopharynx Orophaxynx	PNS – Tip of uvula Tip of uvula – Tip of epiglottis	1. UA, Nasopharynx and Orophaxynx volume 2. UA height 3. UA posterior space 4. UA index (UA volume/UA height) 5. UA, Nasopharynx and Orophaxynx MinCS area 6. UA, Nasopharynx and Orophaxynx AP axial distance (MinCS area) 7. UA, Nasopharynx and Orophaxynx LAT axial distance (MinCS area) 8. UA, Nasopharynx and Orophaxynx Ratio LAT/AP	Bimaxillary Orthognathic Advancement Surgery is highly successful for OSA treatment, improved several morphological pathways and sleep parameters.
Butterfield et al., 2015[34]	Avoid swallowing during image acquisition	YES	NR	Nasopharynx Orophaxynx	PNS – Tip of uvula Tip of uvula – Tip of epiglottis	1. UA, Nasopharynx and Orophaxynx volume 2. UA height 3. UA posterior space 4. UA index (UA volume/UA height) 5. UA, Nasopharynx and Orophaxynx MinCS area 6. UA, Nasopharynx and Orophaxynx AP axial distance (MinCS area) 7. UA, Nasopharynx and Orophaxynx LAT axial distance (MinCS area) 8. UA, Nasopharynx and Orophaxynx Ratio LAT/AP	Bimaxillary Orthognathic Advancement Surgery statistically important on airways for patients with OSA, producing airway morphology comparable to controls.
Conssellu et al., 2015[35]	Avoid swallowing during image acquisition and respiratory movements	NR	YES	Superior UA Inferior UA	Line PNS to Ba – Line parallel to SN through the middle of C2 Line parallel to SN through the middle of C2 – Line Me to IC2	1. UA total, UA Superior and UA Inferior volume	3D image reconstructions accurately confirm morphological changes in the upper airways during MAD therapy.
Van Leeuwen et al., 2015[36]	Relaxed, breathe through your nose and tongue touching the incisors	NR	NR	Upper airway	NR	1. UA volume 2. AP axial distance (MinCS area) 3. LAT axial distance (MinCS area)	Gauge titration is a subjective methodology that provides a guide not only in finding the ideal configuration for reduced airways resistance, but it also allows the practitioner to work with the patient for comfort.

Bruwier et al., 2016[11]	Maximum intercuspation, at the end of expiration and instructed not to breathe and swallow	NR	NA	Upper airway	Line PSN to Ba – Line H to IC3	1. MinCS area 2. AP axial distance (MinCS area) 3. LAT axial distance (MinCS area)	For the orthodontist, the salient parameters to be observed in CBCT are: bone volumes (maxilla and mandible), the sagittal section of the soft palate and the smallest cross section of the VAS.
Buchanan et al., 2016[37]	NR	NR	NA	Upper airway	Hard palate – Tip of epiglottis	1. UA volume 2. MeanCS area 3. UA mean volume (MinCS area) 4. AP axial distance (MinCS area) 5. LAT axial distance (MinCS area) 6. UA height	Individuals with OSA have a narrower airway width, a lower total average airway volume, a smaller average area and volume, and a longer airway length than controls.
Chaves Jr et al., 2016[38]	NR	NR	NR	Superior Oropharynx Inferior Oropharynx	Line PNS to Ba – RGn (All measures and references parallel to line PNS to Ba)	1. Superior Oropharynx AP sagittal distance (PNS-Ba level) 2. Superior Oropharynx AP sagittal distance (Palatal plane level) 3. UA - AP distance (Most constrict area) 4. Inferior Oropharynx AP sagittal distance (B point level) 5. Inferior Oropharynx AP sagittal distance (RGn point level) 6. Superior Oropharynx AP axial distance (Occlusal level) 7. Superior Oropharynx LAT axial distance (Occlusal level) 8. Inferior Oropharynx AP axial distance (Inferior mandibular level) 7. Inferior Oropharynx LAT axial distance (Inferior mandibular level)	The MAD did not significantly modify the upper airway of the patients in the studied sample, but it favorably influenced the improvement of polysomnographic parameters.
Tikuu et al., 2016[39]	To not swallow and maintain light contact between the arches	NR	NA	Oropharynx	PNS – AIC2 (PFP)	1. Oropharynx volume 2. Oropharynx MinCS area 3. Oropharynx AP axial distance 4. Oropharynx LAT axial distance 5. PNS - Oropharynx posterior wall 6. Tip of soft palate - Oropharynx posterior wall 7. Tip of epiglottis - Oropharynx posterior wall 8. Tongue base - Oropharynx posterior wall 9. AIC2 - Oropharynx posterior wall	The reduction in oropharyngeal volume in patients with OSA can be attributed to different anatomical and pathophysiological factors.

						10. RGn –AIC2 11. Soft palate length (PNS – Tip of soft palate) 12. Tongue length (Tip of the tongue – Tongue base) 13. Naso-oropharyns angles (Intersection of middle of naso and oropharynx)	
Shete & Bhad, 2017[40]	Avoid moving the tongue and swallowing	YES	NR	Upper airway	PNS – Tip of epiglottis	1. UA volume 2. MinCS area 3. AP axial distance (MinCS area) 4. LAT axial distance (MinCS area)	Mandibular advancement increased the mean volume of the upper airway and this increase in volume seemed to be related to increased oxygen saturation.
Chen et al, 2017[41]	To keep natural occlusion, keep breathing calmly and avoid swallowing and other movements	YES	NR	Oropharynx	PNS – Base of epiglottis (PFP)	1. Oropharynx volume 2. Oropharynx AP axial distance 3. Oropharynx LAT axial distance 4. Oropharynx heigth 5. Oropharynx MinCS area 6. Maximum velocity during inspiration (m/s) 7. Maximum UA wall stress during inspiration (Pa). 8. Airway resistance during inspiration (Rin) (Pa/L/min) 9. Maximum velocity during expiration (m/s) 10.Maximum UA wall stress during expiration (Pa) 11.Minimum wall static pressure during expiration (Pa) 12.Airway resistance during expiration (Rex) (Pa/L/min)	The most relevant aerodynamic feature of the oropharynx in the collapse of the upper airways in patients with OSA is resistance during expiration.
Rodrigues et al., 2017[25]	Avoid swallowing during image acquisition	YES	NA	Nasopharynx Oropharynx	Region above PNS (PFP) PNS – AIC3 (PFP)	1. UA volume 2. Nasopharynx, volume 3. Oropharynx volume	There is no correlation between airway volume and obstructive sleep apnea, assessed by the apnea-hypopnea index and controlled by body mass index, age, and sex. The volume of the upper airways as an isolated parameter did not correlate with the severity of obstructive sleep apnea syndrome.

Veys et al., 2017[42]	Avoid moving and swallowing	YES	NR	Nasopharynx Oropharynx Hypopharynx	Nasopharynx contour – PNS (PFP) PNS – AIC3 (PFP) AIC3- Epiglottis base (PFP)	1. UA total volume 2. Nasopharynx, Oropharynx and Hypopharynx volume	The Orthognathic surgery significantly increases the volume of the oropharynx and hypopharynx airways and it is associated with improving the quality of life.
Monamy et al., 2018[43]	Teeth in occlusion and not swallowing	NR	NA	Upper airway	PNS – AIC2 (PFP)	1. UA volume 2. MinCS area 3. Sagittal distance PNS-AIC2 4. AP axial distance (AIC2 level) 5. LAT axial distance (AIC2 level) 6. Shape: AP/LAT	CBCT can provide previous findings for referral of suspected patients with OSA for further evaluation.
Frey et al., 2018[44]	Teeth in occlusion	NR	YES	Velopharynx Laryngopharynx	NR	1. Velopharynx and Laryngopharynx MinCS area 2.Velopharynx and Laryngopharynx AP axial distance 3. Velopharynx and Laryngopharynx LAT axial distance	The computational structure showed a low capacity to estimate the extent of the pharynx after surgery.
Molaei et al., 2018[45]	NR	NR	NR	Upper airway	NR	1. UA volume 2. UA area 3. UA height 4. AP sagittal distance (MinCS area) 5. LAT distance (MinCS area) 6. Soft palate height 7. Soft palate sagittal width	The area and length of the upper airways were greater in people with OSA than in healthy people, which means that people with longer upper airways have a higher risk of developing OSA.
Chen et al., 2019[46]	Keep maximum intercuspation and avoid swallowing	NR	NR	Upper airway	PNS – Epiglottis base (PFP)	1. UA volume 2. MinCS area 3. MeanCS area 3. AP axial distance (MinCS area) 4. LAT axial distance (MinCS area) 5. Shape: MinCS area/MeanCS area 6. UA height	No differences were found in the morphology of the upper airways and in the anatomical structures around the upper airway between responders and non-responders to treatment with Mandibular Advancement Splint.

Mostafiz et al., 2019[47]	NR	YES	NA	Nasopharynx Oropharynx Hypopharynx	NR	1.UA volume 2.AP sagittal distance (MinCS area) 4. Shape: AP sagittal distance/LAT (MinCS area)	OSA was associated with response to treatment. Patients with higher Initial OSA and upper airway constriction showed an increased response to treatment with MAS therapy. Airway constriction due to maxillofacial disproportions instead of soft tissue obstruction also showed better response to treatment.
Mouhanna-Fattal et al., 2019[48]	Maximum intercuspation occlusion	NR	NA	Upper airway	NR	1.UA volume	The craniofacial structures did not show significant differences between the groups, but in the control group, the posterior space released for the upper airways was significantly larger and OSA group was significantly less.
Niskanen et al., 2019[49]	NR	NR	NR	Upper airway	Most superior portion of Maxilla – IC2	1. UA volume	Maxillomandibular advancement increases the volume of the upper airways and reduces the symptoms of OSA studied by PSG. Bimaxillary advancement surgery can be considered as treatment for OSA; however, residual AHI can be found in many patients.
Iwasaki et al., 2019[50]	Maintain head position, centric	NR	NR	Pharyngeal airway	Hard palate – Epiglottis base	1.Nasal width (Most large portion) 2.Nasal resistance	Anatomical expansion of the

	occlusion, tongue, and lips relaxed at the end of exhalation			Retropharynx Oropharynx Hypopharynx Intraoral airway	Hard palate – AIC2 AIC2 – AIC3 AIC3 – Epiglottis base (All lines parallel to palatal plane) Soft palate and tongue area inside oral cavity	3. Pharyngeal airway volume 4. Intraoral volume 5. Nasal, Retropharynx, Oropharynx and Hypopharinx velocity 6. Nasal, Retropharynx, Oropharynx and Hypopharinx pressure 7. Nasal resistance 8. Retropharynx, Oropharynx and Hypopharinx AP axial distance following the delimitation references	nasal floor with enlargement of the palatal vault is associated with a reduction in the speed of nasal airflow and a reduction in negative pressure in the pharyngeal airway. This dynamic interaction correlates with a reduction in the apnea-hypopnea index (AHI) and oxygen desaturation index.
Konsong et al., 2020[51]	Keep the occlusion, light breathing, do not swallow and do not move	YES	NR	Superior UA Inferior UA	Palatal plane – Tip of uvula (PFP) Tip of uvula – Superior portion of Hyoid bone (PFP)	1. Total, Superior and inferior UA height 2. Total, Superior and inferior volume 3. Total, Superior and inferior MinCS area 4. Total, Superior and inferior Surface area	Bimaxillary advancement surgery with an advance of less than 10 mm was adequate to increase upper airway by at least 70%.
Lu et al., 2020[52]	Gaze fixed on the horizon, not swallowing and light breathing	NR	NR	Velopharynx Glossopharynx	PSN – Tip of epiglottis (PFP) Tip of uvula – Tip of epiglottis (PFP)	1. Velopharynx and Glossopharynx AP sagittal Min distance 2. Velopharynx and Glossopharynx AP coronal Min distance 3. Velopharynx and Glossopharynx Min volume 4. Velopharynx and Glossopharynx MinCS area	The adjustable oral appliance had considerable clinical efficacy and comfort in elderly patients with OSA, increased the Velotopharynx and Glossopharynx.

NR = not report; NA = not applied; FP = Frankfurt plane; PFP = parallel to Frankfurt plane; CBCT = cone-beam computed tomography; OSA = obstructive apnea; Min = minimum; UA = upper airway; MinCS area = minimum cross-sectional area; MeanCS area = mean cross-sectional area; AP = antero-posterior; LAT= lateral; C2 = second cervical vertebra; AIC2 = most inferior and anterior region of the second cervical vertebra; AIC3 = most inferior and anterior region of the third cervical vertebra; IC2 = most inferior region of the second cervical vertebra; PNS = posterior nasal spine; Ba = basion; RGn = retrognathion; ROI = region of interest.

Table 5: Risk of bias assessment based in the Mixed Methods Appraisal Tool.

Authors/Year	3. Quantitative non-randomized studies					MMTA Score
	3.1	3.2	3.3	3.4	3.5	
Abi-Ramia et al., 2010[30]	CNT	YES	YES	NO	YES	***
Bruwier et al., 2016[30]	CNT	YES	YES	CNT	YES	***
Buchanan et al., 2016[37]	CNT	NO	YES	NO	YES	**
Butterfield et al., 2015[33]	CNT	NO	NO	NO	NO	*
Butterfield et al., 2015[34]	CNT	NO	NO	NO	YES	*
Chaves Jr et al., 2016[38]	YES	YES	YES	NO	YES	****
Chen et al, 2017[41]	CNT	YES	YES	CNT	YES	***
Chen et al., 2019[46]	CNT	YES	YES	CNT	YES	***
Conssellu et al., 2015[35]	CNT	YES	YES	CNT	YES	***
Enciso et al., 2010[29]	YES	YES	YES	NO	YES	****
Enciso et al., 2012[31]	CNT	NO	YES	NO	YES	**
Frey et al., 2018[44]	CNT	NO	YES	CNT	YES	**
Hankell et al., 2009[28]	CNT	NO	YES	CNT	YES	**
Iwasaki et al., 2019[50]	CNT	YES	YES	NO	YES	***
Kongsong et al., 2020[51]	CNT	YES	YES	YES	YES	****
Lu et al., 2020[52]	CNT	YES	YES	NO	YES	***
Molaei et al., 2018[45]	CNT	NO	YES	NO	YES	**
Monamy et al., 2018[43]	YES	YES	YES	CNT	YES	****
Mostafiz et al., 2019[47]	CNT	NO	YES	CNT	YES	**
Mouhanna-Fattal et al., 2019[48]	CNT	NO	YES	CNT	YES	**
Niskanen et al., 2019[49]	CNT	NO	YES	CNT	YES	**
Ogawa et al., 2007[12]	CNT	YES	YES	NO	YES	***
Rodrigues et al., 2017[25]	YES	YES	YES	YES	YES	****
Schendel et al., 2014[32]	CNT	NO	NO	NO	YES	*
Shete&Bhad, 2017[40]	CNT	NO	YES	CNT	YES	**
Shigueta et al., 2008[27]	CNT	NO	YES	NO	NO	*
Tikuu et al., 2016[39]	CNT	NO	YES	NO	YES	**
Van Leeuwen et al., 2015[36]	CNT	NO	YES	NO	YES	**
Veys et al., 2017[42]	CNT	YES	YES	CNT	YES	***

*meet 25%, **50%, ***75%, ****100% of the MMAT criteria. CNT = cannot tell. MMAT = Mixed Methods Appraisal Tool.

III. CAPÍTULO 2

"*Clinical Oral Investigations*"

THREE-DIMENSIONAL CRANIOFACIAL CHARACTERISTICS ASSOCIATED WITH OBSTRUCTIVE SLEEP APNEA SEVERITY AND TREATMENT OUTCOMES

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ABSTRACT

Objectives This study aims to assess craniofacial dimensions in obstructive sleep apnea (OSA) patients treated with a mandibular advancement device (MAD) and to identify anatomic influences on OSA severity and MAD therapy outcomes.

Materials and methods Twenty patients with OSA were prospectively treated with MAD. Clinical, cone-beam computed tomography and polysomnography exams were performed before treatment and 4-6 months after achieving the MAD therapeutic position. Polysomnographic exams and three-dimensional maxillary, mandibular and upper airway (UA) measurements were evaluated. Pearson's correlation and t-tests were applied.

Results Before MAD treatment, the transverse width measured at the frontomaxillary suture and the angle between the mandibular ramus and Frankfurt horizontal were statistically correlated with apnea and the hypopnea index (AHI), while the gonial angle was correlated with therapeutic protrusion. After MAD treatment, all patients showed a significant AHI reduction and an improvement in minimum oxyhemoglobin saturation. The total UA volume, superior and inferior oropharynx volume and area were statistically correlated with MAD therapeutic protrusion. The UA total area showed a statistical correlation with the improvement in AHI, and the superior oropharynx volume and area increased significantly.

Conclusions The transversal frontomaxillary suture width and the mandibular ramus facial angle may influence OSA severity. The gonial angle, volume and area of all UA regions may indicate the amount of protrusion needed for successful MAD treatment.

Clinical relevance The craniofacial characteristics reported as important factors for OSA severity and MAD treatment outcomes impact therapy planning for OSA patients, considering individual anatomic characteristics, prognosis and cost benefits.

Keywords: Cone-Beam Computed Tomography (CBCT); Anatomy; Sleep apnea, Obstructive; Airway Management; Occlusal Splints; Mandibular Advancement Device.

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of apnea and/or hypopnea due to upper airway collapse during sleep. It is considered the most common sleep breathing disorder; it is more prevalent in males in their sixth decade and affects a total of 1 billion individuals worldwide[1-4]. OSA's clinical manifestations include sleep and neurocognitive symptoms such as respiratory pauses during sleep, recurrent awakenings, intense and intermittent snoring, nonrestorative sleep, excessive daytime sleepiness, irritability, depression and anxiety[2]. Moreover, recurrent respiratory pauses may lead to intermittent hypoxemia that increases the risk of developing cardiovascular diseases such as arrhythmia, heart or coronary insufficiency, and stroke. These systemic consequences highlight the importance of OSA's precocious diagnosis and influencing factors[5-8].

The diagnosis of OSA, obtained by polysomnographic examination, is characterized by more than 5 obstructive events per hour of sleep (apnea and hypopnea index - AHI $\geq$ 5 events/hour). In addition, among all the polysomnographic parameters, the AHI and oxyhemoglobin saturation (SpO_2) determine the intensity of OSA, which can be classified as mild (AHI = 5-15 events/hour and SpO_2 = 86 - 91%), moderate (AHI = 15-30 events/hour and SpO_2 = 76 - 85%) or severe (AHI $\geq$30 events/hour and $SpO_2 \leq$ 75%)[9].

Multiple aspects, such as genetic, neuromuscular, and anatomic dysfunctions, may be involved in the pathophysiology of OSA[10]. Among the anatomic factors, it is possible to identify craniofacial variations, which include alterations in the vertical, transversal, anteroposterior, linear, angular dimensions of the craniofacial skeleton, as possible predisposing factors for upper airway (UA) collapse[11-15]. Craniofacial pattern and bone phenotype characterization may be considerable parameters for diagnostic guidance and multidisciplinary planning of OSA treatment. Among the possible therapies, it is possible to identify continuous positive airway pressure (CPAP) and mandibular advancement devices (MADs) as options [16].

Although CPAP is considered the gold standard for OSA treatment, studies have shown MAD as an alternative treatment for patients who are not responsive or not suitable candidates for CPAP treatment. The mechanism of action of a MAD is based on the extension/distension between the oropharynx and the base of the tongue by mandibular advancement, preventing UA collapse. Thus, mandibular characteristics may affect the amount of advancement ability and, consequently, therapeutic outcomes. This fact indicates anatomic variation again as an essential factor, not only anticipating OSA occurrence but also identifying differences in movement patterns and outcomes when using MAD as a therapy option[16-20]. These anatomic components involved in OSA may be analyzed by cone-beam computed tomography (CBCT), which is a useful tool for identifying craniofacial

and upper airway three-dimensional configurations with great resolutions and precision[21]. In addition, all anatomic mechanisms involved in OSA pathogenesis, which may play an important role in the patency of UA and in MAD treatment, and successful outcomes have not been totally elucidated[19]. Therefore, it is hypothesized that craniofacial anatomic variations may influence polysomnographic parameters and MAD therapeutic prognosis. This study aims to evaluate craniofacial linear, angular, area and volumetric dimensions on CBCT images of OSA patients treated with MAD and determine whether these dimensions influence OSA severity and outcomes of MAD treatment.

MATERIALS AND METHODS

Sample and ethical considerations

This observational longitudinal study was approved by the Research Ethics Committee of the Federal University of São Paulo – Brazil (number 0301/10). All volunteers signed the Informed Consent Form (ICF). Patients aged 18 to 65 with a clinical and polysomnographic diagnosis of OSA were consecutively referred for dentistry evaluation and MAD treatment. Sixty-three patients were initially recruited, but 21 patients did not match the eligibility criteria. Thus, 42 patients were selected for the research. Before starting the T1 follow-up, 2 volunteers dropped out of the study, and 20 others were removed for not having performed all the necessary exams, leading to a total sample of 20 patients of both genders. The inclusion criteria consisted of body mass index (BMI) $\leq$ 35 kg/m^2; clinical and polysomnographic diagnosis of OSA (AHI$\geq$ 5/h) according to the International Classification of Sleep Disorders; negative TMD - Temporomandibular Disorder diagnosis by the Research Diagnostic Criteria for Temporomandibular Disorders - RDC/TMD questionnaire (adapted to the Portuguese language)[22] and a mandibular protrusion of at least 7 mm clinically measured with the George Gauge device. This study excluded patients with unsatisfactory dental conditions (active periodontal disease, caries or insufficient teeth to retain the appliance); dental crown/dental root ratio $\leq$1; predominating central apnea in polysomnography (50% or more of central events of the absolute number of events); use of psychoactive medicines; decompensated clinical, neurological or psychiatric diseases; other sleep disorders; and those already undergoing previous OSA treatments.

Based on the study by Consellu et al.[23], who observed that there was a significant increase in the mean total airway volume (+1261.6 ± 1476.2 mm^3) in patients with OSA after treatment with MAD, it is estimated that at least 16 patients need to be evaluated across two time points in the present study to obtain a sample to obtain 95% confidence intervals and 90% power for the alternative hypothesis of this work (examined via paired t-tests).

Thus, the study sample was composed of 20 patients (mean age of 48.35 ± 10.42 years), with a mean weight of 72.90 ± 15.41 kg, height of 1.64 ± 0.10 and BMI of 27.10 ± 4.29. There were 9 males and 11 females. Before MAD treatment (T0), 15 patients showed mild OSA, 3 showed moderate OSA, and 2 showed severe OSA (Table 1).

Study protocol

Exams

All patients underwent clinical, CBCT and polysomnography (PSG) exams at two time points: before treatment (T0) and after achieving the MAD therapeutic position (T1). Therapeutic protrusion (TP) was achieved from 4 to 6 months after MAD placement, and 30 to 48 days after TP was established, volunteers performed the final exams (T1).

Variables

This study analyzed clinical/demographic, polysomnographic and 3D imaging variables. The clinical variables included anthropometric characteristics: sex, age, weight, height, and BMI. Polysomnographic variables included AHI and minimum and medium SpO_2. Three-dimensional image analysis variables included maxillary and mandibular linear, angular, and volumetric measurements, as well as linear and volumetric measurements of the UA.

MAD treatment and measurement of protrusion

For OSA treatment, the MAD used was the Brazilian dental appliance (BRD)[9], which is a maxillomandibular individualized device that allows gradual mandibular advances. The initial advancement was 50% of the total mandibular maximum protrusion ability. Mandibular advancement was made gradually until TP was achieved. TP was on average 97.4 ± 4.8% of the maximum protrusion, ranging from 85 to 100% of the mandible's maximum anterior displacement. The amount of TP was also determined by the improvement of the signs/symptoms recorded in the medical record, and the treatment time until achieving TP was 4-6 months.

Polysomnography

All-night PSGs were performed at the Sleep Disorders Institute with digital-based polysomnography (Embla® N7000, Embla Systems, Inc., Broomfield, CO, USA). Surface electrodes were used for recording

electroencephalography, submental and tibial electromyography, bilateral electrooculogram, and electrocardiography. Breathing was monitored with a nasal cannula with nasal flow measurement by a pressure transducer and oronasal thermistor, and respiratory effort was assessed by chest and abdomen inductance plethysmography. Pulse oximetry was used to measure oxyhemoglobin saturation. The body position for decubitus recording was made using a sensor placed over the sternum bone region. A cervical microphone was used to register the snoring. In this study, an AHI reduction below 5 obstructive events per hour (AHI <5) was considered a criterion for success since OSA treatment success is usually expressed as a ≥50% AHI reduction from baseline or at least an AHI of <10 events/hour[24].

CBCT acquisition protocol

CBCTs were performed at a private dental radiological clinic (Sao Paulo, Brazil) using the i-CAT® device (Imaging Sciences International, Hatfield, PA), configured with 120 Kvp, 3-8 mA, a 0.4-mm voxel size and a field of view (FOV) of 23 cm x 17 cm, allowing total vertical head framing[25, 26]. During the CBCT initial exam, all patients were awake, with a natural head position (Camper's horizontal plane parallel to the ground) and to keep the gaze fixed at a stationary point on the wall. In T0, they were instructed to keep the occluded jaw in the maximum intercuspal position, and in T1, they were instructed with the intraoral appliance placed[25, 27]. The volunteers were instructed to not move, swallow, or take deep breaths to avoid changes in the UA volume during the exam[28, 29]. All images were stored in Digital Imaging and Communications in Medicine (DICOM) files.

Image processing

All CBCT data from T0 and T1 were processed with open-source imaging platforms. The segmentation and mandibular cropping required for image processing were performed using ITK-SNAP 2.4 software (https://www.itksnap.org). The DICOM files were converted into NIfTI files using the same software. To orient and register patients' scans/segmentations, as well as to determine all the linear, angular, and volumetric measurements, Slicer CMF 4.0 software (www.slicer.org) was used.

To apply the 3D head orientation for all T0 scans, the models were moved by orienting its Frankfurt horizontal, midsagittal and transporionic planes to match the axial, sagittal and coronal planes, respectively, at a standard coordinate system in the Slicer software. The cranial registration of T1 scans was made after manual approximation to T0 scan oriented[30]. To perform all measurements, a list of 3D landmarks was used for the maxilla, mandible,

and UA (Tables S1, S2, and S3). All linear, angular, area and volumetric dimensions were obtained in millimeters (mm), degrees (°), squared millimeters (mm^2) and cubic millimeters (mm^3), respectively.

a) Maxillary measurements

Fifteen measurements, linear and angular, were performed on maxillary bone: palatal alveolar bone crest M width, palatal alveolar bone crest PM width, palatal alveolar bone crest C width, intercanine eminence distance, greater palatine foramen distance, nasal width, inferior margin of the zygomaticomaxillary suture distance, infraorbital foramen distance, anterior border of the frontozygomatic suture distance, lateral border of the frontomaxillary suture distance, facial height, ANS-PNS, SNA, SNB and ANB (Table S4). To characterize the craniofacial aspects for these patients, all maxillary measurements were required only for T0 images (Figure 1).

b) Mandibular measurements

Mandibular dimensions were assessed with 19 measurements, including linear (condylar height, condylar width, condylar torque, ramus height, mandibular length, intergonial width, intercondylar width, mandibular corpus anterior width and mandibular linear anterior rotation), angular (mandibular ramus facial angle, gonial angle, condylar inclination, mandibular corpus posterior angle, mandibular corpus curve angle, intercondylar angle, mandibular ramus angular rotation and mandibular anterior angular rotation) and volumetric (condylar volume and total mandibular volume) 3D evaluations (Table S5). All these evaluations were made only in T0 scans (Figure 2), except for the last mandibular linear evaluation (mandibular linear anterior rotation) and the two last mandibular angular measurements (mandibular ramus angular rotation and mandibular anterior angular rotation), which were made comparing landmarks between T0 and T1 images (Figure 3).

c) Upper airway measurements

Linear, volumetric, and surface area measurements were performed in UA (Table S6). The shape of UA in second (C2I) and fourth (C4S) vertebrae point slices was set only in T0 to identify the influence of UA shape on OSA severity and therapy outcomes. The UA shape was estimated based on the modification of the equation developed by Abramson et al.[31]. In addition, 3 volumetric measurements (total upper airway volume, superior oropharynx volume and inferior oropharynx volume) were made in T0 and T1 images to compare changes in this anatomic region before and after MAD treatment (Figure 4).

Study error

To avoid potential sources of bias, intraexaminer reliability was made by repeating the 3D measurements with an interval of 15 days. The data were exported to Microsoft Excel spreadsheets (Microsoft Corporation, Redmond, WA) and analyzed using the Statistical Package for the Social Sciences (SPSS®) version 20.0 for Windows (IBM Corporation, Sommers, NY). The following analyses were performed: (1) intraclass correlation coefficient (ICC) analysis to evaluate systematic errors regarding numerical data; (2) Dahlberg's formula for assessing casual errors of measurements performed.

Statistical approach

The data were stored in Microsoft Excel and exported to SPSS® software version 20.0 for Windows, in which the analysis was performed adopting 95% confidence intervals. Tomographic and polysomnographic measurements, analyzed by the Kolmogorov-Smirnov normality test and Pearson's correlation, were expressed as the mean and standard deviation. The variables were compared between degrees of severity (mild versus moderate/severe) using Student's t-test and between assessment moments (T0 and T1) or sides (right and left) using the paired t-test (parametric data).

RESULTS

Study error

The intraexaminer repeatability of angular and linear measurements showed excellent correlation coefficients (ICCs greater than 0.9). Volume measurements showed adequate ICCs greater than 0.75. Dahlberg's coefficient of at least 0.01 was obtained.

Mandibular protrusion and advancement

The means of maximum and therapeutic protrusion were 11.00±2.22 mm and 10.88±2.20 mm, respectively. Mandibular advancement measurements at point B (mandibular linear anterior rotation) demonstrated an average anterior displacement of 2.49±2.63 mm and inferior displacement of -9.38±2.92 mm. The mandibular ramus and mandibular angular anterior rotation presented on average -3.93±1° (backward rotation) and -4.09±1.2° (downward rotation), respectively (Table 1 and Figure 3).

Polysomnographic findings

All patients showed a marked reduction ($p < 0.001$) in AHI with a mean variation of -6.86±5.23 between T0 and T1. The mean SpO_2 only showed a variance of -0.35±1.11 and did not significantly improve with treatment ($p=0.181$), while the minimum SpO_2 demonstrated a range of 3.15±3.39 and was significantly improved with MAD treatment (0.001*)*. The AHI at T0 was not correlated with the maximum ($p=0.197$; $r=0.301$) or therapeutic protrusion ($p=0.229$; $r=0.282$), and similar results were found with MAD treatment.

Maxillary measurements

A significant correlation was found between the ANS-PNS linear dimension and maximum protrusion [$p=0.043$ ($r=-0.457$)]. The transverse width of the frontomaxillary suture was statistically correlated with the AHI before MAD treatment [$p=0.019$ ($r=-0.519$)]. All other linear and angular measurements of the maxilla were not correlated with AHI at baseline or the AHI variation between T1-T0 (Table 2).

Mandibular measurements

Since no significant differences were identified between the left and right sides, we utilized the average measurements for all bilateral measurements. The mandibular ramus facial angle was correlated with AHI values at T0 [$p=0.031$ ($r=0.896$)], and the gonial angle demonstrated a correlation with therapeutic protrusion [$p=0.049$ ($r=0.837$]). The mandibular linear dimensions, volume and area were not significantly correlated with AHI at T0, the AHI variation with therapy, or protrusion (Table 3).

Upper airway measurements

The superior oropharynx volume ($p=0.003$) and surface area ($p=0.001$) presented highly significant increases with MAD treatment (variances of 1694.77 ± 2228.89 and 349.99 ± 416.77, respectively). The changes between T0-T1 in UA total volume ($p=0.108$) and surface area ($p=0.470$), as well as the inferior oropharynx volume ($p=0.458$) and surface area ($p=237$), were not statistically significant.

The total volume of the UA at baseline and its variation with MAD treatment were correlated with maximum protrusion, $p=0.004$ ($r=0.615$) and $p=0.005$ ($r=0.604$), therapeutic protrusion, respectively $p=0.011$ ($r=0.556$) and $p=0.011$ ($r=0.558$). The total area of the UA in T0 was correlated with AHI at baseline [$p=0.016$ ($r=-0.533$)] and with maximum [$p=0.007$ ($r=0.579$)] and therapeutic protrusion [$p=0.008$ ($r=0.572$)]. The superior oropharynx and inferior oropharynx volume and area in T0 were statistically correlated with both protrusion

variables (Table 4). The total volume of the UA was not correlated with the AHI. UA linear variables were not correlated with AHI at baseline or AHI changes with treatment or protrusion.

DISCUSSION

This study tested associations between 3D craniofacial and upper airway anatomy measurements and OSA severity, outcomes of treatment with a mandibular advancement device, and the amount of protrusion needed for successful therapy. The precise 3D measurements of the maxilla, mandible and upper airway in this study were performed in standardized head orientation during image acquisition and image analysis procedures. Previous authors have evaluated the relationship between anatomic skeletal classes and the development of obstructive sleep apnea and the efficacy of the mandibular advancement device in OSA treatment[32-37]. However, the literature lacks research involving tomographic assessment of the craniofacial anatomy and UA as impact factors in OSA severity and its treatment prognosis.

In the present study, the therapeutic protrusion obtained with MAD was 10.88±2.20 mm. This amount of protrusion measured in the appliance resulted in anterior (2.49±2.63 mm) and inferior (-9.38±2.92 mm) displacement of the mandible measured at point B (mandibular anterior rotation). The overall mandibular displacement with the appliance measured in 3D superimposition relative to the cranial base showed an amount of vertical movement of the mandible higher than anterior movement, a finding also shown in Kim et al.[38]. These outcomes indicate that MAD placement may increase the vertical dimension, leading to mandibular clockwise rotation. It has been reported that the range of mandibular protrusion reduces 0.3 mm for each 1 mm of vertical displacement[39]. Interestingly, there was no correlation between the improvement in AHI and the amount of therapeutic protrusion or the amount of displacement of the mandible.

Therapy with the MAD appliance significantly reduced the AHI in all patients evaluated in this investigation. After MAD treatment, an improvement in the AHI was demonstrated, with 15 patients (75% of the sample) showing an AHI lower than 5, indicating a successful outcome[35, 40]. These findings are in agreement with Metz et al.[35], who identified that the same appliances successfully treated OSA of all severities with efficacy. Although this study demonstrated an AHI decrease in all patients, the AHI in severe cases remained at values greater than 15 awakes per hour, leading to a moderate severity instead of a mild severity. Different findings were reported in an orthognathic surgery systematic review that identified a mean AHI decrease from 63.9/h to 9.5/h ($p < 0.001$), indicating that even the most severe cases could show an AHI lower than 15 associated with mild severity[41].

The increase in the minimum SpO_2 observed in our results was also significantly improved, aiding treatment success. Oxygen saturation findings were also reported by Zhan et al.[42], who identified that the lowest oxygen saturation was significantly higher after MAD therapy.

We assessed measures that may influence OSA severity, as determined by AHI values before MAD treatment (T0). The T0 craniofacial characteristics revealed that the facial width at the level of the frontomaxillary suture and the inclination of the mandibular ramus relative to the Frankfurt horizontal plane (mandibular ramus facial angle) were significantly associated with OSA severity. However, volumetric dimensions of the mandibular skeletal morphology or the airway were not statistically correlated with AHI at baseline. These findings corroborate those studies that described maxillary transversal anatomic variations as an important factor for OSA development[43-45]. However, those authors reported that mandibular linear measurements, such as mandibular length, mandibular width, and mandibular height, were correlated with AHI, while the present study only found a correlation of the mandibular ramus facial angle with AHI values. Our results also differ from the results reported by Johal et al.[46], who found that the vertical maxillary anatomy and angular dimensions (SNA, SNA, ANB) are critical structures for OSA prediction[43, 45-47].

Comparing the UA volume before and after MAD treatment, all patients showed a significant increase in superior oropharynx volume. Similar outcomes were also described by Pahkala et al.[48], who demonstrated that MAD therapy protrusion significantly increased the oropharyngeal volume. In the present study, no significant difference was identified in the inferior oropharynx volume. The inferior oropharynx region demonstrated a volume decrease with treatment (-321.24 ± 1897.24 mm^3), which can likely be explained by the MAD clockwise rotation effect[39].

Therapeutic protrusion with MAD was significantly and proportionally correlated with the gonial angle, and the mandibular ramus facial angle (Co-Go to the Frankfurt plane) was statistically and proportionally correlated with a more severe OSA diagnosis. This fact implies that clinicians may anticipate OSA severity and a greater therapeutic advance for a reduction in OSA symptoms and successful treatment in dolichofacial patients. The mandibular anterior width and intergonial width were not statistically associated with the AHI or the amount of protrusion. Sutherland et al.[40] demonstrated different results, showing that excess intramandibular space area was associated with successful MAD therapy. UA total, superior and inferior oropharynx volume and surface area measured at baseline were also correlated with therapeutic protrusion. These variables may be considered important factors to identify the amount of MAD advancement required for successful OSA treatment. The amount

of therapeutic protrusion, expressed in both anterior and vertical mandibular movement, increased the overall airway volume.

CBCT is an imaging modality of great value for craniofacial anatomic evaluations. While most commercially available software allows adjustment of head position after image acquisition, the standardization of head position and stage of respiration during image acquisition is critical for consistent measurements of airway volume and area across different patients and timepoints[49, 50]. In our study, all patients were carefully instructed to maintain an adequate natural head position and avoid swallowing during image acquisition. Furthermore, the 3D image analysis of hard and soft tissue structures was performed in a standardized head orientation at T0, as defined by Ruellas et al.[30], and all T0 and T1 scans were registered relative to the cranial base. The airway volume and area performed in this study were measured using ITK-SNAP semiautomatic segmentation, which has been reported to be comparable to well-known commercial software, such as Dolphin imaging[51, 52]. The present study data did not find correlations between the volume and shape of the airway and OSA severity at baseline. However, UA's total area was significantly correlated with AHI improvement with treatment and is considered a factor that may influence OSA treatment and outcomes with MAD. While previous studies[53, 54] reported correlations between airway linear, area and/or volume measurements and AHI severity at baseline, Svaza et al.[54] utilized only 2D measurements, Abramson et al.[31] did not standardize head position during or after image acquisition, and Ozer et al.[53] utilized CT scans taken in the supine position. For these reasons, the findings of those studies are not directly comparable to the present study results.

The present study findings indicate that anatomic craniofacial factors may influence OSA severity, MAD outcomes and the amount of protrusion for resolutive mandibular advancement therapy. Such results grant better knowledge to use MAD as a possible treatment option while also considering the indication for consolidated and predictable surgical therapies[41, 55, 56]. Importantly, the findings of this study highlight clinical decisions considering individual patient characteristics, prognosis, and interests.

Since many of the 3D image variables assessed as influencing OSA severity and MAD outcome had not yet been tested in the literature, the comparisons with previous study findings were limited. Moreover, the present study is limited by the lack of a control group. However, it is unrealistic to follow OSA patients without treatment or place the MAD appliance without proper diagnostic indications for ethical reasons. Importantly, our prospective study sample was longitudinally evaluated with polysomnography exams and CBCT images before and after 4-6 months of MAD treatment. Future studies with an adequate sample size of mild, moderate, and severe AHI subgroups are essential, especially considering the possibility of applying more robust statistical evaluations, such

as regression analysis and receiver operating characteristic curve (ROC curve), whether these anatomic variances are risk factors for OSA development and MAD treatment prognosis. Such future studies have the potential to provide further insight to validate craniofacial aspects that may anticipate OSA severity and therapeutic response to MAD.

CONCLUSIONS

In conclusion, 3D anatomic craniofacial measurements play an essential role in influencing OSA severity, MAD outcomes for OSA treatment and the amount of protrusion for resolutive mandibular advancement therapy. A greater transverse width of the frontomaxillary suture may indicate a diagnosis of a less severe OSA, while a greater mandibular ramus facial angle may suggest a more severe OSA. Moreover, greater measurements of gonial angle, UA total, superior and inferior oropharynx volume and surface area were considered anatomic factors that may anticipate the knowledge about greater amount of protrusion needed for a successful MAD treatment. The total UA area also influenced MAD outcomes in patients with OSA.

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AUTHOR CONTRIBUTIONS

Conceptualization and proof outline: [Marcela Gurgel], [Lucia Cevidanes], [Fabio Costa], [Rowdley Pereira], [Antonio Ruellas], [Jonas Bianchi] and [Cauby Chaves Junior]; Project administration and supervision [Lucia Cevidanes], [Fabio Costa] and [Cauby Chaves Junior]; Methodology, Validation and Writing – original draft [Marcela Gurgel] and [Lucia Cevidanes]; Resources and sample [Rowdley Pereira], [PauloCunali], [Lia Bittencourt]; Writing – review & editing [All authors].

DECLARATIONS

Ethical approval The study was approved by the Research Ethics Committee of the Federal University of São Paulo – Brazil (number 0301/10). All volunteers signed the Informed Consent Form (ICF).

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Conflict of Interest The authors declare that they have no conflicts of interest.

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FIGURES AND CAPTIONS

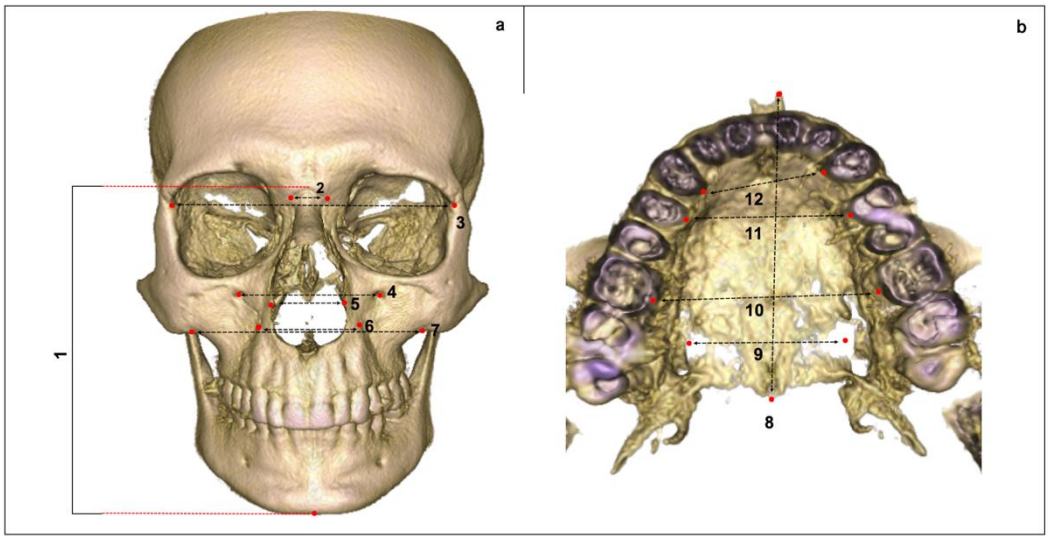

Fig. 1 Maxillary linear measurements (T0). (a) Measurements in a frontal view; (1) Facial height; (2) Lateral border of the frontomaxillary suture distance; (3) Anterior border of the frontozygomatic suture distance; (4) Infraorbital foramen distance; (5) Nasal width; (6) Intercanine eminence distance; (7) Inferior margin of the zygomaticomaxillary suture distance. (b) Measurements in an occlusal view; (8) ANS-PNS; (9) greater palatine foramen distance; (10) palatal alveolar bone crest M width; (l1) palatal alveolar bone crest PM width; (12) palatal alveolar bone crest C width. Landmark placement and measurements described in Tables S1 and S4.

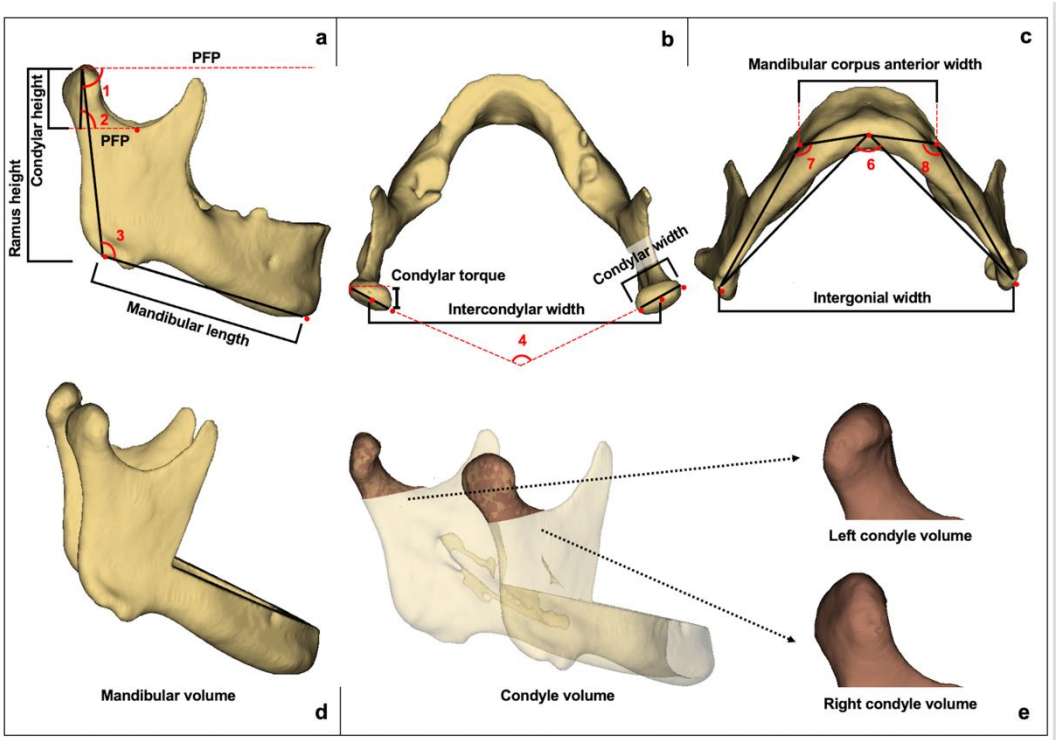

Fig. 2 Mandibular linear, angular and volumetric measurements (T0). (a) Linear and angular measurements in a lateral view; Ramus height; Condylar height; Mandibular length; (1) Mandibular ramus facial angle; (2) Condylar inclination; (3) Gonial angle; (PFP) Parallel line to Frankfurt plane. (b) Condylar torque; Condylar width; Intercondylar width; (4) Intercondylar angle. (c) Mandibular corpus anterior width; Intergonial width; (5) Mandibular corpus posterior angle; (6) Right mandibular corpus curve angle; (7) Left mandibular corpus curve angle. (d) Model without teeth used to calculate mandibular bone volume. (e) Condylar models used to calculate right and left condylar volumes. Landmark placement and measurements described in Tables S2 and S5.

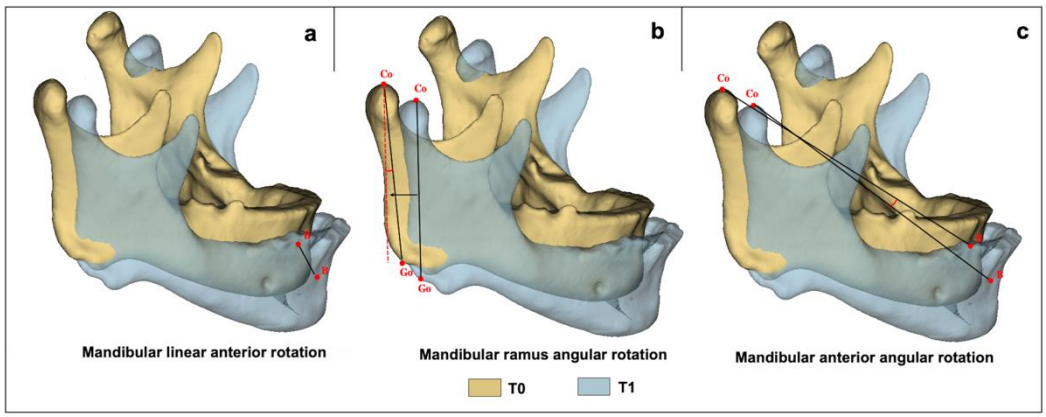

Fig. 3 Mandibular linear and angular measurements comparing T0 and T1. (a) Mandibular linear anterior rotation. (b) Mandibular ramus angular rotation. (c) Mandibular anterior angular rotation. Go = Gonion; Co = Condilyon; B = B point. Landmark placement and measurements described in Tables S2 and S5.

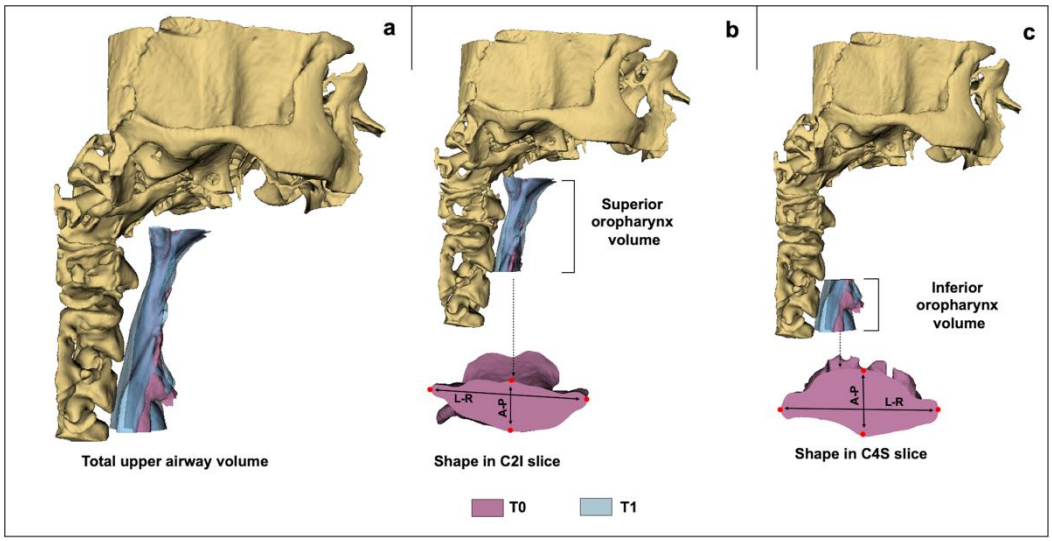

Fig. 4 Upper airway linear measurements in (T0) and volumetric measurements comparing T0 and T1. (a) Model used to calculate the total upper airway volume. (b) Model used to calculate superior oropharynx volume and superior oropharynx surface to identify shape in slice C2I. (c) Model used to calculate inferior oropharynx volume and inferior oropharynx surface to identify shape in slice C4S. L-R = maximum width; A-P = maximum anteroposterior linear distance. Landmark placement and measurements described in Tables S3 and S6.

Table 1: Sample anthropometric, protrusive and rotational characteristics in OSA distribution.

		T0 - OSA Severity		
Anthropometric	**Total Sample (n=20)**	**Mild (n=15)**	**Moderate (n=3)**	**Severe (n=2)**
Age	48.35±10.42	48.27±11.50	50±8.88	46.5±4.5
Weight	72.90±15.41	72.87±16.07	65.33±14.01	84.5±5.5
Height	1.64±0.10	1.62±0.09	1.65±0.18	1.72±0.02
BMI	27.10±4.29	9.93±4.95	23.8±1.73	28.7±2.4
Sex (M/F)	9/11	6/9	1/2	2/0
Protrusion				
Maximum	11.00±2.22	10.93±2.43	11.66±1.52	10.5±1.5
Therapeutic	10.88±2.20	10.80±2.43	11.5±1.32	10.5±1.5
Mandibular rotation				
Mandibular linear anterior (anteroposterior)	2.49±2.63	2.45±2.47	4.32±2.76	0.02±2.86
Mandibular linear anterior (superoinferior)	-9.38±2.92	-9.00±3.18	-10.10±2.13	-11.2±0.83
Mandibular ramus angular	-3.93±1	-3.89 ±1.11	-4.02±0.65	-4.075±0.61
Mandibular anterior angular	-4.09±1.2	-4.04±0.63	-4.07±1.22	-4.91±0.685

OSA = Obstructive sleep apnea. BMI = Body mass index. M = Male. F = Female.

Table 2: Correlation between maxillary measurements with AHI and protrusion.

Maxillary variables	AHI		Protrusion	
	T0	Δ	Maximum	Therapeutic
	p-value (r-value)	p-value (r-value)	p-value (r-value)	p-value (r-value)
Linear				
Palatal alveolar bone crest M	0.862 -0.042)	0.401 (-0.199)	0.260 (0.264)	0.292 (0.248)
Palatal alveolar bone crest PM	0.711 (-0.088)	0.295 (0.246)	0.366 (0.214)	0.358 (0.217)
Palatal alveolar bone crest	0.894 (-0.032)	0.320 (0.234)	0.419 (0.191)	0.435 (0.185)
Intercanine eminence	0.837 (0.049)	0.842 (-0.048)	0.835 (0.050)	0.904 (0.029)
Nasal width	0.062 (0.425)	0.372 (0.211)	0.569 (0.136)	0.466 (0.173)
Greater palatine foramen	0.372 (-0.211)	0.443 (0.182)	0.424 (0.189)	0.563 (0.137)
Anterior border of the frontozygomatic suture	0.864 (0.041)	0.707 (0.090)	0.590 (0.128)	0.702 (0.091)
Lateral border of the frontomaxillary suture	***0.019 (-0.519)**	0.291 (0.249)	0.370 (0.212)	0.377 (0.209)
Inferior margin of the zygomaticmaxillary suture	0.692 (0.094)	0.631 (-0.114)	0.628 (0.116)	0.671 (0.101)
Infraorbital foramens	0.408 (-0.196)	0.998 (0.001)	0.648 (0.109)	0.647 (0.109)
Facial height	0.614 (0.120)	0.486 (-0.165)	0.649 (0.108)	0.677 (0.099)
ANS - PNS	0.664 (-0.104)	0.827 (0.052)	***0.043 (-0.457)**	0.116 (-0.363)
Angular				
SNA	0.378 (0.208)	0.556 (0.140)	0.982 (-0.005)	0.626 (0.116)
SNB	0.785 (-0.065)	0.249 (0.270)	0.676 (-0.100)	0.802 (-0.060)
ANB	0.058 (0.431)	0.313 (-0.238)	0.351 (0.220)	0.133 (0.348)

*p<0.05, Pearson's correlation. AHI = Apnea and hypopnea index.

Table 3: Correlation between mandibular measurements with AHI and Protrusion.

Mandibular variables	AHI		Protrusion	
	T0	Δ	Maximum	Therapeutic
	p-value (r-value)	p-value (r-value)	p-value (r-value)	p-value (r-value)
Linear				
Condylar height	0.666 (-0.103)	0.558 (-0.139)	0.496 (-0.161)	0.534 (-0.148)
Condylar width	0.712 (0.088)	0.750 (-0.076)	0.742 (0.078)	0.974 (0.008)
Condylar width	0.061 (-0.426)	0.593 (0.127)	0.171 (-0.319)	0.191 (-0.305)
Ramus height	0.897 (-0.031)	0.664 (0.104)	0.841 (-0.048)	0.845 (0.047)
Mandibular length	0.619 (-0.119)	0.460 (0.175)	0.955 (-0.013)	0.613 (-0.121)
Intergonial width	0.317 (-0.236)	0.417 (0.192)	0.966 (0.010)	0.425 (-0.189)
Intercondylar width	0.851 (-0.045)	0.886 (0.034)	0.416 (0.192)	0.718 (0.086)
Mandibular corpus anterior width	0.553 (0.141)	0.839 (-0.049)	0.586 (-0.130)	0.636 (-0.113)
Mandibular linear anterior rotation (anteroposterior)	0.480(-0.168)	0.411 (-0.195)	0.826 (0.052)	0.957 (0.013)
Mandibular linear anterior rotation (superoinferior)	0.199 (-0.300)	0.336 (0.227)	0.857 (0.043)	0.792 (0.063)
Angular				
Mandibular ramus facial angle	***0.031 (0.896)**	0.097 (0.685)	0.075 (0.752)	0.156 (0.511)
Gonial angle	0.117 (0.624)	0.110 (0.645)	0.109 (0.647)	***0.049 (0.837)**
Condylar inclination	0.105 (0.659)	0.179 (0.450)	0.295 (0.206)	0.331 (0.153)
Mandibular corpus posterior angle	0.174 (0.464)	0.166 (0.486)	0.223 (0.344)	0.270 (0.249)
Mandibular corpus curve angle	0.343 (0.139)	0.291 (0.213)	0.267 (0.255)	0.255 (0.277)
Intercondylar angle	0.397 (0.083)	0.266 (0.258)	0.188 (0.427)	0.224 (0.343)
Mandibular ramus angular rotation	0.178 (0.452)	0.077 (0.748)	0.160 (0.501)	0.252 (0.285)
Mandibular anterior angular rotation	0.189 (-0.306)	0.835 (-0.050)	0.827 (0.052)	0.922 (0.024)
Volume/area				
Mandibular volume	0.424 (0.189)	0.935 (0.019)	0.473 (-0.170)	0.415 (-0.193)
Condyle volume	0.154 (0.331)	0.885 (-0.035)	0.937 (-0.019)	0.603 (-0.124)

*p <0.05, Paired t test (mean ± SD). AHI = Apnea and hypopnea index.

Table 4: Correlation between UA volumes and protrusion.

UA variables	IAH		Protrusion	
	T0	Δ	Maximum	Therapeutic
	p-value (r-value)	p-value (r-value)	p-value (r-value)	p-value (r-value)
Linear				
Lateral C2I slice	0.371 (0.211)	0.872 (-0.038)	0.196 (0.302)	0.111 (0.367)
Anteroposterior C2I slice	0.955 (-0.013)	0.523 (0.152)	0.711 (0.089)	0.926 (-0.022)
Lateral C2I slice	0.303 (-0.243)	0.154 (0.331)	0.382 (-0.207)	0.146 (-0.338)
Anteroposterior C4S slice	0.245 (0.273)	0.445 (-0.181)	0.067 (0.418)	0.033 (0.478)
Shape in C4S slice	0.795 (0.062)	0.980 (-0.006)	0.891 (-0.033)	0.999 (0.000)
Shape in C4S slice	0.605 (-0.123)	0.533 (0.148)	0.570 (-0.135)	0.575 (-0.133)
Volumetric				
UA total volume				
T0	0.278 (0.255)	0.667 (-0.102)	***0.004 (0.615)**	***0.011 (0.556)**
T1 -T0	0.154 (0.331)	0.302 (-0.243)	***0.005 (0.604)**	***0.011 (0.558)**
UA total surface area				
T0	0.235 (0.278)	***0.016 (-0.533)**	***0.007 (0.579)**	***0.008 (0.572)**
T1 - T0	0.315 (-0.236)	0.353 (-0.219)	0.797 (0.061)	0.616 (0.119)
Superior oropharynx volume				
T0	0.257 (0.266)	0.527 (-0.150)	***0.018 (0.523)**	***0.042 (0.458)**
T1 - T0	0.952 (-0.014)	0.159 (-0.327)	0.220 (0.287)	0.251 (0.269)
Superior oropharynx surface area				
T0	0.229 (0.282)	0.207 (-0.295)	***0.012 (0.552)**	***0.020 (0.517)**
T1 -T0	0.859 (-0.042)	0.524 (-0.151)	0.763 (0.072)	0.769 (0.070)
Inferior oropharynx volume				
T0	0.378 (0.208)	0.832 (-0.051)	***0.005 (0.606)**	***0.009 (0.570)**
T1 - T0	0.397 (-0.201)	0.264 (-0.263)	0.962 (-0.011)	0.836 (0.050)
Inferior oropharynx surface area				

T0	0.135 (0.346)	0.569 (-0.135)	***0.007 (0.583)***	***0.014 (0.542)***
T1 - T0	0.113 (-0.366)	0.255 (-0.267)	0.916 (-0.025)	0.807 (0.058)

* $p < 0.05$, Pearson's correlation. UA = Upper airway, C2I = Most inferior and anterior point of the second cervical vertebra. C4S= Most superior and anterior point of the fourth cervical vertebra.

Table S1: Maxillary landmarks.

Abbreviation	3D landmarks location:	Lateral	Axial	Anteroposterior
A	Point A	Most posterior point of anterior concavity of maxilla	Deepest point along anterior concavity of maxilla	Deepest point along anterior concavity of maxilla
N	Nasion	Most anterior point of frontomaxillary suture	Most anterior and central point of frontomaxillary suture	Most central point of frontomaxillary suture
S	Sella	Most central point of Sella turcica	Most central point of Sella turcica	Most central point of Sella turcica
Ba	Basion	Most inferior point of foramen magnum anterior margin	Most anterior and central point of foramen magnum	Most inferior and central point of foramen magnum
PNS	Posterior Nasal Spine	Most posterior point of hard palate	Most posterior and central point of hard palate	Most posterior and central point of hard palate
RPfor	Right palatine foramen	Most central point of right palatine foramen opening	Most central point of the right palatine foramen opening	Most central point of the right palatine foramen opening, following palatal level
LPfor	Left palatine foramen	Most central point of left palatine foramen opening	Most central point of the left palatine foramen opening	Most central point of the left palatine foramen opening, following palatal level
ANS	Anterior Nasal Spine	Most anterior point of nasal spine	Most anterior and central point of nasal spine	Most anterior point of nasal spine
RP1M	Right palatal bone crest of first molar	Most central point of alveolar bone in the buccal surface of right first molar	Most inferior and central point of alveolar bone in the buccal surface of right first molar	Most inferior and medial point of alveolar bone in the buccal surface of right first molar
RP1PM	Right palatal bone crest of first premolar	Most central point of alveolar bone in the buccal surface of right first premolar	Most inferior and central point of alveolar bone in the buccal surface of right first premolar	Most inferior and medial point of alveolar bone in the buccal surface of right first premolar
RPC	Right palatal bone crest of canine	Most central point of alveolar bone in the buccal surface of right canine	Most inferior and central point of alveolar bone in the buccal surface of right canine	Most inferior and medial point of alveolar bone in the buccal surface of right canine
RCE	Right canine eminence	Most anterior and superior point of right canine eminence in the level of canine root apex	Most anterior and superior point of right canine eminence in the level of canine root apex	Most superior and lateral point of right canine eminence in the level of canine root apex
RlatPA	Right most lateral point of piriform aperture	Most anterior point of piriform aperture in the right side	Most anterior point of piriform aperture in the right side	Most lateral point of piriform aperture in the right side
RInfZS	Right inferior margin of the zygomaticomaxillary suture	Most inferior and central point of right zygomaticomaxillary suture	Most inferior and central point of right zygomaticomaxillary suture	Most inferior and central point of right zygomaticomaxillary suture

RIOFor	Right infraorbital foramen	Most central point of right infraorbital foramen	Most central point of right infraorbital foramen	Most central point of right infraorbital foramen
RAntFZS	Right anterior frontozygomatic suture	Most anterior point of right frontozygomatic suture	Most anterior point of right frontozygomatic suture	Most anterior and central point of right frontozygomatic suture
RFMS	Right border of the frontomaxillary suture	Most anterior and lateral point of right frontomaxillary suture	Most lateral point of right frontomaxillary suture	Most lateral point of right frontomaxillary suture
LFMS	Left border of the frontomaxillary suture	Most anterior and lateral point of left frontomaxillary suture	Most lateral point of left frontomaxillary suture	Most lateral point of left frontomaxillary suture
LP1M	Left palatal bone crest of first molar	Most central point of alveolar bone in the buccal surface of left first molar	Most inferior and central point of alveolar bone in the buccal surface of left first molar	Most inferior and medial point of alveolar bone in the buccal surface of left first molar
LP1PM	Left palatal bone crest of first premolar	Most central point of alveolar bone in the buccal surface of left first premolar	Most inferior and central point of alveolar bone in the buccal surface of left first premolar	Most inferior and medial point of alveolar bone in the buccal surface of left first premolar
LPC	Left palatal bone crest of canine	Most central point of alveolar bone in the buccal surface of left canine	Most inferior and central point of alveolar bone in the buccal surface of left canine	Most inferior and medial point of alveolar bone in the buccal surface of left canine
LCE	Left canine eminence	Most anterior and superior point of left canine eminence in the level of canine root apex	Most anterior and superior point of left canine eminence in the level of canine root apex	Most superior and lateral point of left canine eminence in the level of canine root apex
LLatPA	Left most lateral point of piriform aperture	Most anterior point of piriform aperture in the left side	Most anterior point of piriform aperture in the left side	Most lateral point of piriform aperture in the left side
LInfZS	Left inferior margin of the zygomaticomaxillary suture	Most inferior and central point of left zygomaticomaxillary suture	Most inferior and central point of left zygomaticomaxillary suture	Most inferior and central point of left zygomaticomaxillary suture
LIOFor	Left infraorbital foramen	Most central point of left infraorbital foramen	Most central point of left infraorbital foramen	Most central point of left infraorbital foramen
LAntFZS	Left anterior frontozygomatic suture	Most anterior point of left frontozygomatic suture	Most anterior point of left frontozygomatic suture	Most anterior and central point of left frontozygomatic suture

Table S2: Mandibular landmarks.

Abbreviation	3D landmarks location:	Lateral	Axial	Anteroposterior
B	B point	Located in the largest concavity of the anterior portion of the mental symphysis	Deepest point of the mental symphysis	Deepest point along anterior concavity of maxilla
Me	Mentonian	Most inferior point of the mentonian symphysis	Most inferior and central point of the mentonian symphysis	Most inferior and central point of the mentonian symphysis
RPo	Right Porion	Most superior point of the right external auditory canal	Most superior point of the external right auditory canal	Most superior and lateral point of the right external auditory canal
ROr	Right Orbitale	Most inferior point on the lower portion of right orbit contour	Most inferior and anterior point on the lower portion of right orbit contour	Most inferior and anterior point on the lower portion of right orbit contour
RCo	Right Condylion	Most superior point of right condyle contour	Most superior and central point of right condyle contour	Most superior point of right condyle contour
RLatCoPole	Right Lateral Condyle Pole	Most lateral and central point of right condyle	Most lateral point of right condyle	Most lateral point of right condyle
RMedCoPole	Right Medial Condyle Pole	Most medial and central point of right condyle	Most medial point of right condyle	Most medial point of right condyle
RSig	Right Sigmoid	Deepest point of right mandibular incisure	Deepest and central point of right mandibular incisure	Deepest and central point of right mandibular incisure
RGo	Right Gonion	Most inferior and posterior point of right mandibular angle	Most inferior, posterior and central point of right mandibular angle	Most inferior, posterior and central point of right mandibular angle
RMFor	Right Mental foramen	Most anterior and superior point of right mental foramen	Most superior and central point of right mental foramen	Most superior and lateral point of right mental foramen
LPo	Left Porion	Most superior point of the left external auditory canal	Most superior point of the left external auditory canal	Most superior and lateral point of the left external auditory canal
LOr	Left Orbitale	Most inferior point on the lower portion of left orbit contour	Most inferior and anterior point on the lower portion of left orbit contour	Most inferior and anterior point on the lower portion of left orbit contour

LCo	Left Condylion	Most superior point of left condyle contour	Most superior and central point of left condyle contour	Most superior point of left condyle contour
LLatCoPole	Left Lateral Condyle Pole	Most lateral and central point of left condyle	Most lateral point of left condyle	Most lateral point of left condyle
LMedCoPole	Left Medial Condyle Pole	Most medial and central point of left condyle	Most medial point of left condyle	Most medial point of left condyle
LSig	Left Sigmoid	Deepest point of right mandibular incisure	Deepest and central point of right mandibular incisure	Deepest and central point of right mandibular incisure
LGo	Left Gonion	Most inferior and posterior point of left mandibular angle	Most inferior, posterior and central point of left mandibular angle	Most inferior, posterior and central point of left mandibular angle
LMFor	Left Mental foramen	Most anterior and superior point of right mental foramen	Most superior and central point of right mental foramen	Most superior and lateral point of right mental foramen
RMedpointLcoMco	Right median point between RLatCoPole and RMedCoPole	Automatically placed with 3D tools	Automatically placed with 3D tools	Automatically placed with 3D tools
LMedpointLcoMco	Left median point between LLatCoPole and LMedCoPole	Automatically placed with 3D tools	Automatically placed with 3D tools	Automatically placed with 3D tools
RSigEx	Right Sigmoid extension	Sigmoid linear extension to the most posterior portion of right condyle	Sigmoid linear extension to the most posterior portion of right condyle	Sigmoid linear extension to the most posterior l portion of right condyle
LSigEx	Left Sigmoid extension	Sigmoid linear extension to the most posterior portion of left condyle	Sigmoid linear extension to the most posterior portion of left condyle	Sigmoid linear extension to the most posterior portion of left condyle

Table S3: Upper Airway landmarks.

Abbreviation	3D landmarks location:	Lateral	Axial	Anteroposterior
SupA	Superior A	Most anterior point of Superior oropharynx tangent to the most inferior point of second cervical vertebra		
SupP	Superior B	Most posterior point of Superior oropharynx tangent to the most inferior point of second cervical vertebra		
SupR	Superior R	Right greater width point of Superior oropharynx tangent to the most inferior point of second cervical vertebra		
SupL	Superior L	Left greater width point of Superior oropharynx tangent to the most inferior point of second cervical vertebra		
InfA	Inferior A	Most anterior point of Inferior oropharynx tangent to the most superior point of fourth cervical vertebra		
InfP	Inferior P	Most posterior point of Inferior oropharynx tangent to the most superior point of fourth cervical vertebra		
InfR	Inferior R	Right greater width point of Inferior oropharynx tangent to the most superior point of fourth cervical vertebra		
InfL	Inferior L	Left greater width point of Inferior oropharynx tangent to the most superior point of fourth cervical vertebra		
C2I	Second Vertebra point	Most inferior and anterior point of the second cervical vertebra		
C4S	Fourth Vertebra Point	Most superior and anterior point of the fourth cervical vertebra		

Table S4. Maxillary linear and angular dimensions.

Type	Measurement	Description
Linear	Palatal alveolar bone crest M width	Transverse distance between RP1M and LP1M
	Palatal alveolar bone crest PM width	Transverse distance between RP1PM and LP1PM
	Palatal alveolar bone crest C width	Transverse distance between RPC and LPC
	Intercanine eminence distance	Transverse distance between RCE and LCE
	Greater palatine foramens distance	Transverse distance between RPfor and LPfor
	Nasal width	Transverse distance between RLatPA and LLatPA
	Inferior margin of the zygomaticomaxillary sutures distance	Transverse distance between RInfZS and LInfZS
	Infraorbital foramens distance	Transverse distance between RIOFor and LIOFor
	Anterior border of the frontozygomatic sutures distance	Transverse distance between RAntFZS and LAntFZS
	Lateral border of the frontomaxillary sutures distance	Transverse distance between RFMS and LRFMS
	Facial height	Vertical distance between N and Me
	ANS-PNS	Anteroposterior distance between ANS and PNS
Angular	SNA	Obtained connecting S, N and A points
	SNB	Obtained connecting S, N and B points
	ANB	Obtained connecting A, N and B points

Table S5. Mandibular linear, angular and volumetric dimensions.

Type	Measurement	Description
Linear	Condylar height	Right and left vertical dimension from RCo/LCo to RSigEx/LSigEx.
	Condylar width	Right and left lateral dimension between RLatCoPole/LLatCoPole and RMedCoPole/LMedCoPole.
	Condylar torque	Right and left anteroposterior dimension between RLatCoPole/LLatCoPole and RMedCoPole/LMedCoPole.
	Ramus height	Right and left vertical dimension from RCo/LCo to RGo/LGo.
	Mandibular length	Right and left anteroposterior dimension between RGo/LGo and Me.
	Intergonial width	Lateral dimension between RGo and LGo.
	Intercondylar width	Lateral dimension between RCo and LCo
	Mandibular corpus anterior width	Lateral dimension between RMFor and LMFor.
	Mandibular linear anterior rotation	Vertical and anteroposterior dimension between B point from T0 and T1 images.
Angular	Mandibular ramus facial angle	Right and left angle obtained by intersecting the PF and the line formed between RCo/LCo and RGo/LGo, considering pitch as 3D angle space plane.
	Gonial angle	Right and left angle obtained by connecting RCo/LCo, RGo/LGo and Me, considering pitch as 3D angle space plane.
	Condylar inclination	Right and left angle obtained by connecting RCo/LCo,RMedpointLcoMco/LMedpointLcoMco and RSigEx/LSigEx, considering pitch as 3D angle space plane.
	Mandibular corpus posterior angle	Obtained among the RGo, Me and LGo, considering yaw as 3D angle space plane.
	Mandibular corpus curve angle	Right and left angle obtained connecting RGo/LGo, RMFor/LMFor and Me, considering yaw as 3D angle space plane.
	Intercondylar angle	Obtained by intersecting the line formed between RLatCoPole and RMedCoPole with the line formed between LLatCoPole and LMedCoPole, considering yaw as 3D angle space plane.
	Mandibular ramus angular rotation	Right and left angle obtained by intersecting the line formed between RCo/LCo and RGo/LGo from T0 and the line formed between RCo/LCo and RGo/LGo from T1, considering pitch as 3D angle space plane.
	Mandibular anterior angular rotation	Right and left angle obtained by intersecting the line formed between RCo/LCo and B point from T0 and the line formed between RCo/LCo and B point from T1, considering pitch as 3D angle space plane.
Volumetric	Condylar volume	Right and left condylar volume with inferior limit represented for a line tangent to RSig/LSig and parallel to Frankfurt plane (FP).
	Total mandibular volume	The inferior limit for mandibular volumetric measurement was a line parallel to mandibular plane and tangent to RMFor/LMFor points (line MPMe). The anterior limit was a line tangent to the most anterior portion of coronoid process, touching the line MPMe with a 90° angle.

Table S6. Upper airway linear and volumetric dimensions.

Type	Measurement	Description
Linear	Shape in C2I slice (ShC21)	Obtained by dividing the maximum anteroposterior distance (SupA – SupP distance) by the maximum width (SupR– SupL distance) of the AU measured in the region of C2I
	Shape in C4S slice (ShC4S)	Obtained by dividing the maximum anteroposterior distance (InfA – InfP distance) by the maximum width (InfR– InfL distance) of the AU measured in the region of C4S
Volumetric	Total upper airway volume	From Ba-PNS to C4S level (parallel to Ba-PNS)
	Superior oropharynx volume	From Ba-PNS to C2I level (parallel to Ba-PNS)
	Inferior oropharynx volume	From C2I to C4S (parallel to Ba-PNS)

III. CAPÍTULO

"*PLOS ONE*"

THREE-DIMENSIONAL COMPARISON BETWEEN THE EFFECTS OF MANDIBULAR ADVANCEMENT DEVICE AND BIMAXILLARY ORTHOGNATHIC SURGERY ON UPPER AIRWAY

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Abstract

Introduction: Mandibular advancement device (MAD) and bimaxillary orthognathic surgery (BOS) are viable treatment options to maintain the upper airway (UA) patency. However, the differences in the treatment response to these therapies are unclear. This study aimed to evaluate three-dimensionally the UA dimensions of patients after MAD and BOS, and to compare the effect of both therapies in UA and mandibular rotation. Methods: This retrospective cohort study compared two groups: 17 patients with polysomnographic obstructive sleep apnea diagnosed by polysomnography treated with MAD and 17 BOS patients to correct Class II malocclusion. Cone-beam computed tomography (CBCT) from before (T0) and after (T1) both treatments were evaluated. Total UA, superior/inferior oropharynx volume and surface area; mandibular linear and angular measurements were assessed. Student's t, paired t, multifactorial ANOVA tests and Pearson correlation were applied. Results: The MAD group showed statistical increase in superior oropharynx volume and area. The BOS group showed significant improvement in all UA regions and the increase in superior oropharynx was significantly higher than in the MAD group. The mandibular rotational movements significantly differed, while MAD group showed statistic displacement for an inferior and backward position, a statistically significant anterior and superior movement was identified in BOS group. The anterior and vertical displacements showed direct correlations with the inferior oropharynx volume and rotational movements of inferior oropharynx in both groups. Conclusions: MAD therapy increased volume and surface area of the superior oropharynx portion and BOS treatment achieved higher improvements in all UA regions. MAD therapy led to clockwise mandibular rotations and BOS led to counterclockwise mandibular rotations.

Keywords: Cone-Beam Computed Tomography (CBCT); Three-dimensional assessment; Upper airway; Obstructive sleep apnea; Bimaxillary orthognathic surgery; Mandibular advancement device.

Introduction

Upper airway (UA) anatomy and patency are related to different sleeping breath disorders. The most prevalent respiratory sleep disease that may be affected by preexisting narrow UA is Obstructive Sleep Apnea (OSA). OSA is defined by the presence of recurrent episodes of apnea and /or hypopnea due to UA collapse during sleep. It is considered a chronic disease that affect mainly advanced ages with a prevalence exceeding 50% of the population in some countries, being more common in males than in females.[1-4]

OSA plays an important role in the development of symptoms, such as anxiety and depression, and sleep pattern. Patients with OSA may develop intense and intermittent snoring, breathing pauses during sleep, recurrent and wheezing awakenings, non-restorative sleep and excessive daytime sleepiness, leading to a negative social impact and poor quality of life. In addition to these symptoms, a transient pulmonary hypertension with a stimulation of sympathetic nervous system, presents in OSA, leads to an increase in blood pressure. Moreover, the phenomenon of hypoxemia and subsequent reoxygenation, repeated numerous times during the night, causes reperfusion changes with the formation of free radicals, increasing oxidative stress in OSA patients. All these cardiovascular changes are associated with a significant increase in mortality risk.[3, 5, 6]

Several therapies, such as sleep hygiene techniques, physical conditioning and weight loss, pharmacological treatment, continuous positive airway pressure (CPAP), maxillofacial surgeries and intraoral devices, had been proposed for UA patency maintenance. The CPAP, gold standard for UA patency maintenance and OSA treatment, is a machine connected to a facial mask that assures the UA space applying external air pressure. However, when there is

no acceptance or compliance to CPAP therapy, mandibular advancement devices (MAD's) and orthognathic surgeries may be required as treatment options.[7-9]

The MAD therapy mechanism of action is based on gradual advancement of the mandible with the use of a removable intraoral device. The successive mandibular advancement distends the UA tissues. This distention prevents the collapse between the posterior wall of the oropharynx and the base of the tongue, ensuring air flow by the maintenance of airway morphology.[3, 10] Compared with CPAP, MAD treatment may result in similar beneficial changes in cardiovascular symptoms.[11]

Bimaxillary orthognathic surgery (BOS) with mandibular advancement is also a viable treatment option to maintain UA patency, especially in patients with severe mandibular retrusion. Mandibular retrognathism and/or retrusion reduces the space between the posterior pharyngeal wall and the mandibular body, bringing the tongue and soft palate to a posterior position. This increases the chance to develop respiratory disorders such as OSA.[12] When BOS is made for Class II malocclusion correction, it may result in changes on the tongue, lips, soft palate and hyoid bone position. Consequently, the UA is enlarged by moving the anterior pharyngeal in an anterior direction. However, authors have reported losses in improvement of UA patency in long term evaluation of patients treated with surgical advancement of the mandible.[13-17]

Three-dimensional assessment of MAD and BOS treatment effects mandibular rotations using Cone-beam computed tomography (CBCT). Differently of the medical traditional computed tomography (CT), the CBCT converges the x-rays to the craniofacial area, leading to a decrease in the exposure time during the image acquisition. Moreover, CBCT may generate scans with greater accuracy and resolution. Three-dimensional images have allowed evaluation of the total volume of the UA, different cross-section regions of this structure and mandibular characteristics.[17-19]

The investigation of UA physiological and anatomic changes with MAD and BOS therapy is of critical importance to plan the best treatment option in patients with a reduced UA, higher risk to develop OSA or confirmed OSA diagnosis. The efficacy of both treatments, MAD and BOS, in improving UA patency has been described as being comparable to CPAP outcomes.[20] However, no previous study has compared MAD and BOS therapy. We hypothesize that there are different patterns of mandibular movements, as well as different effects in volume and area of UA when comparing MAD and BOS mandibular advancement. In this context, the aim of this study is to evaluate in three-dimensions the UA changes and mandibular rotation of patients after MAD treatment for OSA and after BOS for Class II correction.

Material and methods

Study design

This is a retrospective cohort study that compares CBCT scans taken before and after treatment of two groups of patients, MAD and BOS, matched by weight, height and body mass index (BMI). The MAD group was composed of 17 patients with polysomnographic diagnosis of OSA referred from a sleep disorder center for treatment with MAD. These patients had polysomnographic and CBCT exams taken before treatment (T0) and with the appliance placed after achieving MAD therapeutic position (T1). The therapeutic protrusion (TP) was achieved from 4 to 6 months after the MAD initial placement. Thirty to 48 days after TP was established, volunteers performed the final polysomnography and CBCT (T1). The BOS group consisted of 17 patients who had bimaxillary orthognathic surgery to correct Class II malocclusion at the Sao Paulo State University. This comparison group had CBCTs exams before surgery (T0) and at least one year after surgery (T1). The inclusion criteria were available CBCT scans from

adults (older than 19 years) at both T0 and T1 time points with good image quality for accurate assessment of the areas of interest; matching height and weight in the study groups. Subjects who did not have matching height and weight were excluded. A flowchart of the study design is shown in Fig 1.

Ethical considerations

This study was approved by the Research Ethics Committee of the Federal University of São Paulo – Brazil (number 0301/10) (MAD treatment) and by Research Ethics Committee of São Paulo State University (number 3.717.097) (BOS treatment). All volunteers signed the Informed Consent Form (ICF) and had their privacy rights assured.

Sample size

Sample size calculation was performed using the findings of Consellu et al.[21]Using measures of the total total airway volume, we estimated at least 16 patients in two time points in the present study in order to obtain a sample that represents with 90% power and 95% confidence the alternative hypothesis of this work (paired t-test).

MAD treatment

The MAD treatment was performed using the Brazilian dental appliance (BRD)[8], which is an individualized MAD that allows gradual mandibular advances (Fig 2). The initial advancement was 50% of the total mandibular maximum protrusion capacity from each patient individually. The mandibular advancement was made gradually with 1mm per week until achieving TP, which was determined by the OSA clinical symptoms release.

Bimaxillary orthognathic surgery

The patients from the BOS group were treated with two-jaw surgery to allow maxillomandibular advancement and adjustment of the occlusal plane in a counterclockwise displacement. Thus, osteotomies were performed in maxilla, being stabilized with 4 bone plates associated to 2mm diameter screws and bone grafting whether necessary. The mandibular advance surgery was performed by bilateral mandibular sagittal split osteotomies associated to a counterclockwise displacement of the occlusal plane. In order to stabilize the mandibular repositioning, 1 bone plate was allocated in the posterior body region and 2 -3 in the bicortical portion and 2mm diameter screws were placed in the ascending ramus on each side.[22]

Variables

The demographic variables included the anthropometric characteristics: sex, age, weight, height, and BMI. Three-dimensional image analysis variables included UA volume and area, and mandibular linear and angular measurements.

CBCT acquisition

CBCT images from both groups were performed at a private dental radiological clinics (Sao Paulo, Brazil) using the i-CAT® scanner (Imaging Sciences International, Hatfield, PA), configured with 120Kvp, 3-8mA and 0.4mm voxel size and field of view (FOV) of 23 cm x17 cm, allowing the total vertical head framing.[23, 24] During the image acquisition, all patients were in an upright posture, awake, in natural head position (Camper's horizontal plane parallel to the ground) and were instructed to gaze at a stationary point on the wall. CBCT scans were

taken in maximum intercuspal position.[23, 25, 26] All patients were instructed to not move, swallow or take deep breaths during the exam in order to avoid changes in the UA volume.[27] The images were stored in DICOM files (Digital Imaging and Communications in Medicine).

Image processing and measurements

Open-source imaging platforms were used to process all CBCT data at T0 and T1. ITK-SNAP 2.4 software (https://www.itksnap.org) was used to convert the DICOM in NIfTI files and obtain the segmentation required for image analysis. Orientation, registration and digital surface model creation of patients' scans/segmentations, as well as all linear, angular and volumetric/area measurements, were performed using 3D Slicer software 10.4 (www.slicer.org) (Fig 3). The digital models were moved by orienting their Frankfurt horizontal, midsagittal and transporionic planes to match the axial, sagittal and coronal planes, respectively, at a standard coordinate system from Slicer software, in order to apply the 3D head orientation for all T0 scans. T1 scans cranial registration were performed after manual approximation to T0 scan oriented.[28] To perform all measurements, a list of 3D landmarks was used for mandible and UA (Supplementary Table S1). All linear, angular, area, and volumetric dimensions were obtained, respectively, in millimeters (mm), degrees (°), squared millimeters (mm^2) and cubic millimeters (mm^3).

Upper airway measurements

In order to identify UA volume and area in T0 and T1 from the two groups, UA was delimited in Superior oropharynx and Inferior oropharynx and 3 measurements were performed (Fig 4):

- Total upper airway volume/surface area: From Ba-PNS to C4S level (parallel to Ba-PNS).
- Superior oropharynx volume/surface area: From Ba-PNS to C2I level (parallel to Ba-PNS).
- Inferior oropharynx volume/surface area: From C2I to C4S (parallel to Ba-PNS).

Mandibular measurements

Three mandibular measurements were performed in both groups (Fig 5):

- Mandibular linear displacement: Anteroposterior and vertical dimension between B point from T0 and T1 images.
- Mandibular ramus angular rotation: Right and left angle obtained by intersecting the line formed between Co-Go from T0 and the line formed between Co-Go from T1, considering the angle of pitch in the 3D space.
- Mandibular anterior angular rotation: Right and left angle obtained by intersecting the line formed between Co-B from T0 and the line formed between Co-B from T1, considering T0 and the line formed between Co-Go from T1, considering the angle of pitch in the 3D space.

Study error

Intraexaminer reliability was performed blindly by one experienced examiner, repeating the 3D measurements with an interval of 15 days between the measurements in order to avoid potential sources of bias. The data were exported to Microsoft Excel spreadsheets (Microsoft Corporation, Redmond, WA) and analyzed using the Statistical Package for the Social Sciences

(SPSS®) version 20.0 for Windows (IBM Corporation, Sommers, NY). Intraclass correlation coefficient (ICC) to evaluate systematic errors regarding numerical data and Dahlberg's formula for assessing casual errors of measurements were performed.

Statistical methods

The data were stored in Microsoft Excel and exported to the SPSS® software version 20.0 for Windows, in which the analyzes were performed adopting 95% confidence. Mean and standard deviation were calculated from all measures. Kolmogorov-Smirnov normality test was also applied for all the variables. Moreover, Student's t test was made in order to compare MAD and BOS groups, as well as T0 and T1 CBCTs. Left and right sides were submitted to paired t test (parametric data). The multifactorial ANOVA test was used in all variables in order to adjust age factor and group factor. The variables correlations were analyzed by Pearson correlation.

Results

Study error

The intraexaminer repeatability of angular and linear measurements showed excellent correlation coefficients (ICCs>0.9). Volume measurements showed adequate ICCs>0.75. Dahlberg's coefficient of at least 0.01 was observed.

Sample description

In the MAD group, the TP was on average 97.4 ± 4.8% of the maximum protrusion, ranging from 85 to 100% of the mandible's maximum anterior displacement, this group was composed of 9 males and 8 females (aged from 34 to 60), while BOS group was composed of

7 males and 10 females (aged from 20 to 57).There was no statistical difference regarding the distribution by sex between the two study groups (p^b=0.492). The mean age of the patients in the MAD group was significantly greater than in the BOS group (p^a<0.00). Weight (p^a=0.693), height (p^a=0.616) and BMI (p^a=0.223) did not differ significantly between groups. Due to the statistical difference between the age of the two groups, this variable was considered as an adjustment for the other analyzes (Table 1).

Upper airway measurements

MAD group

Although the UA total volume and surface area in T1 was greater than in T0, no statistical difference was found in total volume (p^b=0.142) and surface area (p^b=0.159). In the superior oropharynx, MAD group showed a statistically significant increase in volume (p^b=0.003) and surface area (p^b=0.003) after MAD treatment. This group did not show statistical difference in inferior oropharynx volume (p^b=0.247) and surface area (p^b=0.073) between T0 and T1 (Table 2).

BOS group

In this group, UA total volume (p^b=0.003) and surface area (p^b=0.001) statistically increased in T1. BOS group also showed a significant increase in the superior oropharynx volume (p^b=0.003) and surface area (p^b=0.001) after the surgery. In addition, the inferior oropharynx volume (p^b<0.001) and surface area (p^b=0.001) were significantly greater in T1 as well (Table 2).

Comparison between MAD and BOS groups

No statistical difference in UA total volume was found between the groups before treatment (p^a=0.788). However, in T1 the BOS group showed greater increase in UA total volume than the MAD group (p^a=0.020). The age factor was considered as determinant factor for this finding, once group factor showed a p^d=0.310 (Table 2).

The UA superior oropharynx volume in T0 did not differ between the groups (p^a=0.238). Both groups showed a significant increase in the superior oropharynx volume after the treatments (p^b=0.003). However, this increase in the superior volume was greater in BOS group (p^a=0.010). This finding was not interfered by age (p^d=0.037). The superior oropharynx area significantly increased in MAD and BOS groups. This amount of increase was higher in BOS group (p^a=0.017) and the age was not determinant for this outcome (p^d=0.043). (Table 2).

The UA inferior oropharynx volume (p^a=0.325) and area (p^a=0.264) did not differ at T0 comparing the groups. At the T1 CBCT, the inferior volume (p^a=0.024) and area (p^a=0.012) were greater in the BOS group than in the MAD group. The age was a determinant factor in inferior oropharynx volume (p^d=0.148) and area (p^d=0.103) (Table 2).

Mandibular measurements

The mandibular linear anterior displacement was statistically greater (p^a=0.010) in the BOS group (6.47±4.67) than in the MAD group (2.75±3.08). The mandibular linear vertical measurement showed statistical difference comparing MAS and BOS groups (p^a <0.001). In the MAD group (-9.29±3.06), patients demonstrated a more inferior vertical position of the mandible after treatment than the BOS group patients (1.66±4.32), which showed an upward vertical displacement (Table 3).

The mandibular ramus angular rotation and mandibular anterior angular rotation were statistically different between the groups ($p^a<0.001$). While the MAD group showed a clockwise rotation pattern (-3.97±1.07 and -4.08±1.30), the BOS group demonstrated a counterclockwise (2.40±3.43 and 3.41±2.79). The age factor did not influence mandibular measurements outcomes (p-values[c] equal or less than 0.001) (Table 3).

Correlations between the measures

In the MAD group, the mandibular linear anterior displacement was correlated with superior [p=0.002 (r=-0.697)] and inferior [p=0.004 (r=0.658)] oropharynx volume, suggesting that greater amounts of mandibular advancement are correlated to a decrease in the superior oropharynx and an increase in the inferior oropharynx. Mandibular anterior angular rotation was correlated with mandibular linear displacement in an inferior direction [p=0.020 (r=0.557)], clockwise mandibular rotation (Table 4).

In the BOS group, the superior oropharynx volume was correlated to mandibular mandibular anteroposterior [p=0.029 (r=-0.530)] and vertical displacement [p=0.047 (r=0.488)]. This analysis suggests that greater amounts of mandibular advancement may lead to a lowest gain in the superior oropharynx volume, while a great mandibular superior displacement is correlated with better improvements in this UA region. Mandibular ramus angular rotation was correlated with the mandibular anteroposterior linear displacement [p=0.001 (r=0.743)]. Mandibular anterior angular rotation was correlated with both mandibular linear displacements, anteroposterior [p=0.000 (r=0.785]) and superoinferior [p=0.000 (r=0.753)]. This outcome may imply that greater amounts of mandibular linear displacements are correlated to a counterclockwise rotation pattern (Table 4).

Discussion

The present study evaluated and compared upper airway volume and area, as well as mandibular rotation in patients undergoing either intraoral treatment with mandibular advancement device for obstructive sleep apnea or bimaxillary orthognathic surgery for Class II malocclusion correction. Although, mandibular advancement device and orthognathic surgery have been compared to CPAP effects in several studies, the literature lacks comparisons between the treatment outcomes of these two types of treatments.[16, 17, 20, 22, 25, 28] The assessments of these therapies' effects are important for treatment planning when the objectives include increasing the airway dimensions, preventing or treating sleep breathing disorders, such as obstructive sleep apnea.

This study findings showed that the MAD group did not present a significant increase of the UA total volume and area at T1. However, the superior oropharynx volume and surface area demonstrated a statistically significant increase. This superior enlargement was adequate to improve PSG parameters, such as apnea and hypopnea index and minimum oxyhemoglobin In the OSA group. Although the inferior oropharynx volume and area decreased, the decrease was not statistically significant. These findings were similar to the outcomes of Barbero et al.[29], which demonstrated that the superior portions of UA are mostly affected by MAD. These authors reported that the velopharynx was the region with largest volume in all studied appliance positions.[29]

Our results showed that, in the BOS group, the UA total volume and area significantly increased 1 year after surgery. Moreover, this increase was significant in both the superior and inferior oropharynx regions. These findings agree with Marcussen et al.[30], who demonstrated statistical increases in velopharynx and oropharynx after BOS for Class II treatment. Gurani at

al.[31] also identified a statistically relevant UA volume increase of 26% immediately after the bimaxillary orthognathic surgery. However, the authors identified a loss in volume of 20 % after 2-years. The loss in volume gain was also reported in a study that identified an increase in total volume and area, as well as in nasopharynx, oropharynx and hypopharynx. Nevertheless, the reported losses in volume and area started at 1 year after surgery.[13-15]

In the present study, the total, superior, and inferior volume and area of the oropharynx were statistically greater at T1 in the BOS group than in the MAD group. This finding may be explained by the mandible movement pattern from each group. In the MAD group the amount of mandible advancement achieved was significantly smaller, while the vertical component was greater in the MAD group compared with the BOS group. The MAD group showed clockwise mandibular rotation and the BOS group demonstrated a counterclockwise mandibular rotation 1 year after surgery. It has been reported that MAD treatment may increase vertical dimensions and that the amount of resultant mandibular protrusion is reduced 0.3 mm for each 1 mm of vertical displacement.[26, 32] This change in the vertical dimension occurs due to the design of the oral appliance may interfere in the amount of mandibular advancement and rotation. Such clockwise rotational pattern with the oral device was associated with greater gain in volume and area in the superior portion of the UA but not in the inferior oropharynx region. According to Barbero et at.[29], MADs with lower bite-raising are more effective in increasing airway volume than larger bite-raising appliances, showing that the appliance vertical dimension plays an important role in MAD outcomes. The oral appliance used in this study was the BRD, which is composed by two acrylic blocks for maxillomandibular support, aiming to maintain a more stable mandibular position when compared with other types of appliances.[29] A stable mandibular advancement is essential to control mouth opening during sleep and to reduce the mandibular clockwise rotation. However, even with the BRD design, the mandible clockwise movement still interfered with the objective to improve UA volume. In surgical patients, the

counterclockwise rotation pattern leads to gains in UA volume and airway area in general, both in superior and inferior oropharynx portions.[8]

In this study, the surgery group also demonstrated that the mandibular advancement and vertical superior displacement were directly correlated with greater dimensions in superior oropharynx and most of the counterclockwise rotation variables. These outcomes are in agreement with Marcussen et al.[30] who identified that counterclockwise rotation were correlated to velopharynx and glossopharynx volume improvement. Controversially, comparing surgical mandibular advances with and without counterclockwise rotation, a meta-analysis study reported that it was not possible to identify which procedure is more effective in improving UA volume.[5] In both groups, greater amounts of the real mandibular anterior displacement (measured by the distance between B point in T0 and B point in T1) were correlated with a reduced gain in the superior volume. Although it is challenging to justify this outcome, it shows a relevant point in the amount of mandibular advancement that should be applied in the treatments. This finding indicates that a limit on the amount of advancement for good UA patency may exist and better results may be obtained by a balanced amount of advancement instead of a large anterior displacement.

Importantly, our findings may guide the clinician's decision regarding the treatment of choice to increase the UA. The UA may be improved by both therapies at different levels, ways and quantities. The BOS treatment improved UA dimensions in all UA regions by a counterclockwise mandibular rotation, leading to a gain of great amount of volume and area. On the other hand, the MAD patients group had mainly increase in the superior portion of the UA by a clockwise mandibular movement with lesser volume and area improvements than the comparison group. The BOS seems to be the most effective option to increase the UA. Nonetheless, BOS is also a more invasive and risky treatment and studies have demonstrated loss in volume gain in long-term evaluations[13-15, 31], while MAD is a more conservative

therapy that is efficient for the superior UA portion. Despite the temporomandibular disorders being associated with MAD treatment as a possible adverse effect, this intraoral appliance therapy is not irreversible. Once the patient demonstrates any collateral effect, the treatment may be interrupted before severe consequences, being an extremely conservative therapy option.

The limitation of this study was the lack of polysomnographic exams before and after the treatments in both groups. Moreover, it was not possible to match the age factor between the groups. However, the age factor only interfered in three of the variables measured.

Image analysis is an important tool for supervising UA 3D aspects and treatments associated to changes in this anatomic region. In the present study, the image assessment was performed using a standardized head position in both groups, as described by Ruellas et al.[28] The mandibular and upper airway measurements were made with common head orientation and registration between the scans obtained before and after treatment, using 3D slicer tools and ITK-SNAP semi-automatic segmentation. Both software demonstrated accuracy and precision comparable to Dolphin imaging analyzes. Once the CBCT image is not indicated for sleep disorders diagnosis, the limitation of this study was the lack of polysomnographic exams before and after the treatments in both groups. Moreover, it was not possible to match the age factor between the groups. However, the age factor only interfered in three of the variables measured.[33-35]

There is still a gap in literature in comparing upper airway patency and mandibular movement between patients treated with MAD and BOS. Therefore, to confront our outcomes with previous studies is a challenge, and more scientific studies accessing these variables together are strongly necessary. The knowledge about the UA and mandibular rotation effects of these treatments is essential to select the proper therapy, analyzing the individual needs and

cost benefit, leading to successful outcomes in treat or to prevent diseases related to UA patency.

Conclusions

MAD increased only the superior oropharynx volume and surface area. BOS increased total upper airway, as well as superior and inferior oropharynx volume and surface area. BOS treatment achieved greater volume and area in all UA regions compared to MAD treatment. The UA improvement occurred in both therapies by different mandibular movements. MAD treatment resulted in a clockwise rotation, while BOS showed a counterclockwise rotation. In MAD and BOS groups greater amounts of the real mandibular anterior displacement obtained in T1 were correlated with a reduced gain in the superior volume, highlighting the importance of considering a balance in planning the amount of advancement for each patient.

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FIGURES AND CAPTIONS

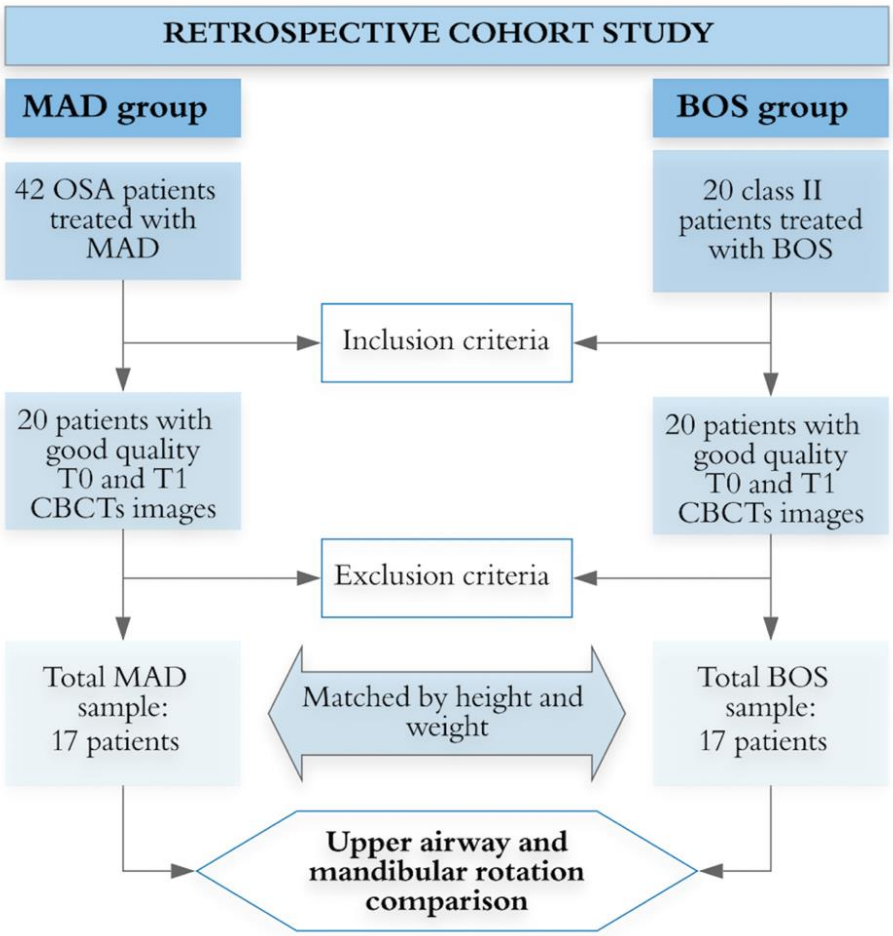

Fig 1. Study design. MAD = Mandibular advancement device. OSA = Obstructive Sleep Apnea. CBCT = Cone-Beam Computed Tomography. BOS = Bimaxillary Orthognathic Surgery.

Fig 2. Mandibular advancement device used in the study.

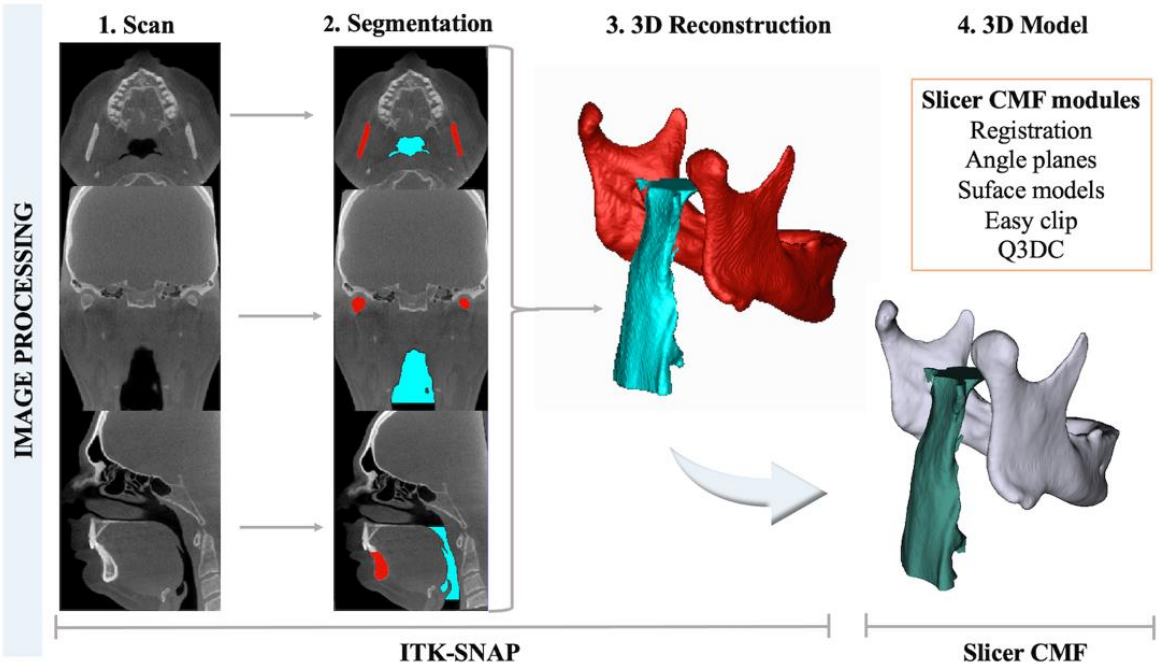

Fig 3. Image processing. (1) Scan axial, sagittal and coronal view (ITK-Snap). (2) semi-automated mandibular and upper airway segmentations (ITK-Snap). (3) Automated 3D reconstruction (ITK-Snap). (4) 3D model created in 3D slicer by the software extensions and modules.

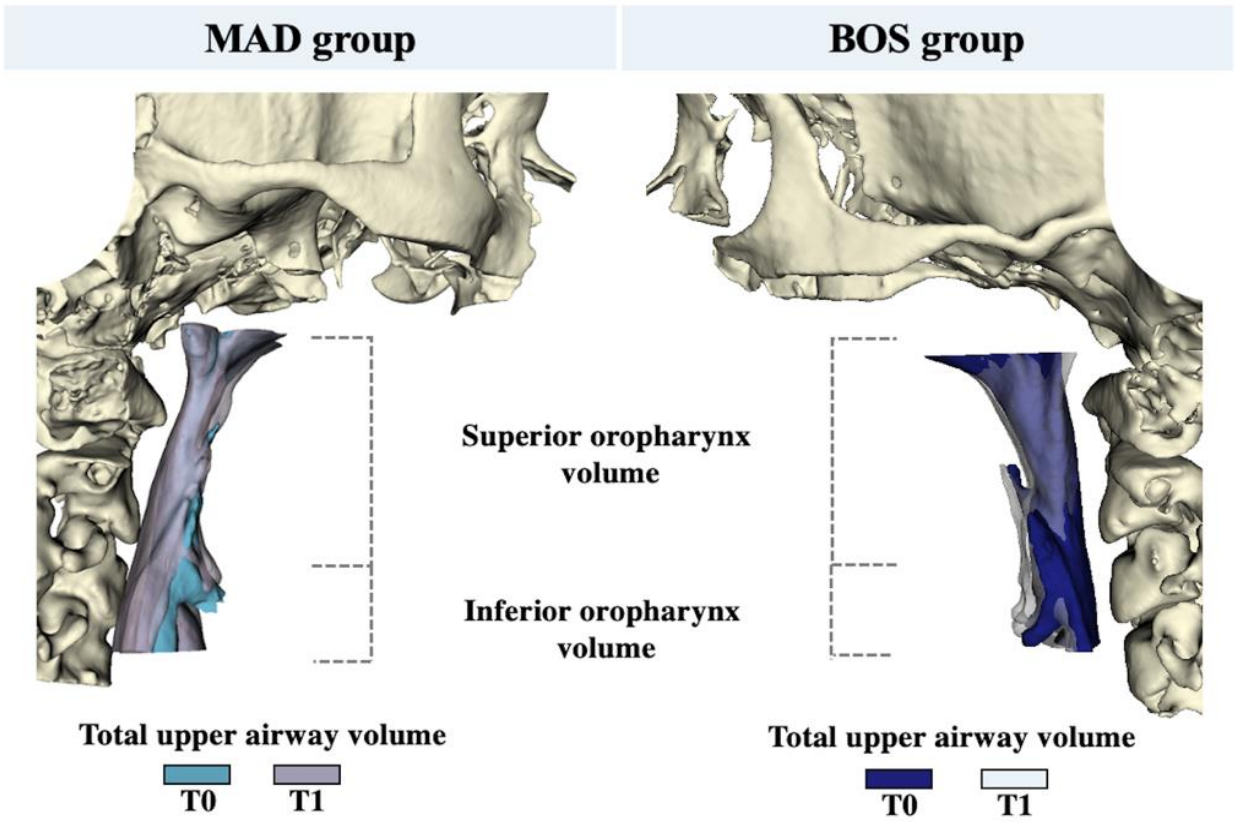

Fig 4. Total upper airway, superior and inferior oropharynx volume before (T0) and after (T1) Mandibular advancement device (MAD) and Bimaxillary Orthognathic Surgery (BOS) treatments.

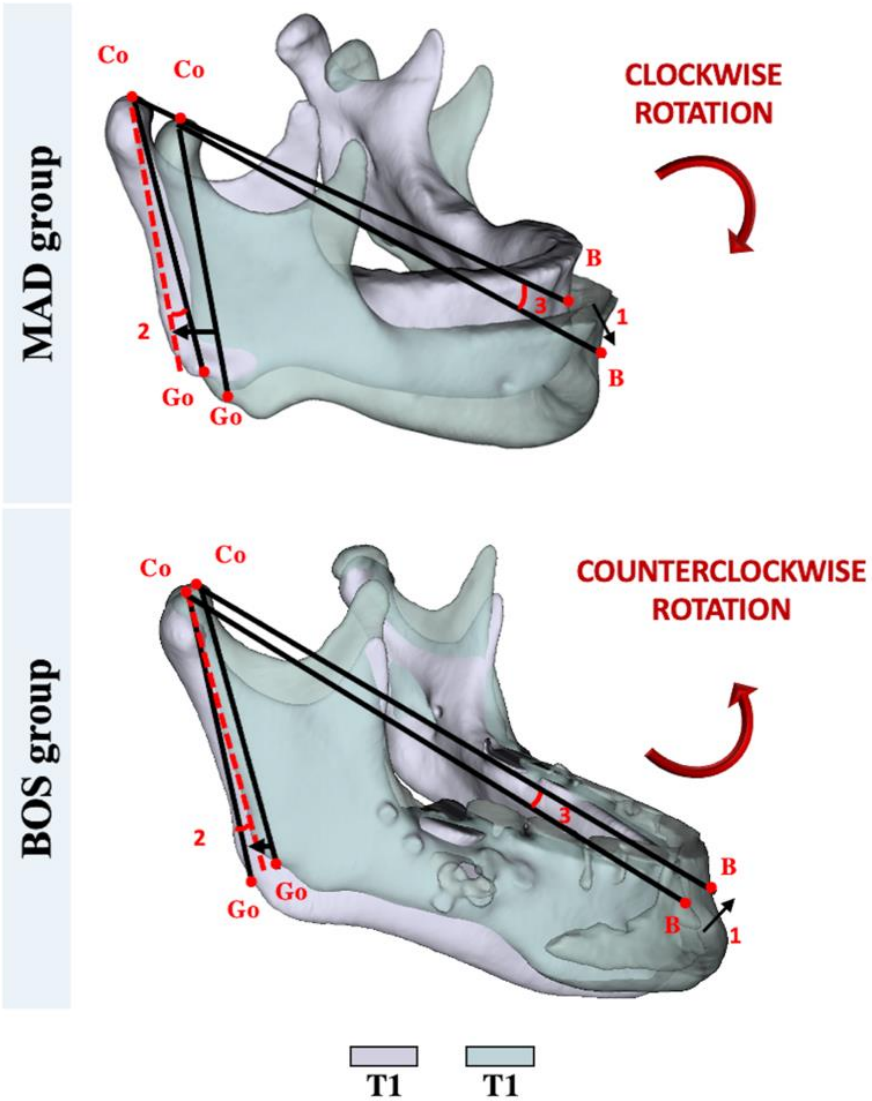

Fig 5. Mandibular measurements. (1) Mandibular linear displacement; (2) Mandibular ramus angular rotation; (3) Mandibular anterior angular rotation. Co = Condylion. Go = Gonion. B = B point. OSA = Obstructive Sleep Apnea. BOS = Bimaxillary Orthognathic Surgery.

Table 1: Sample description.

	Groups		p-Value[a]
	MAD (n=17)	**BOS** (n=17)	
Anthropometric characteristics			
Sex (M/F)	9/8	7/10	0.492[b]
Age	47.35±9.33	34.00±11.20	***0.001***
Weight	70.76±16.01	68.59±15.89	0.693
Height	1.65±0.13	1.67±0.11	0.616
BMI	25.83±3.32	24.38±3.48	0.223

* $p < 0.05$, [a]Student's t test; [b]Pearson's chi-square test (n). M= male. F= female. BMI = Body mass index. OSA = Obstructive sleep apnea. BOS = Bimaxillary orthognathic surgery.

Table 2: Upper airway measurements

	Groups		Multifactorial analysis		
	MAD	**BOS**	**p-value[a]**	**p-value[c]**	**p-value[d]**
UA total volume					
T0	12860.12±4442.52	13485.22±8376.86	0.788	0.064	0.413
T1	14130.82±4258.66	19984.25±8906.67	***0.020***	0.059	0.310
p-value[b]	0.142	***0.003***			
UA total surface area					
T0	5380.06±1245.42	5153.73±1790.80	0.672	***0.036***	0.121
T1	5685.71±1297.52	6662.65±1992.15	0.100	***0.016***	0.914
p-value[b]	0.159	***0.001***			
Superior oropharynx volume					
T0	7993.69±2397.96	10030.88±6559.56	0.238	0.249	0.726
T1	10049.33±3555.98	15248.59±6946.79	***0.010***	0.903	***0.037***
p-value[b]	***0.003***	***0.003***			
Superior oropharynx surface area					
T0	3440.90±736.27	3780.54±1665.06	0.447	0.839	0.609
T1	3836.44±860.38	5100.30±1821.71	***0.017***	0.992	***0.043***
p-value[b]	***0.003***	***0.001***			
Inferior oropharynx volume					
T0	4863.08±2382.66	4105.69±2019.74	0.325	0.422	0.210
T1	4311.76±2267.63	6183.29±2338.97	***0.024***	0.396	0.148
p-value[b]	0.247	***<0.001***			
Inferior oropharynx surface area					
T0	2279.50±722.15	2034.82±515.63	0.264	0.218	0.109
T1	2082.07±707.66	2731.81±709.37	***0.012***	0.338	0.103
p-value[b]	0.073	***0.001***			

* $p < 0.05$, [a]Student's t test; [b]Paired t test (mean ± SD); [c]Multifactorial ANOVA Age factor; [d]Multifactorial ANOVA Group factor. OSA = Obstructive sleep apnea. BOS = Bimaxillary orthognathic surgery. UA =Upper airway.

Table 3: Mandibular measurements.

	Groups			Multifactorial analysis	
	MAD	**BOS**	**p-value[a]**	**p-value[b]**	**p-value[c]**
Mandibular linear displacement					
Anteroposterior	2.75±3.08	6.47±4.67	***0.010***	***0.026***	***0.001***
Superoinferior	-9.29±3.06	1.66±4.32	***<0.001***	0.076	***<0.001***
Mandibular ramus angular rotation	-3.97±1.07	2.40±3.43	***<0.001***	0.024	***<0.001***
Mandibular anterior angular rotation	-4.08±1.30	3.41±2.79	***<0.001***	0.003	***<0.001***

* p <0.05, [a]Student's t test; [b]Multifactorial ANOVA Age factor; [c]Multifactorial ANOVA Group factor. OSA = Obstructive sleep apnea. BOS = Bimaxillary orthognathic surgery.

Table 4: Correlation between mandibular linear anterior rotation and groups variables.

	Mandibular linear displacement Anteroposterior	**Mandibular linear displacement Superoinferior**
MAD		
ΔSuperior oropharynx	***p=0.002 (r=-0.697)****	p=0.186 (r=0.337)
ΔInferior oropharynx	***p=0.004 (r=0.658)****	p=0.485 (r=-0.182)
Mandibular ramus angular rotation	p=0.211 (r=0.320)	p=0.963 (r=-0.012)
Mandibular anterior angular rotation	p=0.103 (r=0.409)	***p=0.020 (r=0.557)****
BOS		
ΔSuperior oropharynx	***p=0.029 (r=-0.530)****	***p=0.047 (r=0.488)****
ΔInferior oropharynx	p=0.208 (r=0.322)	p=0.092 (r=-0.422)
Mandibular ramus angular rotation	***p=0.001 (r=0.743)****	p=0.397 (r=0.220)
Mandibular anterior angular rotation	***p=0.000 (r=0.785)****	***p=0.000 (r=0.753)****

*p<0.05, Pearson correlation.

IV. CONCLUSÃO GERAL

VI. CONCLUSÃO GERAL

Através da revisão sistemática, foi possível elucidar que dentre todos os protocolos relatados para avaliação da VAS com TCFC em pacientes com AOS, o mais comum foi a posição do paciente durante o exame e delimitação da VAS através de tecidos duros como referência. A meta-análise mostrou que diferentes metodologias podem interferir na acurácia dos resultados. Não foi encontrado um protocolo padronizado e validado para avaliação tomográfica da VAS em pacientes com AOS.

As análises craniofaciais em 3D demonstraram que a largura transversal no nível da sutura frontomaxilar e o ângulo mandibular facial influenciaram na severidade da AOS. Além disso, o ângulo goníaco, bem como volume e área em todas as subdivisões da VAS indicaram a quantidade de avanço mandibular necessária para um tratamento eficaz. Esses achados evidenciam a importância dos fatores anatômicos na severidade e planejamento do tratamento da AOS com AAM.

Comparando-se o tratamento com a aparelho de avanço mandibular e cirurgia ortognática de avanço bimaxilar, foi possível constatar que o aparelho foi capaz de aumentar o volume da VAS, porém esse ganho ocorreu apenas na orofaringe superior. Enquanto isso, no grupo cirúrgico foi obtido um maior volume em todas as regiões da VAS. Ambos os tratamentos foram capazes de aumentar o volume da VAS, porém através de mecanismos diferentes. O avanço mandibular com aparelho gerou aumento na VAS por uma rotação no sentido horário e o avanço cirúrgico demonstrou eficácia através de um padrão de rotação mandibular anti-horário. Nos dois grupos, quanto maior o avanço medido entre a distância entre o ponto B antes e após os tratamentos, menor as dimensões da VAS, ressaltando que clinicamente deve-se considerar um equilíbrio entre a quantidade de avanço e ganho nas medidas da VAS.

V. REFERÊNCIAS
INTRODUÇÃO GERAL

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ANEXOS

ANEXO 1 – REGIMENTO INTERNO PROGRAMA DE PÓS-GRADUAÇÃO EM

UNIVERSIDADE FEDERAL DO CEARÁ
FACULDADE DE FARMÁCIA, ODONTOLOGIA E ENFERMAGEM

CAPÍTULO VI

DOS EXAMES E DA DEFESA DE DISSERTAÇÃO E TESE

Art. 45 - O Exame Geral de Qualificação de que trata o *Artigo 50 das Normas para os Cursos de Pós-Graduação da UFC* deverá ser realizado perante uma comissão julgadora composta de no mínimo 03 (três) membros efetivos e um suplente, tendo o orientador como seu presidente.

§1º - O Exame Geral de Qualificação deverá ser realizado antes da matrícula na atividade acadêmica dissertação ou tese e será composto por duas fases. A primeira constará da defesa do projeto de pesquisa, a qual deverá ser realizada até seis meses após o ingresso no curso (nível Mestrado) ou até 12 meses (nível Doutorado). A segunda fase constará da defesa da pesquisa (uma pré-defesa) e deverá ser realizada até 45 dias antes da defesa da dissertação ou da tese.

§2º - As duas fases do Exame Geral de Qualificação constarão de sessão pública com: (1) aula expositiva com duração de 30 a 40 minutos; (2) arguição pelos membros da banca avaliadora com duração de 20 minutos para cada componente desta, bem como 20 minutos destinados às respostas do aluno para cada avaliador.

§3º - As bancas das duas fases do Exame Geral de Qualificação serão compostas por 2 (dois) avaliadores e pelo orientador.

§4º - No caso de não cumprimento do prazo estipulado no §1º, o orientador deverá encaminhar à coordenação do PPGO, antes de seu vencimento e ouvido o aluno, solicitação de ampliação do prazo, mediante justificativa e descrição da etapa de desenvolvimento do projeto.

§5º - O aluno que não obtiver aprovação no Exame Geral de Qualificação terá direito à nova oportunidade, com data a ser definida pela Coordenação do PPGO.

§6º - O aluno só poderá defender a dissertação ou tese após aprovação no Exame Geral de Qualificação de que trata este artigo.

Art. 46 – As dissertações e as teses apresentadas ao Programa de Pós-Graduação em Odontologia da Universidade Federal do Ceará poderão ser produzidas em formato alternativo ou tradicional. O formato alternativo estabelece: a critério do orientador e com a aprovação da Coordenação do Programa, que os capítulos poderão conter cópias de artigos e/ou relatórios de patentes de autoria ou coautoria do candidato, publicados ou submetidos para publicação em revistas científicas, escritos no idioma exigido pelo veículo de divulgação.

§1º - O orientador e o candidato deverão verificar junto às editoras a possibilidade de inclusão dos artigos na dissertação ou tese, em atendimento à legislação que rege o direito autoral, obtendo, se necessária, a competente autorização, deverão assinar declaração de que não estão infringindo o direito autoral transferido à editora.

§2º - A dissertação e a tese em formatos tradicionais ou formatos alternativos deverão seguir as normas preconizadas pelo Guia para Normalização de Trabalhos Acadêmicos da Biblioteca Universitária disponível no sítio http://www.biblioteca.ufc.br. As partes específicas do formato alternativo deverão ser feitas em concordância com o *Manual de Normalização para Defesa de dissertação de Mestrado e tese de Doutorado no formato Alternativo do PPGO,* disponível no sítio http://www.ppgo.ufc.br.

§3º - As dissertações defendidas no formato alternativo deverão constar de, no mínimo, 01(um) capítulo, enquanto que as teses no mesmo formato deverão constar de, no mínimo, 02 (dois) capítulos.

§4º - Admite-se que a dissertação ou a tese sejam escritas e/ou defendidas em língua estrangeira seguindo as diretrizes definidas no regimento interno do Programa;

ANEXO 2 – DECLARAÇÃO DE AUTORIZAÇÃO DE DIREITO AUTORAL

DECLARAÇÃO

As cópias de artigos de minha autoria, já publicados ou submetidos para publicação em revistas científicas sujeitas a arbitragem, que constam da minha Dissertação de Doutorado, intitulada: "AVALIAÇÃO TRIDIMENSIONAL DA VIA AREA SUPERIOR EM PATIENTES COM APNEIA OBSTRUTIVA DO SONO: REVISÃO SISTEMÁTICA, ESTUDO DA INFLUÊNCIA CRANIOFACIAL, EFEITO DO APARELHO DE AVANÇO MANDIBULAR E CIRURGIA ORTOGNÁTICA BIMAXILAR", não infringem os dispositivos da Lei n.° 9.610/98, nem o direito autoral de qualquer editora.

Fortaleza, 30 de abril de 2021.

*

Marcela Lima Gurgel
Autor RG n.° *

*

Fábio Wildson Gurgel Costa
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*A versão original e assinada pelos autores está à disposição para consulta de sua veracidade com a autora MLG através do e-mail marcela.gurgel@yahoo.com.br

ANEXO 3 – PARECER CONSUBSTANCIADO DO COMITÊ DE ÉTICA EM PESQUISA DA UNIVERSIDADE FEDERAL DE SÃO PAULO

UNIFESP
UNIVERSIDADE FEDERAL DE SÃO PAULO
1933

Universidade Federal de São Paulo
Escola Paulista de Medicina

Comitê de Ética em Pesquisa
Hospital São Paulo

São Paulo, 30 de Abril de 2010.
CEP 0301/10

Ilmo(a). Sr(a).
Pesquisador(a) LIA RITA AZEREDO BITTENCOURT
Co-Investigadores: Paulo Afonso Cunati, Lia Rita Azeredo Bittencourt (orientadora)
Disciplina/Departamento: Medicina e Biologia do Sono da Universidade Federal de São Paulo/Hospital São Paulo
Patrocinador: AFIP.

PARECER DO COMITÊ DE ÉTICA INSTITUCIONAL

Ref: Projeto de pesquisa intitulado: **"Avaliação da eficácia e complicações do avanço rápido do aparelho intra-oral no tratamento da apnéia obstrutiva do sono".**

CARACTERÍSTICA PRINCIPAL DO ESTUDO: Intervenção terapêutica.
RISCOS ADICIONAIS PARA O PACIENTE: Risco mínimo, desconforto mínimo, sem procedimento invasivo.
OBJETIVOS: Avaliar a eficácia e complicações do avanço rápido do aparelho intra-oral no tratamento da apnéia obstrutiva do sono. Comparar o avanço rápido com o avanço lento do aparelho intra-oral no tratamento da Apnéia Obstrutiva do Sono. Avaliar a contribuição dos exercícios mandibulares na adesão de pacientes com apnéia do sono, submetidos ao avanço rápido e ao avanço lento do aparelho intra-oral..
RESUMO: Participarão do estudo pacientes com idade entre 19-65 anos, portadores de síndrome da apnéia obstrutiva do sono (SAOS) leve/moderada, provenientes do ambulatório de distúrbios respiratórios do sono do Departamento de Psicobiologia da UNIFESP, encaminhados para o uso do aparelho intra-oral (AIO). O diagnóstico de SAOS será confirmado pela aplicação de um questionário, da Escala de sonolência de Epworth e da polissonografia de uma noite inteira. Serão incluídos os pacientes cujos índices de apnéia e de hipopnéia estão acima de cinco e abaixo de 30 (SAOS leve a moderada). Serão constituídos 4 grupos: G1- grupo de avanço lento- receberá o AIO montado em 50% da protrusão máxima e seguirá o protocolo de avanço mandibular de 0,5 mm a cada semana, até atingir a posição de Ptmax; o grupo 2- grupo de avanço lento com exercícios mandibulares receberá o AIO montado em 50% da protrusão máxima e exercícios mandibulares; o grupo 3- grupo de avanço rápido- receberá o AIO montado em 50% da protrusão máxima e seguirá o protocolo de avanço rápido (0,25 mm/dia) até atingir a posição de Ptmax; o grupo 4- grupo de avanço rápido com exercícios mandibulares e seguirá o protocolo de avanço rápido. Os 4 grupos receberão instruções de como usar corretamente o AIO, de como preencher os diários do sono sobre o uso do AIO e instruções para a execução dos exercícios mandibulares para os dois grupos que deles farão uso. Os pacientes serão submetidos a um protocolo de avaliações constituídas por exame de PSG, questionário para avaliação da SAOS, questionário da Escala de Sonolência de Epworth, questionário de avaliação da qualidade de vida SF-36 e RDC/DTM. Os pacientes dos grupos 1 e 2 (avanço lento) sofrerão avaliações clínicas semanais até que a posição de protrusiva máxima seja alcançada. Os pacientes dos gurpos de avanço rápido (G3 e G4) serão avaliados clinicamente, a cada 72 horas, e por questionário/entrevista diariamente..

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FUNDAMENTOS E RACIONAL: Até o presente momento a literatura não discute qual o máximo de avanço progressivo possível dos AIOs, em curto período de tempo, no tratamento da SAOS, sem que ocorram efeitos colaterais. O desencadeamento de uma DTM durante o tratamento com AIO é um efeito colateral importante, que poderia ser mais facilmente desencadeado pelo avanço rápido do aparelho intra-oral..

MATERIAL E MÉTODO: Estão descritos os procedimentos do estudo, apresentando os instrumentos utilizados na coleta de dados.

TCLE: Apresentado adequadamente, de acordo com a Res CNS 196/96.

DETALHAMENTO FINANCEIRO: AFIP - R$ 72252,00.

CRONOGRAMA: 12 meses.

OBJETIVO ACADÊMICO: Pós-Doutorado.

ENTREGA DE RELATÓRIOS PARCIAIS AO CEP PREVISTOS PARA: **25/4/2011** e **24/4/2012**.

O Comitê de Ética em Pesquisa da Universidade Federal de São Paulo/Hospital São Paulo **ANALISOU** e **APROVOU** o projeto de pesquisa referenciado.

1. Comunicar toda e qualquer alteração do projeto e termo de consentimento livre e esclarecido. Nestas circunstâncias a inclusão de pacientes deve ser temporariamente interrompida até a resposta do Comitê, após análise das mudanças propostas.
2. Comunicar imediatamente ao Comitê qualquer evento adverso ocorrido durante o desenvolvimento do estudo.
3. Os dados individuais de todas as etapas da pesquisa devem ser mantidos em local seguro por 5 anos para possível auditoria dos órgãos competentes.

Atenciosamente,

*

Prof. Dr. José Osmar Medina Pestana
Coordenador do Comitê de Ética em Pesquisa da
Universidade Federal de São Paulo/ Hospital São Paulo

0301/10

*A versão original e assinada pelos autores está à disposição para consulta de sua veracidade com a autora MLG através do e-mail marcela.gurgel@yahoo.com.br

Rua Botucatu, 572 - 1º andar – conj. 14 - CEP 04023-062 - São Paulo / Brasil
Tel.: (011) 5571-1062 - 5539.7162

São Paulo, 18 de Agosto de 2010.
CEP 0301/10
CONEP

Ilmo(a). Sr(a).
Pesquisador(a) LIA RITA AZEREDO BITTENCOURT
Disciplina/Departamento: Medicina e Biologia do Sono da
Universidade Federal de São Paulo/Hospital São Paulo

Ref: Projeto de pesquisa intitulado: **"Avaliação da eficácia e complicações do avanço rápido do aparelho intra-oral no tratamento da apnéia obstrutiva do sono".**

Prezado(a) Pesquisador(a).

O Comitê de Ética em Pesquisa da Universidade Federal de São Paulo/Hospital São Paulo **ANALISOU** e **APROVOU** **Adendo 1 (versão de 10/Ago/2010; avaliar as codições bioquímicas gerais e anatômicas da via aérea superior, antes e após o avanço rápido do aparelho intra-oral no tratamento da apnéia obstrutiva do sono)** do projeto de pesquisa acima referenciado.

Atenciosamente,

*

Prof. Dr. José Osmar Medina Pestana
Coordenador do Comitê de Ética em Pesquisa da
Universidade Federal de São Paulo/ Hospital São Paulo

*A versão original e assinada pelos autores está à disposição para consulta de sua veracidade com a autora MLG através do e-mail marcela.gurgel@yahoo.com.br

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ANEXO 4 – PARECER CONSUBSTANCIADO DO COMITÊ DE ÉTICA EM PESQUISA DA UNIVERSIDADE ESTADUAL DE SÃO PAULO- FACULDADE DE ODONTOLOGIA – CAMPU ARARAQUERA

UNESP - FACULDADE DE ODONTOLOGIA - CAMPUS ARARAQUARA

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Preditores de mudanças tridimensionais do espaço aéreo faringiano em pacientes hiperdivergentes submetidos a osteotomias maxilomandibulares.

Pesquisador: João Roberto Gonçalves

Área Temática:

Versão: 2

CAAE: 20655119.0.0000.5416

Instituição Proponente: Faculdade de Odontologia de Araraquara - UNESP

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.717.097

Apresentação do Projeto:

O crescimento craniofacial vertical severo em adultos necessita do reposicionamento superior da maxila associado ao avanço mandibular e rotação anti-horária do plano oclusal para reestabelecer a função e a estética. Ainda são escassos os estudos que avaliam as alterações tridimensionais da via aérea faringiana após ampla rotação do complexo maxilomandibular.

O objetivo desse estudo será identificar se as mudanças promovidas por essa conduta cirúrgica resultam em alterações significativas no espaço aéreo faringiano. Será realizado um estudo retrospectivo longitudinal, utilizando TCFC de 70 indivíduos submetidos a cirurgia ortognática de avanço mandibular e rotação antihorária do plano oclusal em dois tempos distintos (T1-pré cirúrgico e T2-pós cirúrgico de acompanhamento).

O Software Dolphin Imaging® será utilizado para avaliar as dimensões das vias aéreas superiores, incluindo volume, área, mínima área axial e cálculo da relação LAT/AP. Será realizado testes t de Student para comparação entre as médias de T2 e T1 e Correlação de Pearson entre as mudanças volumétricas (T2-T1) das vias aéreas e dos valores cefalométricos (T2-T1). Serão identificados preditores das mudanças volumétricas por meio de modelo de regressão linear múltipla.

Objetivo da Pesquisa:

Avaliar as alterações tridimensionais do espaço aéreo faringiano após avanço bimaxilar com

diferentes amplitudes de rotação anti-horária do plano oclusal em pacientes hiperdivergentes.

Avaliação dos Riscos e Benefícios:

Riscos: Por se tratar de um estudo observacional retrospectivo, o único risco pertinente ao projeto seria a identificação do paciente. Desse modo, toda a equipe executora se compromete com anonimato dos indivíduos participantes. Um código numérico será atribuído a cada indivíduo participante previamente à analise, a fim de conservar sua identidade.

Benefícios: O presente estudo contribuirá com a literatura para melhor compreensão da relevância de diferentes amplitudes de rotações anti-horárias do plano oclusal no aumento do espaço aéreo faringiano, visando planejamentos cirúrgicos que incluam a menor e mais efetiva rotação anti-horária do plano oclusal.

Comentários e Considerações sobre a Pesquisa:

O projeto de pesquisa apresenta grande relevância para o planejamento das cirurgias ortognáticas.

Considerações sobre os Termos de apresentação obrigatória:

Os termos obrigatórios foram apresentados.

Conclusões ou Pendências e Lista de Inadequações:

Não existem pendências.

Considerações Finais a critério do CEP:

Protocolo APROVADO em reunião de 21 de novembro de 2019.

O pesquisador deverá encaminhar relatórios parciais a cada 01 (um) ano até o prazo final da pesquisa, quando deverá encaminhar o relatório final.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1379180.pdf	03/10/2019 15:22:48		Aceito
Outros	RESPOSTAS_PENDENCIAS_CEP.pdf	03/10/2019 15:21:24	KARINA TOSTES BORSATO	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_CEP_1.pdf	03/10/2019 15:20:26	KARINA TOSTES BORSATO	Aceito

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Continuação do Parecer: 3.717.097

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Orçamento	orcamento.pdf	08/08/2019 15:00:55	KARINA TOSTES BORSATO	Aceito
Declaração de Pesquisadores	Equipe_executora.pdf	02/08/2019 14:10:03	KARINA TOSTES BORSATO	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Dispensa_de_TCLE.pdf	02/08/2019 14:09:36	KARINA TOSTES BORSATO	Aceito
Folha de Rosto	Folha_de_rosto.pdf	02/08/2019 14:08:49	KARINA TOSTES BORSATO	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

ARARAQUARA, 21 de Novembro de 2019

Assinado por:
Andréa Gonçalves
(Coordenador(a))

ANEXO 5 - NORMAS DE SUBMISSÃO DE ARTIGO CIENTÍFICO À *ORAL SURGERY, ORAL MEDICINE, ORAL PATHOLOGY AND ORAL RADIOLOGY*

ELSEVIER

ORAL SURGERY, ORAL MEDICINE, ORAL PATHOLOGY AND ORAL RADIOLOGY

The Official Publication for the American College of Oral and Maxillofacial Surgery, American Academy of Oral and Maxillofacial Radiology, American Academy of Oral Medicine, and the American Academy of Oral and Maxillofacial Pathology

AUTHOR INFORMATION PACK

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ISSN: 2212-4403

DESCRIPTION

Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology is required reading for anyone in the fields of oral surgery, oral medicine, oral pathology, oral radiology or advanced general practice dentistry. It is the only major dental journal that provides a practical and complete overview of the medical and surgical techniques of dental practice in four areas. Topics covered include such current issues as dental implants, treatment of HIV-infected patients, and evaluation and treatment of TMJ disorders. The official publication for nine societies, the *Journal* is recommended for initial purchase in the Brandon Hill study, Selected List of Books and Journals for the Small Medical Library.

The *Journal* is ranked 43rd of 90 journals by impact factor in the Dentistry, Oral Surgery and Medicine category on the 2017 Journal Citation Reports®, published by Thomson Reuters.

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The *Oral and Maxillofacial Surgery Section* aims to publish an extensive range of original articles that advances patient care through enhanced understanding of diagnosis, surgical and adjunctive treatment of diseases, and injuries and defects involving both the functional and esthetic aspects of the hard and soft tissues of the oral and maxillofacial regions. The section also seeks research regarding both the basic science of and management of persons with oral and maxillofacial conditions. Articles presenting ethical, original, well-documented, and reproducible research are given preference.

The *Oral Medicine Section* aims to publish a broad range of original articles that help clinicians understand more thoroughly the pathobiology, etiology, diagnosis, prevention, and management of oral conditions related to underlying medical conditions, including diseases of the head, neck, and oral mucosal structures, orofacial pain conditions, salivary gland disorders, and taste disorders. The section also seeks research regarding the dental management of persons with medical problems and/or complicated medical conditions. The published findings must contribute substantively to the body of oral medicine literature and should lead to improved clinical decision-making and enhanced care of medically-related disorders or conditions affecting the oral and maxillofacial region. Articles presenting original, well-documented, and reproducible research are preferred.

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3. Clinicopathologic Conference (CPC). Manuscripts that document interesting, challenging, or unusual cases that present unexpected or interesting diagnostic challenges. The presentation should simulate clinical work-up, including the formulation of a detailed and well thought out differential diagnosis. The complete diagnostic evaluation, management, and follow-up must be included. CPC articles must be organized into six parts: (1) Title: Provide a descriptive clinical title that does not reveal the final diagnosis. (2) Clinical presentation: Describe the clinical and imaging characteristics of the lesion. Use clinical photographs and radiographs as appropriate. (3) Differential diagnosis: List and discuss lesions to be considered as reasonable diagnostic possibilities. The authors are reminded that the most important part of the CPC manuscript is the clinical differential diagnosis, where the authors guide the readership through their own diagnostic thought process. This will require the formulation of a list of the most probable diagnostic possibilities (ideally at least 5-6 entities) based on the clinical presentation, medical history, and/or radiographic studies. (4) Diagnosis: Histopathologic findings illustrated with appropriate photomicrographs. (5) Management: Describe the treatment of the patient and response to treatment. (6) Discussion: Concentrate on the most interesting aspect(s) of the case. No abstract is needed for CPC manuscripts. Limit the number of references to no more than 25.

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BEFORE YOU BEGIN

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Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

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Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

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  Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) The rise of modern genomics, 3rd edn. Wiley, New York, pp 230-257

- Online document

  Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1. Accessed 26 June 2007

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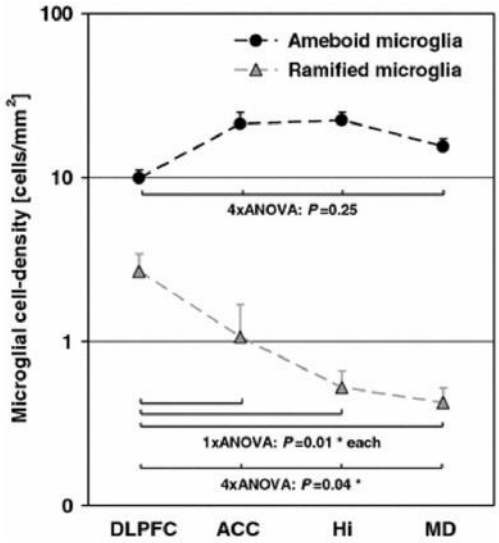

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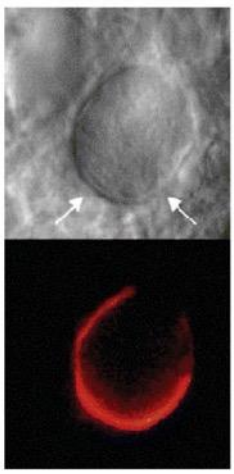

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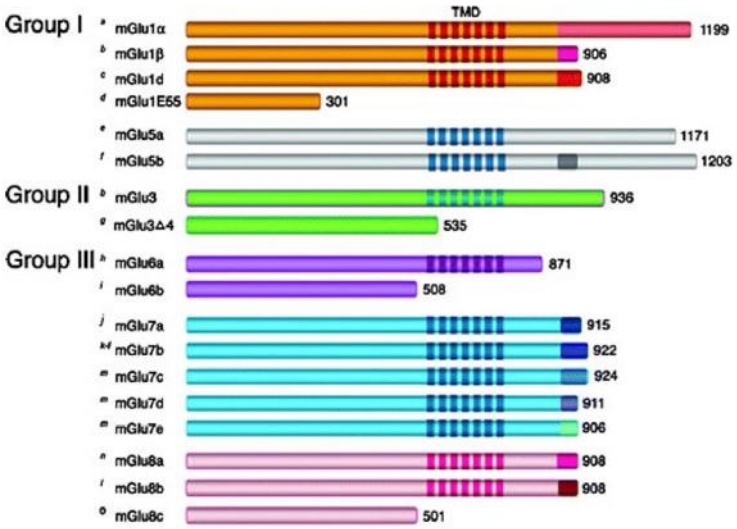

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Compliance with Ethical Standards

To ensure objectivity and transparency in research and to ensure that accepted principles of ethical and professional conduct have been followed, authors should include information regarding sources of funding, potential conflicts of interest (financial or non-financial), informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals.

Authors should include the following statements (if applicable) in a separate section entitled "Compliance with Ethical Standards" when submitting a paper:

- Disclosure of potential conflicts of interest
- Research involving Human Participants and/or Animals
- Informed consent

Please note that standards could vary slightly per journal dependent on their peer review policies (i.e. single or double blind peer review) as well as per journal subject discipline. Before submitting your article check the instructions following this section carefully.

The corresponding author should be prepared to collect documentation of compliance with ethical standards and send if requested during peer review or after publication.

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The corresponding author collects the conflict of interest disclosure forms from all authors. In author collaborations where formal agreements for representation allow it, it is sufficient for the corresponding author to sign the disclosure form on behalf of all authors. Examples of forms can be found

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The corresponding author will include a summary statement in the text of the manuscript in a separate section before the reference list, that reflects what is recorded in the potential conflict of interest disclosure form(s).

Please make sure to submit all Conflict of Interest disclosure forms together with the manuscript.

See below examples of disclosures:

Funding: This study was funded by X (grant number X).

Conflict of Interest: Author A has received research grants from Company A. Author B has received a speaker honorarium from Company X and owns stock in Company Y. Author C is a member of committee Z.

If no conflict exists, the authors should state:

Conflict of Interest: The authors declare that they have no conflict of interest.

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Research involving human participants, their data or biological material

Ethics approval

When reporting a study that involved human participants, their data or biological material, authors should include a statement that confirms that the study was approved (or granted exemption) by the appropriate institutional and/or

national research ethics committee (including the name of the ethics committee) and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. If doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards, the authors must explain the reasons for their approach, and demonstrate that an independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study. If a study was granted exemption from requiring ethics approval, this should also be detailed in the manuscript (including the reasons for the exemption).

Retrospective ethics approval

If a study has not been granted ethics committee approval prior to commencing, retrospective ethics approval usually cannot be obtained and it may not be possible to consider the manuscript for peer review. The decision on whether to proceed to peer review in such cases is at the Editor's discretion.

Ethics approval for retrospective studies

Although retrospective studies are conducted on already available data or biological material (for which formal consent may not be needed or is difficult to obtain) ethics approval may be required dependent on the law and the national ethical guidelines of a country. Authors should check with their institution to make sure they are complying with the specific requirements of their country.

Ethics approval for case studies

Case reports require ethics approval. Most institutions will have specific policies on this subject. Authors should check with their institution to make sure they are complying with the specific requirements of their institution and seek ethics approval where needed. Authors should be aware to secure informed consent from the individual (or parent or guardian if the participant is a minor or incapable) See also section on **Informed Consent**.

Cell lines

If human cells are used, authors must declare in the manuscript: what cell lines were used by describing the source of the cell line, including when and from where it was obtained, whether the cell line has recently been authenticated and by what method. If cells were bought from a life science company the following need to be given in the manuscript: name of company (that provided the cells), cell type, number of cell line, and batch of cells.

It is recommended that authors check the NCBI database for misidentification and contamination of human cell lines. This step will alert authors to possible problems with the cell line and may save considerable time and effort.

Further information is available from the International Cell Line Authentication Committee (ICLAC).

Authors should include a statement that confirms that an institutional or independent ethics committee (including the name of the ethics committee) approved the study and that informed consent was obtained from the donor or next of kin.

Research Resource Identifiers (RRID)

Research Resource Identifiers (RRID) are persistent unique identifiers (effectively similar to a DOI) for research resources. This journal encourages authors to adopt RRIDs when reporting key biological resources (antibodies, cell lines, model organisms and tools) in their manuscripts.

Examples:

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Plasmid: mRuby3 plasmid **RRID:Addgene_104005**

Software: ImageJ Version 1.2.4 **RRID:SCR_003070**

RRIDs are provided by the Resource Identification Portal. Many commonly used research resources already have designated RRIDs. The portal also provides authors links so that they can quickly register a new resource and obtain an RRID.

Clinical Trial Registration

The World Health Organization (WHO) definition of a clinical trial is "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes". The WHO defines health interventions as “A health intervention is an act performed for, with or on behalf of a person or population whose purpose is to assess, improve, maintain, promote or modify health, functioning or health conditions” and a health-related outcome is generally defined as a change in the health of a person or population as a result of an intervention.

To ensure the integrity of the reporting of patient-centered trials, authors must register prospective clinical trials (phase II to IV trials) in suitable publicly available repositories. For example www.clinicaltrials.gov or any of the primary registries that participate in the WHO International Clinical Trials Registry Platform.

The trial registration number (TRN) and date of registration should be included as the last line of the manuscript abstract.

For clinical trials that have not been registered prospectively, authors are encouraged to register retrospectively to ensure the complete publication of all results. The trial registration number (TRN), date of registration and the words 'retrospectively registered' should be included as the last line of the manuscript abstract.

Standards of reporting

Springer Nature advocates complete and transparent reporting of biomedical and biological research and research with biological applications. Authors are recommended to adhere to the minimum reporting guidelines hosted by the EQUATOR Network when preparing their manuscript.

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Checklists are available for a number of study designs, including:

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Systematic reviews and meta-analyses (PRISMA) and protocols (Prisma-P)

Diagnostic/prognostic studies (STARD) and (TRIPOD)

Case reports (CARE)

Clinical practice guidelines (AGREE) and (RIGHT)

Qualitative research (SRQR) and (COREQ)

Animal pre-clinical studies (ARRIVE)

Quality improvement studies (SQUIRE)

Economic evaluations (CHEERS)

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Ethics approval'.

Examples of statements to be used when ethics approval has been obtained:

• All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of A (No. ...).

• This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date.../No. ...).

• Approval was obtained from the ethics committee of University C. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

• The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the University of D (Ethics approval number: ...).

Examples of statements to be used for a retrospective study:

• Ethical approval was waived by the local Ethics Committee of University A in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

• This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of XYZ who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the IRB of XYZ.

• This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University B approved this study.

Examples of statements to be used when no ethical approval is required/exemption granted:

• This is an observational study. The XYZ Research Ethics Committee has confirmed that no ethical approval is required.

• The data reproduced from Article X utilized human tissue that was procured via our Biobank AB, which provides de-identified samples. This study was reviewed and deemed exempt by our XYZ Institutional Review Board. The BioBank protocols are in accordance with the ethical standards of our institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

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Informed consent

All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to what they have said during a study or an interview, as well as to any photograph that was taken. This is especially true concerning images of vulnerable people (e.g. minors, patients, refugees, etc) or the use of images in sensitive contexts. In many instances authors will need to secure written consent before including images.

Identifying details (names, dates of birth, identity numbers, biometrical characteristics (such as facial features, fingerprint, writing style, voice pattern, DNA or other distinguishing characteristic) and other information) of the participants that were studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scholarly purposes and the participant (or parent/guardian if the participant is a minor or incapable or legal representative) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases. Detailed descriptions of individual participants, whether of their whole bodies or of body sections, may lead to disclosure of their identity. Under certain circumstances consent is not required as long as information is anonymized and the submission does not include images that may identify the person.

Informed consent for publication should be obtained if there is any doubt. For example, masking the eye region in photographs of participants is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic profiles, authors should provide assurance that alterations do not distort meaning.

Exceptions where it is not necessary to obtain consent:

• Images such as x rays, laparoscopic images, ultrasound images, brain scans, pathology slides unless there is a concern about identifying information in which case, authors should ensure that consent is obtained.

• Reuse of images: If images are being reused from prior publications, the Publisher will assume that the prior publication obtained the relevant information regarding consent. Authors should provide the appropriate attribution for republished images.

Consent and already available data and/or biologic material

Regardless of whether material is collected from living or dead patients, they (family or guardian if the deceased has not made a pre-mortem decision) must have given prior written consent. The aspect of confidentiality as well as any wishes from the deceased should be respected.

Data protection, confidentiality and privacy

When biological material is donated for or data is generated as part of a research project authors should ensure, as part of the informed consent procedure, that the participants are made aware what kind of (personal) data will be processed, how it will be used and for what purpose. In case of data acquired via a biobank/biorepository, it is possible they apply a broad consent which allows research participants to consent to a broad range of uses of their data and samples which is regarded by research ethics committees as specific enough to be considered “informed”. However, authors should always check the specific biobank/biorepository policies or any other type of data provider policies (in case of non-bio research) to be sure that this is the case.

Consent to Participate

For all research involving human subjects, freely-given, informed consent to participate in the study must be obtained from participants (or their parent or legal guardian in the case of children under 16) and a statement to this effect should appear in the manuscript. In the case of articles describing human transplantation studies, authors

must include a statement declaring that no organs/tissues were obtained from prisoners and must also name the institution(s)/clinic(s)/department(s) via which organs/tissues were obtained. For manuscripts reporting studies involving vulnerable groups where there is the potential for coercion or where consent may not have been fully informed, extra care will be taken by the editor and may be referred to the Springer Nature Research Integrity Group.

Consent to Publish

Individuals may consent to participate in a study, but object to having their data published in a journal article. Authors should make sure to also seek consent from individuals to publish their data prior to submitting their paper to a journal. This is in particular applicable to case studies. A consent to publish form can be found

here. (Download docx, 36 kB)

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Consent to participate' and/or 'Consent to publish'. Other declarations include Funding, Conflicts of interest/competing interests, Ethics approval, Consent, Data and/or Code availability and Authors' contribution statements.

Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

Sample statements for **"Consent to participate"**:

Informed consent was obtained from all individual participants included in the study.

Informed consent was obtained from legal guardians.

Written informed consent was obtained from the parents.

Verbal informed consent was obtained prior to the interview.

Sample statements for **"Consent to publish"**:

The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 1a, 1b and 1c.

The participant has consented to the submission of the case report to the journal.

Patients signed informed consent regarding publishing their data and photographs.

Sample statements if identifying information about participants is available in the article:

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

Images will be removed from publication if authors have not obtained informed consent or the paper may be removed and replaced with a notice explaining the reason for removal.

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List of Repositories

Research Data Policy

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Datasets that are assigned digital object identifiers (DOIs) by a data repository may be cited in the reference list. Data citations should include the minimum information recommended by DataCite: authors, title, publisher (repository name), identifier.

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