Review Article

Cephalometric predictors of treatment outcome with mandibular advancement devices in adult patients with obstructive sleep apnea: a systematic review

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Objective: The efficacy of mandibular advancement devices (MADs) in the treatment of obstructive sleep apnea (OSA) ranges between 42% and 65%. However, it is still unclear which predictive factors can be used to select suitable patients for MAD treatment. This study aimed to systematically review the literature on the predictive value of cephalometric analysis for MAD treatment outcomes in adult OSA patients. **Methods:** The MEDLINE, Google Scholar, Scopus, and Cochrane Library databases were searched through December 2014. Reference lists from the retrieved publications were also examined. English language studies published in international peer-reviewed journals concerning the predictive value of cephalometric analysis for MAD treatment outcome were considered for inclusion. Two review authors independently assessed eligibility, extracted data, and ascertained the quality of the studies. **Results:** Fifteen eligible studies were identified. Most of the skeletal, dental, and soft tissue cephalometric measurements examined were widely recognized as not prognostic for MAD treatment outcome; however, controversial and limited data were found on the predictive role of certain cephalometric measurements including cranial base angle, mandibular plane angle, hyoid to mandibular plane distance, posterior nasal spine to soft-palate tip distance, anterior nasal spine to epiglottis base distance, and tongue/oral cross sectional area ratio thus justifying additional studies on these parameters. **Conclusions:** Currently available evidence is inadequate for identification of cephalometric parameters capable of reliably discriminating between poor and good responders to MAD treatment. To guide further research, methodological weaknesses of the currently available studies were highlighted and possible reasons for their discordant results were analyzed.
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INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of complete or partial closure of the upper airway during sleep that lead to sleep fragmentation and oxygen desaturation.[1] This sleep-related breathing disorder is associated with daytime sleepiness, impaired quality of life, poor work performance, neurocognitive decline, increased risk of motor vehicle accidents and, in the long term, an increased risk of cardio-vascular disease and mortality.[2] Nasal continuous positive airway pressure (nCPAP) maintains a positive pressure in the upper airway through a nose mask worn during sleep and is currently the most effective treatment option for OSA patients.[3] Nevertheless, adherence to this therapy is low, with rates between 60% and 80%. The availability of alternative treatment options is therefore of the utmost importance.[4] Mandibular advancement devices (MADs), which hold the mandible forward with the aim of preventing collapse of the upper airway during sleep provide a less invasive, more comfortable, and less costly treatment alternative for patients with mild to moderate OSA who do not tolerate, do not respond to, or are not appropriate candidates for treatment with nCPAP, or those who fail behavioral measures such as weight loss or sleep position change. MADs can also be used in patients with severe OSA who fail treatment attempts with nCPAP or who are not appropriate candidates for upper airway surgery.[5,6]

Patients undergo a repeat sleep study with MAD *in situ* to determine its effectiveness, which usually ranges between 42% and 65%.[7] Clinical prediction of MAD treatment outcome would allow advanced selection of suitable candidates for this treatment before manufacturing the device, thus avoiding inappropriate delays in therapy and waste of resources. Accordingly, this topic has been defined by the American Academy of Sleep Medicine as an important area for future research.[5,6]

Previous studies have suggested that lateral cephalometry can identify craniofacial characteristics that could have an impact on treatment response.[5,8-10] Cephalometry is a low-cost, simple, and widely available radiographic technique, and it is therefore suitable as a screening procedure. Nevertheless, the clinical utility of cephalometric measurements in the prediction of MAD treatment outcomes in OSA remains controversial. A recently published review by Saffer et al.[11] found no clear predictors of MAD treatment success. However, cephalometric and anatomical factors were not investigated because no randomized controlled trials addressing this issue were included in the review. The aim of this study was to fill this gap by conducting a systematic review of published studies examining the ability of cephalometric parameters to predict MAD treatment response in adult patients with OSA.

MATERIALS AND METHODS

Search strategy

An electronic literature search was carried out on the following databases: MEDLINE, Google Scholar, Scopus, and the Cochrane Library. To identify the relevant studies the following search terms were used: "obstructive sleep" AND (apnea OR apnoea) AND (predict* OR outcome OR effect OR efficacy) AND ("oral appliance" OR "mandibular advancement device" OR "mandibular repositioning appliance") AND (craniofacial OR skeletal OR cephalometr*). The reference lists of all relevant publications were checked for additional studies. Searches were updated to December 2014.

Screening and study selection

In the first phase of selection, duplicates were removed and irrelevant articles were excluded by reviewing the titles and abstracts from the search results. In the next phase, the full texts of potentially relevant papers were evaluated to determine if they met the eligibility criteria. The inclusion criteria were:

- Type of study: Randomized or non-randomized controlled trials, cohort or case-control studies (with a minimum sample size of 10 patients in each group) addressing the research question of the predictive value of cephalometric analysis in oral appliance treatment outcomes in adult OSA patients. Studies had to be published in English in an international peer-reviewed literature
- Population: Male or female adult patients (≥ 18 years old) with a polysomnographic diagnosis of OSA (i.e., 5 or more respiratory events [apneas or hypopneas] per hour of sleep)
- Intervention: Treatment with any MAD for OSA

The exclusion criteria were:

- Lack of a clear description of inclusion/exclusion criteria
- Previous and/or current surgical or pharmacological interventions
- Limitation to severe OSA patients

Two reviewers (DRI, SIP) independently screened paper titles and abstracts, with access to full texts where necessary to select studies into the review. Disagreements were resolved by discussion. Where resolution was not possible, a third reviewer (GAB) was consulted. The selected studies underwent data extraction and quality assessment.

Data extraction and quality assessment of selected studies

Two review authors (DRI, SIP) independently performed

the data extraction. Extracted data included: first author, year of publication, study design, sample size, patient demographic and clinical characteristics, MAD type, degree of protrusion and vertical opening, time interval between polysomnographic evaluations, outcome (i.e., cephalometric parameters that differed significantly between good and poor responders). Selected studies were assigned to a class of evidence according to the classification of study designs by Jovell and Navarro-Rubio (Table 1).[12]

Data synthesis

A narrative synthesis was carried out. Data were sorted according to MAD type (1-piece or 2-piece appliances). Given the lack of homogeneity in the study settings, a quantitative synthesis seemed inappropriate. Therefore no meta-analysis was performed.

RESULTS

The electronic database search and the review of the relevant publication reference lists yielded 939 potentially relevant titles and abstracts after duplicates were removed from a total of 1,034 records. Following the first phase of evaluation, 907 publications were rejected based on the title and the abstract. One further study was excluded because full text was not obtained by searching paper and digital format sources, nor after attempting to contact the authors by e-mail correspondence.[13] In the second phase, analysis of the full text of the remaining 31 studies led to the exclusion of 16 additional publications. Fifteen studies were therefore selected for the systematic review.[5,8-10,14-24] The relevant data from each study are reported in Table 2. The PRISMA flow diagram (Figure 1) shows the number of articles reviewed in each phase of this systematic review.[25]

Cephalometric variables that were analyzed in the

selected studies are listed in Table 3. The landmarks and reference lines necessary to define these parameters are shown in Figure 2.

Cephalometric skeletal measurements

Cranial base
- 1-piece MAD: Svanholt et al.[24] found that the distance between the sella turcica and the deepest point in the posterior cranial fossa was lower in the group that responded positively to MAD therapy.
- 2-piece MAD: Both cranial base and anterior cranial base lengths were reported to be non-predictive of MAD treatment outcome.[5,8,22] Two studies addressed the predictive value of cranial base angle with contrasting results; one found an increased cranial base angulation to be predictive of MAD treatment success[22] and the other did not.[5]

Sagittal jaw relationship
- 1-piece MAD: Data concerning sagittal jaw relationship were controversial. SNA and ANB were recognized either as predictive of treatment success when decreased[10,24] or as non-predictive[10,14,18] of treatment outcome. SNB was found to be non-predictive[14,18] or predictive of treatment success when increased10 or decreased.[24]
- 2-piece MAD: The majority of papers indicated that sagittal jaw relationship cephalometric parameters were not suitable for predicting treatment outcome (SNA,[5,8,9,19-22] SNB,[5,19-22] ANB,[5,17,20-22] Wits appraisal[20]). However, a decreased SNB value[8,9] or an increased ANB value[8] were occasionally reported as predictive of treatment success.

Vertical craniofacial dimensions
- 1-piece MAD: Vertical craniofacial dimension parameters were usually recognized as non-predictive of

Table 1. Levels of scientific evidence

Level of evidence	Type of study	Strength of evidence
Level 1	Meta-analyses of randomized controlled trials	Good
Level 2	Large-sample randomized controlled trials	
Level 3	Small-sample randomized controlled trials	Good to fair
Level 4	Non-randomized controlled prospective trials	
Level 5	Non-randomized controlled retrospective trials	
Level 6	Cohort studies	Fair
Level 7	Case-control studies	
Level 8	Non-controlled clinical series, descriptive studies	Poor
Level 9	Anecdotes or case reports	

Derived from Jovell and Navarro-Rubio.[12]

Table 2. Summary of the main characteristics of the 15 studies selected for the systematic review

First author, year	Design of the study	Level of evidence*	Subjects, n (% male) [withdrawals]	Age (yr)	BMI (kg/m²)	bAHI (events/h)	Country	Inclusion criteria
Endo, 2003[10]	Prospective case-control study	7	103 (-) [-]	GR: 51.2 PR: 51.1	GR: 24.5 PR: 24.7	GR: 21.1 ± 19.5 PR: 22.3 ± 19.7	Japan	AHI ≥ 10; no previous surgical operations
Hoekema, 2007[8]	Prospective case-control study	7	51 (-) [2]	49.2 ± 9.5	32.2 ± 6.1	38.0 ± 29.8	Netherlands	Age > 20 years; AHI ≥ 15 or AHI ≥ 5+symptoms
Kim, 2014[14]	Retrospective case-control study	7	86 (88.4) [-]	51.5 ± 9.8	GR:25.98 ± 3.15 PR: 26.17 ± 2.78	GR: 19.79 ± 17.32 PR: 30.08 ± 23.28	South Korea	AHI > 5; no sleep-related medication or previous oropharyngeal surgery
Lee, 2009[15]	Retrospective case-control study	7	50 (92) [-]	50.2 ± 9.8 (21-69)	GR: 25.5 ± 2.5 PR: 26.9 ± 2.6	AI: GR: 37.6 ± 28.4 AI: PR: 34.6 ± 17.4	South Korea	AHI > 5
Lee, 2010[16]	Retrospective case-control study	7	76 (89.5) [-]	51.7 ± 0.3 (21-69)	< 35	38.9 ± 19.7	South Korea	AHI > 5
Liu, 2001[17]	Prospective case-control study	7	47 (89.4) [-]	49.1 (25-80)	29.61 ± 6.49	CR: 44.21 ± 11.57 PaR: 42.46 ± 19.33 NR: 28.69 ± 8.80	USA	Mild to severe OSAS; suitability for MAS treatment
Marklund, 1998[18]	Prospective case-control study	7	32 (100) [-]	Median: 57 (37-72)	Median: 28	Median: 23	Sweden	AHI of at least 15 in the supine and/ or the lateral position
Mehta, 2001[5]	Prospective case-control study	7	28 (67.9) [4]	48 ± 9 (35-73)	29.4 ± 3.1	27 ± 17	Australia	AHI > 10/h; symptoms of OSA ≥ 2; suitability for MAS treatment; no sedatives
Menn, 1996[19]	Prospective case-control study	7	29 (95.7) [6]	53 ± 11 (37-69)	29 ± 5	RDI: 37 ± 23	USA	Age > 18 yrs; RDI ≥ 10; suitability for MAS treatment
Milano, 2013[20]	Prospective case-control study	7	23 (87.0) [-]	54.0 ± 11.1 (20-67)	27.8 ± 4.4	24.5 ± 13.9	Italy	Age > 18 yrs; AHI > 5; at least 2 OSAS symptoms
Mostafiz, 2011[21]	Prospective case-control study	7	53 (79.2) [-]	49.5 ± 11.8	28.7 ± 4.2	CR: 28.4 ± 14.4 PaR: 34.8 ± 15.1 NR: 40.6 ± 12.7	Australia	Age > 18 yrs; AHI > 10/h, suitability for MAStreatment No other sleep or medical disorders
Ng, 2012[22]	Retrospective case-control study	7	72 (76.4) [-]	49.0 ± 11	30.2 ± 5.6	GR: 26.8 ± 14.4 PR: 28.1 ± 19.3	Australia	AHI ≥ 10/h; symptoms of OSA ≥ 2; suitability for MAS treatment
Rose, 2002[23]	Prospective case-control study	7	57 (89.5) [-]	56.5 ± 7.3 (35-73)	26.4 ± 2.0	22.0 ± 12.2	Germany	Mild to moderate OSA; suitability for MAS treatment
Shen, 2012[9]	Prospective case-control study	7	52 (92.3) [-]	43.4 ± 10.3 (18-)	24.8 ± 2.6	GR: 34.1 ± 15.1 PR: 38.6 ± 19.1	Taiwan	Age > 18 yrs; AHI > 10; suitability for MAS treatment
Svanholt, 2014[24]	Prospective case-control study	7	27 (85.2) [-]	GR: 53.66 ± 7.27 PR: 52.02 ± 10.5	GR: 27.13 ± 2.35 PR: 32.16 ± 5.42	GR: 28.46 ± 15.17 PR: 43.52 ± 25.64	Denmark	AHI > 5

Table 2. Continued

First author, year	MAD type (protrusion) [vertical opening]	Follow up	Success criteria	Outcome (responders)
Endo, 2003[10]	Monobloc type MAD (70 % of max protrusion) [2 mm]	Within 3 months	AHI red > 50%	Larger SNB, lower ANB, shorter MP-H, shorter ANS- H, shorter ANS-Eb
Hoekema, 2007[8]	Thornton adjustable positioner type-1 (individual) [-]	2/3 months	AHI < 5/h or (AHI red > 50%) and AHI < 20/h and no symptoms	Higher ANB, smaller SNB, larger OJ, OB and N-ANS
Kim, 2014[14]	Monobloc type MAD (60 % of max protrusion) [minimum]	3 months	AHI red > 50% and AHI < 10/h	Lower PNS-Go
Lee, 2009[15]	Monobloc type MAD (60% of max protrusion) [without open bites]	At least 3 months	AHI red > 50% and AHI < 20/h	No cephalometric predictors of treatment outcome
Lee, 2010[16]	Monobloc type MAD (60% of max protrusion) [without open bites]	At least 3 months	AHI red > 50% and AHI < 20/h	Lower PNS-P
Liu, 2001[17]	MAD (two pieces) (2/3 max protrusion [for a start]) [minimum]	-	GR: AHI red > 75%; MR: AHI red: 25% to 75%; PR: AHI red < 25%	Larger ratio of the vertical airway length to the cross-sectional area of the soft palate
Marklund, 1998[18]	MAD (one piece) (4-6 mm [for a start]) [5 mm between incisors]	Up to 2 months	AHI < 15	Normal (or low) SN-MP and lower ANS-Me
Mehta, 2001[5]	MAD (two pieces) (individual) [3/4 mm]	19.7 ± 8.8 weeks	Resolution of symptoms and AHI < 5/h	Larger RPAS and larger SN-MP
Menn, 1996[19]	MAD (two pieces) (max protrusion - 3 mm) [5-7 mm]	Mean: 104 days	RDI red ≥ 50% and RDI ≤ 20	No cephalometric predictors of treatment outcome
Milano, 2013[20]	Silensor (two pieces) (50/60% for a start) [-]	2-3 months	AHI < 5/h	Lower MP-H and lower SN-MP < 29°
Mostafiz, 2011[21]	SomnoDent (two pieces) (maximum comfortable limit of mandibular protrusion) [-]	6-8 weeks	GR: AHI red > 50%, AHI > 5/h. MR: AHI red > 50%, AHI > 5/h; PR: AHI red < 50%	Greater tongue/oral enclosure CSA ratio
Ng, 2012[22]	SomnoMed (two pieces) (maximum comfortable limit of mandibular advancement) [-]	6 weeks	AHI red ≥ 50% (alone or in addition to AHI < 20/ <10/ < 5/h)	Shorter PNS-P, increased Ba-SN; larger SNMP
Rose, 2002[23]	Karwetzky's modified activator (two pieces) (individual) [individual]	6-12 weeks	Age > 60: AHI < 5/h and AI < 2/h; age < 60: AHI < 10/h and AI < 5/h.	Lower SN-MP; larger SGo:NMe; higher H-MP, lower H-Me
Shen, 2012[9]	IST-Appliance (two pieces) (individual) [-]	6 weeks	AHI red > 50% and AHI < 10/h	Smaller SNB ; shorter N-Me; narrower MinRGA
Svanholt, 2014[24]	Monobloc type MAD (75 % of max protrusion) [-]	4 weeks	AHI red > 75%	Lower SNA, lower SNB, lower SNPg, lower S-D

Values are presented as number only, number (%), or mean ± standard deviation (range).
*According to the classification of study designs by Jovell and Navarro-Rubio.[12]
n, Number; -, not reported; GR, good responders; PR, poor responders; CR, complete responders; PaR, partial responders; NR, nonresponders; BMI, body mass index; AHI, apnea hypopnea index; bAHI, baseline AHI; h, hour; AI, apnea index; RDI, respiratory disturbance index; AHI red, AHI reduction; MAD, mandibular advancement device.
Suitability for MAD treatment, good dental health, > 10 teeth/dental arch, no periodontal disease, TMJ dysfunction or exaggerated gag reflex.
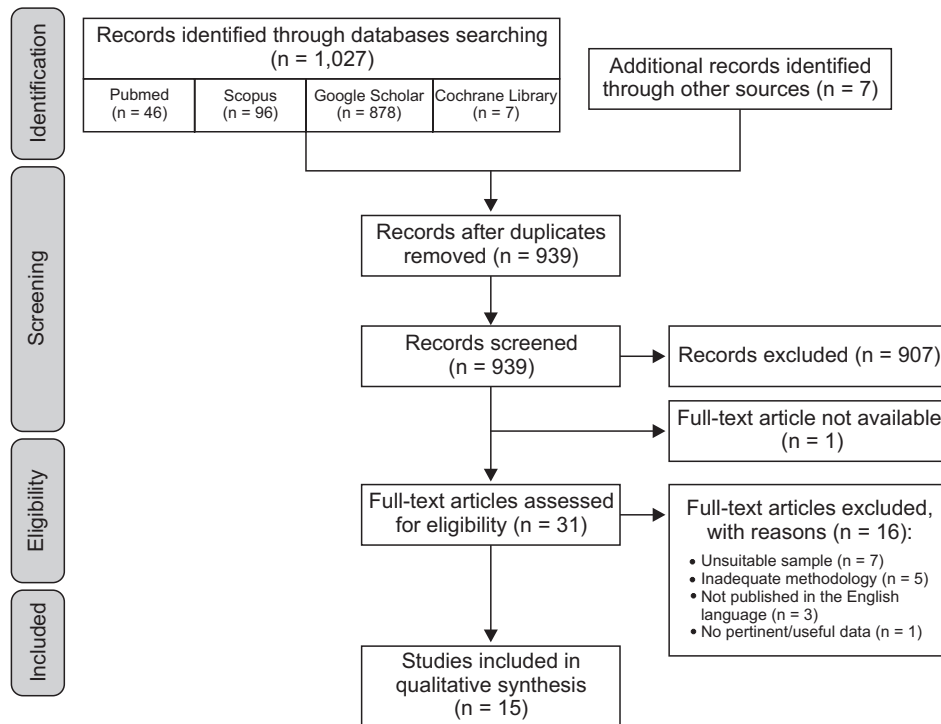See Table 3 for the definition of cephalometric variables.

Figure 1. Flow chart of literature search and study selection.

treatment outcome,[14,24] with the exception of lower anterior face height,[18] lower posterior face height,[14] and mandibular plane angle,[18] which were occasionally identified as predictive of treatment success when decreased.

- 2-piece MAD: Saddle angle, articular angle, gonial angle, palatal plane angle, posterior face height, and the ratio between upper anterior face height and lower anterior face height were not useful for predicting MAD treatment outcomes.[9,20-23] The majority of the papers ascribed a non-predictive role to anterior face height, upper anterior face height, lower anterior face height, and the ratio between posterior face height and anterior face height, but a lower anterior face height value[9] as well as higher values of upper anterior height[8] and of the ratio of posterior face height to anterior face height[23] were also occasionally found in good responders. Data on the predictive role of mandibular plane angle were conflicting: 3 out of 7 studies found it to be non-predictive of treatment outcomes,[8,9,21] 2 studies indicated an increased value as a predictor of treatment success,[5,22] and 2 studies reported a decreased value as a predictor of treatment success.[20,23]

Maxillary and mandibular lengths
- 1-piece MAD: Endo et al.[10] found that maxillary and mandibular lengths were not predictive of MAD

treatment outcome.
- 2-piece MAD: There was general agreement that maxillary and mandibular lengths, ramus height, and corpus length were not suitable for prediction of MAD treatment outcome.[5,17,20-22]

Hard palate
- 1-piece MAD: Hard palate length did not appear to be predictive of MAD treatment outcome.[10,16]
- 2-piece MAD: Ng et al.[22] claimed that hard palate length was not predictive of MAD treatment outcome.

Hyoid bone
- 1-piece MAD: Endo et al.[10] found decreased values of MP-H, H-Me, and ANS-H to be predictive of MAD treatment success, whereas Kim et al.[14] supported a non-predictive role of H-Me and ANS-H.
- 2-piece MAD: There was general agreement that H-RGN, C3ia-H, H-Go, Go-H-Me were not suitable for predicting MAD treatment outcomes.[9,17,20,21] Rose et al.[23] found that decreases in H-Me and ANS-H were predictive of treatment success, while Hoekema et al.[8] did not. Data on MP-H were conflicting. Five out of 7 studies found it to be non-predictive,[5,8,9,19,21] while the two others reported that decreased MP-H[20] and increased MP-H[23] were predictive of treatment success.

Table 3. Summary of cephalometric variables

Variable	Measurement
Cephalometric skeletal measurements	
Cranial base	
Cranial base length (mm)	Ba-S-N
Anterior cranial base length (mm)	S-N
Cranial base angle (°)	BaSN
Distance between sella turcica and the deepest point in posterior cranial fossa (mm)	S-D
Sagittal jaw relationship	
Anteroposterior position of the maxilla (°)	SNA
Anteroposterior position of the mandible (°)	SNB
	SN-Pg
Anteroposterior relationship between maxilla and mandible (°, mm)	ANB
	Wits appraisal (distance between A and B projections onto the occlusal plane)
Vertical craniofacial dimensions	
Anterior face height (mm)	N-Me
Upper anterior face height (mm)	N-ANS
Lower anterior face height (mm)	ANS-Me
Posterior face height (mm)	S-Go
Lower posterior face height (mm)	PNS-Go
Posterior face height : anterior face height (ratio)	S-Go : N-Me
Upper anterior face height : lower anterior face height (ratio)	N-ANS : ANS-Me
Saddle angle (°)	N-S-Ar
Articular angle (°)	S-Ar-Go
Gonial angle (°)	Ar-Go-Me
Mandibular plane angle (°)	SN-MP
	FP-MP
	PP-MP
Palatal plane angle (°)	SN-PP
Maxillary and mandibular lengths	
Maxillary length (mm)	Cd-A
Mandibular length (mm)	Cd-Gn
Ramus height (mm)	Ar-Go
	Cd-Go
Corpus length (mm)	Go-Me
	Go-Gn
Hard palate	
Length (mm)	ANS-PNS
Hyoid bone	
Vertical position (mm)	H-MP or Hy-MP (perpendicular)
	H-Go (vertical measure)

Table 3. Continued

Variable	Measurement
Horizontal anterior position (mm)	H-RGN
	H-ANS (horizontal measure)
	H-Me or Hy-Me
Horizontal posterior position (mm)	H-C3ia
Hyoid angle (°)	Go-H-Me
Cervical vertebrae	
Linear distance between RGN and C3 (mm)	RGN-C3ia
Craniocervical angle (°)	C2C4-SN
	C2si-S-N
Cephalometric dental measurements	
Maxillary incisor inclination (°)	U1 (U1i-root apex)-PP
	U1 (U1i-root apex)-SN
Mandibular incisor inclination (°)	L1 (L1i-root apex)-MP
Interincisor angle (°)	IIAA: U1 (U1i-root apex)-L1(L1i-root apex)
Maxillary molar inclination (°)	U6 (U6c-mesial root apex)-SN
	U6 (U6c-mesial root apex)-PP
Mandibular molar inclination (°)	L6 (L6c-mesial root apex)-MP
Maxillary molar height (mm)	MXMH (U6c-PP perpendicular)
	U6c-FP (perpendicular)
Mandibular molar height (mm)	MDMH (L6c-PP perpendicular)
Maxillary molar distance to mandibular molar (mm)	U6L6SN (U6c-L6c projected on S-N plane)
Overjet (mm)	Horizontal distance of Uli to Lli
Overbite (mm)	Vertical distance of Uli to Lli
Cephalometric soft tissue measurements	
Soft palate	
Length (mm)	PNS-P or PNS-Ut
Thickness (mm)	Maximum thickness of the soft palate (perpendicular to PNS-P)
Depth (mm)	PNS-P (horizontal)
Cross-sectional area (mm^2)	SPXA (area confined by outline of soft palate through PNS and P)
Palatal angle (°)	ANS-PNS-P
Tongue	
Tongue length (mm)	TGL (TT-Eb)
Tongue height (mm)	TGH (maximum height perpendicular to TT-Eb)
Tongue cross sectional area (mm^2)	Tongue CSA or TGXA or TNGXA (region within the outline of the dorsum of the tongue surface and lines that connect TT, RGN, H and Eb).
	TA (Triangle area constructed TGL as the base and TGH as the height)
Tongue : oral cross sectional area (ratio)	Tongue CSA : Oral CSA
Epiglottis	
Linear distance between ANS and Eb (mm)	ANS-Eb

Table 3. Continued

Variable	Measurement
Upper Airway	
Width (mm)	
At the level of soft palate	SPAS or SP-PAS or Superior Posterior (along parallel line to Go-B line)
	MAS or middle airway (along parallel line to Go-B line through P)
	MinRPA or narrowest palatal airway (minimal width perpendicular to posterior pharyngeal wall)
	RPAS (Phw-Spt)
At the level of tongue base	PAS or IAS or IAS1 (distance between posterior pharyngeal wall and the dorsal base of tongue surface, measured on a line intersecting Go and B Point)
	Posterior Inferior (distance between base of tongue and posterior pharyngeal wall)
	MinRGA or narrowest lingual airway (minimal width perpendicular to posterior pharyngeal wall)
	TB-PAS (at the level of the tongue base)
	PPW'-BT'
Through C3	IAS2 (along parallel line to Go-B line)
Vertical length (mm)	VAL (PNS-Eb)
Cross-sectional area (mm^2)	
Nasopharynx cross-sectional area	NASOXA (area outlined by line between R and PNS, extension of palatal plane to posterior pharyngeal wall and posterior pharyngeal wall)
Oropharynx cross-sectional area	OROXA (area outlined by inferior border of nasopharynx, posterior surface of soft palate, line parallel to palatal plane from point P to dorsal surface of tongue, posterior inferior surface of tongue, line parallel to palate plane through point Et, and posterior pharyngeal wall)
Cross-sectional area (mm^2)	
Hypopharynx cross-sectional area	HYPOXA (area outlined by inferior border of oropharynx, posterior surface of epiglottis, line parallel to palatal plane through point C4, and posterior pharyngeal wall)
Pharinx cross-sectional area	PHYNXA (sum of NASOXA, OROXA and HYPOXA)
Facial contours	
Facial convexity (°)	N'-Prn-Pog'
Prominence of the nose (mm)	Prn-S (vertical)
Upper lip position (mm)	Distance UL-E line
Lower lip position (mm)	Distance LL-E line

See Figure 2 for definitions of landmarks and reference lines used in this table.

Cervical vertebrae
- 1-piece MAD: Svanholt et al.[24] found that the prevalence of and severity of morphological deviations of the upper spine were greater in the group of patients that failed MAD.
- 2-piece MAD: Neither the linear distance between RGN and C3ia[21] nor the craniocervical angle[21,22] seemed to be predictive of MAD treatment outcome.

Cephalometric dental measurements
- 1-piece MAD: Studies investigating dental parameters agreed on the lack of predictive value of these measurements for treatment outcome.[14,24]
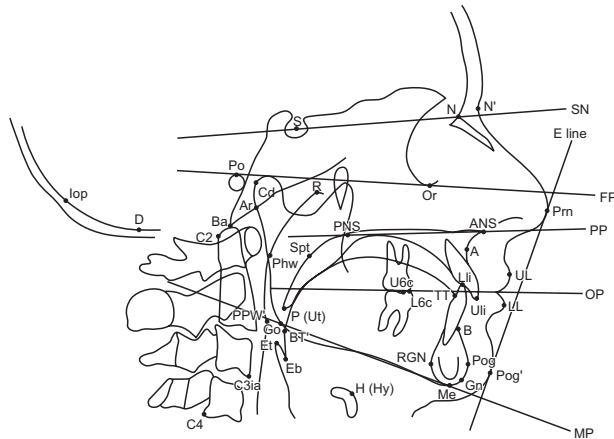- 2-piece MAD: Overjet and overbite were widely

Figure 2. Diagrammatic representation of landmarks and reference lines. A, Subspinale; ANS, anterior nasal spine; Ar, articulare; B, supramentale; Ba, basion; BT', base of tongue; C2, tangent point on the dorsal surface of C2 vertebra to a line from C4; C3ia, C3 vertebra infe- roanterior; C4, C4 vertebra inferoposterior; Cd, condylion; D, the deepest point in posterior cranial fossa; E line, Ricketts-E line; Eb, epiglottis base; Et, tip of epiglottis; FP, Frankfurt Plane; Gn, gnathion; Go, gonion; H (Hy), hyoidale; Iop: internal occipital protuberance; L1i, lower incisor tip; LL, lower lip; Me, menton; MP, mandibular plane; N, nasion; N', soft tissue nasion; OP, occlusal plane; Or, orbitale; P (Ut), soft-palate tip; Phw, posterior pharyngeal wall; PPW', posterior pharyngeal wall interseption; PNS, posterior nasal spine; Po, porion; Pog, pogonion; Pog', soft tissue pogonion; PP, palatal plane; Prn, nasal tip; R, roof of pharynx; RGN, retrognathion; S, sella; SN, S-N plane; Spt, tangent point on a line parallel to PNS-P on the dorsal surface of the soft palate at the maximum width; TT, tongue tip; U6c, maxillary first molar point; U1i, upper incisor tip; UL, upper lip.

recognized as non-predictive of treatment success.[9,17,20,22,23] However, Hoekema et al.[8] found that increased overjet and overbite were progno- stically favorable. Increased maxillary molar height also seemed to be associated with a better chance of successful treatment.[17] None of the other cepha- lometric dental measurements exhibited predictive value.[21,23]

Cephalometric soft tissue measurements

Soft palate
- 1-piece MAD: Soft palate depth and thickness and palatal angle were identified as non-predictive of treatment outcomes,[10,14] whereas data concerning soft palate length, which, when decreased,[16] was recognized both as non-predictive of treatment

outcome[14,15] and predictive of treatment success, were controversial.
- 2-piece MAD: Shen recognized soft palate thickness as non-predictive of treatment outcome.[9] The role of soft palate length was controversial. Two out of 6 studies found that decreased soft palate length was predictive of treatment success[9,22] while 4 did not.[8,19-21]

Tongue
- 1-piece MAD: There was general agreement that the cephalometric variables of tongue length, height, and cross-sectional area were not useful for predicting MAD treatment outcomes.[10,14,15]
- 2-piece MAD: Tongue-related cephalometric variables were widely recognized as non-predictive of MAD treatment outcome[9,17,22,23] with the sole exception of tongue/oral enclosure cross-sectional ratio, which Mostafiz et al.[21] found was increased in complete responders.

Epiglottis
- 1-piece MAD: Only 1 study examined the predictive role of the distance between ANS and Eb in treatment outcomes, finding that the greater this distance, the less effective the treatment.[10]
- 2-piece MAD: No study investigated the predictive role of epiglottis parameters.

Upper airway
- 1-piece MAD: Upper airway parameters were unani- mously recognized as non-predictive of MAD treat- ment outcome.[10,14,16]
- 2-piece MAD: Neither vertical length nor cross- sectional area were found to be predictive of out- come.[9,17,20] Concerning the upper airway widths, only 1 study (Shen et al.[9]) found significantly decreased retroglossal width in good responders. The majority showed a non-predictive role for retropalatal width, although Mehta et al.[5] and Liu et al.[17] found an increased retropalatal space in good and poor res- ponders, respectively.

Facial contours
- 1-piece MAD: Kim et al.[14] found no differences in profile measurements between good and poor res- ponders.
- 2-piece MAD: No profile measurements were found to be predictors for treatment outcome with 2-piece MAD.[20]

DISCUSSION

MADs are increasingly used for treatment of mild to

moderate OSA because they provide a less invasive, more comfortable, and less costly alternative to nCPAP. Nevertheless, MADs are not as efficacious as nCPAP, and the treatment success rates range from 42% to 65%.[7] As certain craniofacial characteristics, including reduced posterior airway space, abnormally long soft palate, and low position of the hyoid, are commonly found in OSA patients it seems reasonable to assume that the efficacy of MAD may relate to morphological factors.[26]

Several modalities for assessing upper airway morphology have been recommended, including magnetic resonance, nasopharyngoscopy (in an awake state or during drug-induced "sleep"), computed tomography, and lateral cephalometry.[8,9,27-29] Cephalometry is low-cost, simple, and widely available, and these advantages may offset the disadvantages of the cephalogram being a 2-dimensional projection of a 3-dimensional structure that is performed in an awake state and in an upright position whereas the pathology of OSA arises with the patient lying down during sleep. Therefore, we aimed to provide a systematic review of cephalometric parameters predictive of MAD treatment outcome.

Summary of the evidence

Within the limitations of the selected studies, some consideration can be made with regard to cephalometric parameters predictive of MAD treatment response. Data on the skeletal cephalometric measurements were conflicting. Among the cranial base cephalometric values, cranial base angle and the distance between the sella turcica for 2-piece MADs and the deepest point in the posterior cranial fossa for 1-piece MADs were suggested as possible prognostic factors. However, the data are still too limited to draw any conclusion.

The lack of predictive value of sagittal jaw relationships (SNA, SNB, SN-Pg, ANB, Wits appraisal) as well as linear parameters related to vertical jaw dimensions (anterior face height, lower anterior face height, lower posterior face height, upper anterior face height, ratio between posterior face height and anterior face height) was almost unanimously confirmed. On the other hand, the mandibular plane angle was associated with widely conflicting results, with some studies reporting a non-predictive role and other studies reporting both increased and decreased predictive values for treatment success. It is therefore impossible to draw any definite conclusion on this parameter based on the available data. Hyoid bone position also showed widely conflicting results, with some studies reporting a non-predictive role for MP-H and others reporting both increased and decreased predictive value for treatment success. Available data for H-Me and ANS-H were rather limited. Therefore, the prognostic value of hyoid bone parameters needs further investigation. A possible

predictive role of upper spine morphological deviations for 1-piece MAD was suggested. Further study will be required to evaluate these findings.

With regard to dental cephalometric parameters, overjet and overbite, although being reported as predictive of MAD treatment outcome by Hoekema et al.[8] alone, were mostly considered unlikely to carry any prognostic significance. Furthermore Liu et al.[17] found that in 2-piece MADs, efficacy was decreased with greater eruption of the maxillary molars. However, being as this study was the only one examining this parameter, the recognition of a predictive role for the distance between the maxillary first molar and Frankfort plane seems premature. Therefore, further research on this parameter is also warranted.

Cephalometric soft tissue measurements did not seem to be very useful in predicting MAD treatment response. Soft palate length was recognized both as predictive of treatment success when decreased and as not significantly different between good and poor responders. Therefore, prediction of treatment outcome based on this measurement is not yet unjustified and will require further investigation. Greater ratio between tongue and oral cross sectional area[21] and shorter distance between Eb and ANS[10] have been shown to be associated with treatment success in 2- and 1-piece MAD, respectively; however additional studies will be needed to confirm these results. Although some studies have suggested a predictive role for retropalatal and retroglossal widths in treatment with 2-piece MAD, the results were controversial. The inconsistency of predictive values of upper airway cephalometric parameters was foreseeable because cephalometry is not the preferred imaging technique for evaluation of these anatomic structures. Indeed, there appears to be a strong linear relationship between 2-dimensional cephalometric and 3-dimensional computed tomography reconstructions for tongue, soft palate, and nasopharynx, while the configuration of oropharynx and hypopharynx appears to be less consistent.[30]

Limitations

Study level

The question of the predictive role of cephalometric parameters has not been addressed by randomized clinical trials because the variables of interest are not under the control of the investigators. The inclusion of observational studies therefore appeared necessary. The study design adopted in all of the studies selected for this review was case-control (either prospective and retrospective) rather than cohort: 2 or 3 groups differing in MAD treatment outcome (good and poor responders or nonresponders, partial and complete responders) were

prospectively or retrospectively identified and compared on the basis of cephalometric parameters. As a result, the findings score low in terms of strength of evidence. A selection bias may have occurred because the sample was not randomly selected. Moreover in some of the prospective studies patients were included after they had been allowed to choose whether or not they wanted to participate or after they had decided entirely for themselves not to accept treatment with nCPAP (self-selection bias).[18,19] Finally, a few studies reported that some patients dropped out (attrition bias).[5,8,19]

MAD treatment success has been associated with female sex, a younger age, a lower body mass index (BMI), and a lower baseline apnea-hypopnea index (AHI) but, due to the design of the studies included in this review, these baseline characteristics could not be properly addressed and may actually show systematic differences between good responders and poor responders (confounding bias).[17,22] In the 13 studies that reported male-female ratio, males had considerably more representation, ranging from 67.9% to 100% of the sample.[5,9,14-24] With the exception of the study by Mehta et al.,[5] none of the others investigated the differences in sex distribution between good responders and poor responders. Six studies found no age difference between good and poor responders,[5,10,14,15,19,24] while 4 studies found age to be significantly lower in good responders.[17,20-22] Eight studies failed to find a predictive role for BMI,[5,10,14,15,19,20,22,23] while 3 studies reported lower BMI in good responders.[8,21,24] Only 1 paper addressed the issue of weight gain or loss between the initial and the final evaluations.[19] Six out of 14 studies did not account for potential differences in baseline AHI,[8,16,18-20,23] whereas comparison between good and poor responders in terms of AHI or apnea index led to significant differences in 2 studies, with lower values associated with treatment success,[14,21] and no significant differences in 6 studies.[5,9,10,15,17,22]

With regard to observer bias, only 3 studies reported that the operator who performed the cephalometric analysis or the polysomnography was blinded to the treatment outcome.[5,14,22] None of the selected studies included a power analysis or a sample size calculation. The presence of potentially underpowered studies could lead to inconsistent or misleading results, because they may find no significant difference between study samples even in the presence of a real difference in the general population.

Review level

The findings of the present systematic review were also limited by the heterogeneity in the methodology of the included studies. Respiration was analyzed in terms of AHI in the majority of the investigations, but some of the earlier studies evaluated the respiratory disturbance index (RDI).[19] The definition of sleep apnea was based either on AHI > 5, AHI ≥ or > 10, AHI ≥ or > 15, or RDI ≥ 10. Success criteria included RDI reduction of ≥ 50% and RDI ≤ 20, AHI < 5, AHI < 15, or AHI reduction of > 50% alone or in association with AHI < 20, < 10, or < 5. A certain degree of variability was present with respect to the type of MAD (monobloc or two pieces), as well as to the amount of protrusion (from 50 or 60% of maximum protrusion to the most advanced position without causing any discomfort) or vertical opening (ranging from "minimum" to 15 mm). The time interval between diagnostic and with-appliance polysomnography ranged from few weeks to several months. The cephalometric parameters also varied substantially between different studies. Because of the lack of homogeneity among the studies, any attempt to summarize the study results seemed unjustified. This, a narrative synthesis was carried out without performing a meta-analysis.

No "grey literature" or articles in non-English languages were included in the present review. Therefore the review is also subject to publication bias and language bias.

CONCLUSION

This review found controversial and limited data on the predictive role of certain cephalometric parameters for MAD treatment outcome. Therefore selection criteria for suitable candidates for MAD treatment by cephalometric analysis are currently inadequate. Although no definitive clinical recommendations can be made, this systematic review highlights the methodological weaknesses of the currently available studies, analyzes the possible reasons for their discordant results, and encourages and guides further research in this field. Prospective cohort studies in large samples with cephalometric prediction made prior to the MAD construction are required to clarify the clinical utility of lateral cephalometry for adult OSA patients who are considering oral appliances as a therapeutic option.

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