Development and Validation of Semi-automatic Segmentation Technique of Mandibular Condyles from CBCT images

by

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ABSTRACT

Objectives: Mandibular condyle contains an important growth site that contributes to the eventual anteroposterior position of the mandible, and is a crucial component in establishing normal temporomandibular function. To accurately assess the change in the volume and morphology of the mandibular condyle using cone-beam computed tomography image (CBCT), it is paramount to establish a validated method to segment the mandibular condyle from the surrounding structures. In this study, a systematic review was conducted to investigate the available condylar segmentation techniques from three-dimensional images, and its reported accuracy and reliability. Semi-automatic condylar segmentation technique was developed and validated for its accuracy compared to the reference model and its reliability. A pilot study was completed to assess the condylar volumetric changes in adolescent orthodontic patients treated with different Class II fixed appliances.

Methods: Systematic review was conducted using three electronic databases. CBCT images of three dry study skulls and three corresponding 3D-printed mandibles were used to semi-automatically segment the mandibular condyles and the computed volumes were compared to the volumes obtained from the physical models. Sixty CBCT images from thirty adolescent patients from three groups (Herbst appliance, Xbow appliance, and control group) at two time points were assessed using the developed semi-automatic condylar segmentation method.

Results: Condylar volume computed using semi-automatic segmentation technique was found to be accurate when compared to the volume determined from dry 3D-printed mandible. Intra and Inter-rater reliability were excellent. Statistically significant increase in condylar volume was observed in adolescent patients in all three groups, but the magnitude of condylar volume increase among different groups were not statistically significant.

Conclusion: Condylar volume computed from the described segmentation technique was highly accurate when compared to the physical condylar volume measurements; and is a reliable approach to evaluate volume changes in mandibular condyles in growing patients treated with fixed Class II appliances. The limited results from the pilot study suggests that the condylar volume increase in growing patients is primarily due to the normal condylar growth and is not necessarily enhanced or impeded by the use of fixed class II appliances.

PREFACE

This thesis is an original work by Justin Kim. No part of this thesis has been previously published.

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Chapter 1: Introduction

1.1 Statement of the Problem

Mandibular condyle is a principal component of temporomandibular joint (TMJ) complex thereby a crucial factor in establishing normal TMJ function[1]. In orthodontics, mandibular condyle is an important growth site that significantly impacts the anteroposterior length and position of the mandible thereby determining the eventual maxillomandibular anteroposterior relationship[2,3] . The potential ability of mandibular condyle and surrounding osseous structures to continuously remodel in the presence of external stimulus has strongly interested many researchers and clinicians over the years, giving rises to several orthodontic appliances and approaches to utilize this capability to accomplish orthodontic objectives[4,5] .

Whether the mandibular condyle undergoes growth, remodelling or pathological degenerative resorption, some degrees of morphological and volumetric changes of the condyle is to be expected. Cone-beam computed tomography (CBCT) produces a three-dimensional reproduction of dentofacial structures[6] , and this potentially allows for volumetric analysis of mandibular condyles, given an appropriate imaging parameter[7] . Both volumetric and morphological analysis of a dentofacial structure often requires an accurate and reliable method to segment the particular anatomical structure from the images[8] . There are some inherent complexities of segmentation of mandibular condyle when compared to other osseous dentofacial structures including superimpositions of multiple osseous structures, low condylar osseous density and proximity to the disc[9] .

Although several condylar segmentation techniques are routinely employed in studies and clinical settings, a comprehensive review of the accuracy and reliability of these techniques has not been completed. Furthermore, to the best of our knowledge, assessment of volumetric changes in condyles in growing patients treated with functional orthodontic appliances with a validated condylar segmentation technique has not been reported. It is imperative that an accurate and reliable condylar segmentation method be developed and validated to substantiate the validity of the condylar volumetric analysis.

1.2 Research objectives

Objective #1:

- Systematically review the literature surrounding segmentation of the mandibular condyle using three-dimensional imaging modalities.

Objective #2:

- Develop a method to segment the mandibular condyle from CBCT images reliably and validate its accuracy.

Objective #3:

- Using the developed condylar segmentation method to evaluate volumetric changes in mandibular condyles in patients treated with different fixed Class II appliances.

1.3 Research questions

1) What are the available segmentation techniques to segment the mandibular condyle from three-dimensional images, and what are its reported accuracy and reliability?

2) What are the steps to develop an accurate and reliable method to segment the mandibular condyle from CBCT images, and how should the developed method be validated?

3) Are there any differences in condylar volumetric changes in patients treated with fixed functional appliance compared to those treated with fixed class II appliance and those treated without any inter-arch mechanics?

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Chapter 2: Reliability and accuracy of segmentation of mandibular condyles from different three-dimensional imaging modalities: A Systematic Review

2.1 Introduction:

The study of mandibular condyle morphology provides fundamental knowledge to improve our understanding of the craniofacial growth, functional orthopedic treatments utilizing condylar remodeling and growth, and temporomandibular pathology[1,2] . The condyle undergoes continuous remodelling process, and it is a significant area influencing the overall mandibular growth[3]. Abnormal mandibular condylar growth and development may become a significant risk factor for temporomandibular disorder and dysfunction (TMD)[2] and sagittal, traversal and/or vertical malocclusion development. Such malocclusion includes class II malocclusion, which affects almost one-third of the North American population[4] . Condylar remodelling can dynamically respond to external stimuli, from which many orthodontic Class II appliances aim to take advantage to encourage an orthopedic effect during adolescence age for a more favorable orthodontic result[5-7]. Condylar pathology such as temporomandibular joint osteoarthritis, which is radiographically found in 14% of older adults, leading to morphological changes in condyle can contribute to joint pain and dysfunction[2] . Accurate assessment of condylar osseous abnormalities is essential in both diagnosis and development of TMD treatments[8].

There are various three-dimensional imaging modalities used to assess the craniofacial structures including mandibular condyles. While computed tomography (CT) continues to be the gold standard for osseous structure assessment, its use by many clinicians has been limited because of the relatively high radiation dose and relatively limited availability of the CT machine in private practice settings[9] . Cone-beam computed tomography (CBCT) is increasingly becoming integral in the field of dentistry including orthodontics, oral and maxillofacial radiology and implant dentistry due to its high accuracy with minimum patient discomfort, and relatively low ionizing radiation exposure compared to the conventional CT scans[9,10] .

Traditionally, the superimposition of two-dimensional cephalometric radiographs have been used for assessing morphological changes in various craniofacial structures whether it be due to growth, pathology, surgical manipulation, or functional orthopedic treatment; however, many limitations arise including superimpositions of craniofacial structures, magnification, distortion, and inability to assess three-dimensionally the changes in size and shape[11]. Use of CBCT imaging has allowed three-dimensional (3D) superimposition of images while performing the 3D assessment of morphologic changes of dento-facial structures during growth and the evaluation of orthodontic treatment effects[12]. Several articles have been published recently to assess the efficacy of CBCT in TMJ imaging[13-15]. Although magnetic resonance imaging (MRI) is considered the gold standard imaging modality for evaluating soft tissue based TMJ dysfunctions, it has been shown to be ineffective in properly assessing TMJ osseous changes when compared to conventional CT and CBCT imaging[16] .

Due to the advantages of CBCT imaging, including accurate osseous assessment capability and relatively low radiation of CBCT imaging, in particular, there has been a great interest lately in using CBCT imaging to assess condyle shape and volume[1,7,17]. Accurate and reliable methods to assess condylar shape and volume can potentially have a significant impact on our understanding of condylar osseous changes in growth, orthopedic functional appliances, TMJ dysfunctions, and surgical manipulation[4,8,13]. Segmentation processes may directly impact the validity of morphological assessment[18]. Despite recent developments in the three-dimensional analysis of various craniofacial structures, the segmentation process of the condyles continues to be tedious and difficult[18,19]. Engelbrecht, in using CBCT images, found condylar segmentation along with segmentation of the lingual region of the mandible to be the least reliable from the mandibular structures[18]. This finding may be due to relatively low density of bone in the condylar area, overlapping cranial base bony structures and close proximity to the articular disc.

The objective of the review is to critically synthesize the literature surrounding segmentation of the mandibular condyle using three-dimensional imaging modalities. Specifically, analyzing the reliability and accuracy of methods used for three-dimensional condyle segmentation.

2.2 Materials and Methods:

Protocol and registration

Protocol registration was completed via PROSPERO.

Eligibility criteria

The study question was formulated using the PICOS format.

- Population: Human mandibular condyles from general population exhibiting no gross condylar pathology or anatomical abnormalities
- Intervention: Mandibular condyle segmentation from the obtained images using three-dimensional imaging modalities (including CBCT, MSCT, MRI)

- Comparison: Surface laser-scanned mandibular condyle micro-CT scan images, and direct measurements from cadaveric condyles
- Outcomes: Reliability and accuracy of condylar segmentation methods
- Study design: Diagnostic studies. If the pertinent diagnostic information is available clinical trials, cohort studies, case-control, cross-sectional studies would also be considered

Information sources

Three electronic databases PubMed, MEDLINE (Ovid SP), and EMBASE were used to conduct the systematic search from their establishment date to November 18, 2018.

Search strategy

For each electronic database, the systematic search was conducted using the combination of keywords and Medical Subject Headings (MeSH) as shown in the appendix.

Study selection

Two reviewers (JK and HN) independently reviewed the titles and abstracts of the resultant electronic database search. Thereafter, the two reviewers compared their selected articles. Articles that exhibited obvious irrelevance to the research topic were excluded at this stage. If insufficient information was available in the abstract, the full content of the article was obtained for both reviewers and they determined jointly for the final selection of the article during a second selection phase including full-texts.

Data collection process

Two reviewers independently reviewed and extracted the necessary data from each of the selected articles. Subsequently, the reviewers compared the extracted data to resolve any discrepancies.

Data items

Data items including sample type and size, imaging protocol, segmentation protocol, outcomes, and reliability and accuracy, if available, of the method used were obtained from the selected studies.

Risk of bias in individual studies

Two reviewers used the Quality Assessment of Diagnostic Accuracy Studies tool-2 (QUADAS-2)[20] to evaluate the risk of bias for each selected study. Subsequently, the reviewers compared the QUADAS-2 results to resolve any discrepancies.

Summary measures

Reported reliability and accuracy measurements, including mean differences in condylar volume, linear and angular measurements between the landmarks, shape analysis, dice-coefficients, Pearson correlation coefficients (PCC), intra-class correlation (ICC) were considered.

Synthesis of results

A meta-analysis was not possible due to the significant heterogeneity of the segmentation tools used and resulting data discrepancies.

Risk of bias across studies

No additional analyses completed

Additional analyses

GRADE approach was used to assess and summarize the findings extracted from the selected studies.

2.3 Results:

Study selection

Electronic database searches yielded 802 articles and 413 articles were screened after the duplicates were excluded. Only 41 articles were considered for full-text review. 9 articles were found to fulfill the inclusion criteria and were selected for qualitative analysis. PRISMA flow chart of the article selection process is presented in Figure 2.1.

Study characteristics

Study characteristics including sample size, imaging modality and protocol, segmentation protocol, reliability and accuracy method along with reliability and accuracy data are summarized in Table 2.1. The included articles were published between 2011 and 2018, and sample size ranged from 10 to 40 condyles.

Seven of the studies used CBCT as the imaging modality. One assessed both CBCT and multi-slice CT images compared with microCT[21]. One used 3D ultrashort time-to-echo (UTE) MRI as the imaging modality[22]. Segmentation protocols varied but were classified into three general types: including threshold-based volume segmentation (Figure 2.2), manual segmentation and semi-automated software algorithm aided segmentation (Figure 2.3). The parameters reported by the studies included median surface distance error, linear measurements, mean curvature value and condylar volume. Condylar volume was the most commonly reported measurement (seven of the included studies)[21-27] .

Risk of bias within studies

The selected articles were assessed for risk of bias using the QUADAS-2 tool and are summarized in Table 2.2. Most common risk of bias factor was a failure to report the blinding of results of reference standard[21-27]. In addition, non-randomization of sample obtained[18,25,26,28] or unclear reporting of sample selection[21,22], and failure to report the accuracy of segmentation tools[23,24,27] were also considered to generate a significant potential risk of bias.

Results of individual studies

Results of the included studies are summarized in Table 2.1.

Threshold-based volume segmentation reliability:

Threshold-based volume segmentation technique (Figure 2.2) demonstrated an excellent intra-observer (ICC>0.98) and inter-observer (ICC>0.95) agreement[26] . Engelbrecht *et al*.[18] and Fourie *et al*.[28] did not present a reliability data on the segmentation completed by the commercial lab.

Threshold-based volume segmentation accuracy:

Threshold-based volume segmentation technique by Engelbrecht *et al.*[18] and Fourie *et al.*[28] presented the accuracy data in terms of mean deviation of condyle width and mean linear deviation of condylar landmarks from the reference model, which was a laser-scanned 3D model of macerated mandible (Table 2.1). Mean linear deviation of condylar landmarks was <1.72±1.99mm for the clinician segmentation group and <0.92±0.81mm for the commercial segmentation group, and the mean deviation was higher for all measured condylar landmarks in the clinician group when compared to the commercial segmentation group[28]. This trend was also seen in the mean deviation of condyle width[18]. Garcia-Sanchez *et al*.[26] compared both the condylar volume and three condylar linear measurements between the threshold-based volume segmented condyle and the dry condyles after removal of soft tissues using physical measurements and water displacement method. The reported mean differences in linear measurements (-0.004±0.027~0.019±0.084mm) were significantly lower than that of Engelbrecht *et al.* study[18].

Manual segmentation reliability

Bayram *et al*[25] study utilized the threshold-based volume segmentation followed by the manual segmentation of condyles from CBCT images (Figure 2.3). They reported an excellent agreement among three observers in segmentation of condyles (PCC=0.990-0.997). No intra-observer reliability data was provided.

Excellent inter-observer reliability was observed in UTE MRI manual segmentation (ICC=0.997-0.999)[22].

Manual segmentation accuracy

Bayram *et al.* reported that no statistically significant differences (p=0.314-0.515) were found between the manually segmented condylar volume and the condylar volume determined from the reference model, which was calculated using a water displacement method from the impression of the physical dry mandible models[25].

3D UTE MRI manual segmentation was validated by comparison to the microCT scan of the condyle[22] ; percentage deviation ranging from 5.7±6.5% to 6.6±6.2%, and ICC >0.892.

Semi-automatic segmentation reliability

Semi-automatic segmentation method by Xi *et al.*[23,24] reported the reliability results in mean discrepancy in distance maps of the condylar surface and mean differences in condylar volume, of which equals to intra-observer difference of 0.5% and interobserver difference of 0.3% in relation to the mean condylar volume. The intra-observer mean discrepancy between the condylar contours was 0.22mm, and 0.13mm for the inter-observer. They reported 85% and 93% of calculated distances between the condylar surface had an intra- and inter-observer distance smaller than 0.5mm, respectively. Nicolielo *et al.*[21] utilized another semi-automatic segmentation method for MSCT and CBCT images, and the segmentation from MSCT images reported significantly higher intra- and inter-observer reliability at ICC values of 0.96 and 0.93, respectively, compared to ICC values of 0.73 and 0.60 obtained from CBCT condylar segmentation. Comparative intra-examiner reliability for condylar volume measurement using semi-automatic segmentation was reported by da Silva *et al.*[27] (ICC=0.94).

Semi-automatic segmentation accuracy

Xi *et al.*[24] reported the validity of their semi-automatic segmentation technique by comparing it to the validation group in the previous study[23], which was also obtained from the software segmentation of CBCT images thus not an appropriate reference model for reporting accuracy. Accuracy data was not reported in the study by da Silva *et al.* [27]. In terms of total condylar mineralized bone volume, semi-automatically segmented condyles from MSCT and CBCT were significantly higher at 1834mm^3 and 1732mm^3, respectively, when compared to the reference model obtained from micro-CT scan at 1167mm^3. The same study assessed part-comparison analysis of condylar surface contour, and results showed mean over-estimation of bone segmentation of 0.3mm±0.2mm for MSCT and 0.4mm±0.3mm for CBCT[21] .

Synthesis of results

Due to the heterogeneity of the selected studies in terms of imaging modality and measured parameters used, a meta-analysis was not justifiable.

Risk of bias across studies

As a meta-analysis was not possible for this systematic review, risk of bias across studies was not assessed.

Additional analysis

GRADE summary of findings is summarized in Table 2.3. Threshold-based segmentation exhibited moderate certainty of evidence in the accuracy but scored very low in the reliability. Manual segmentation scored low certainty of evidence in both accuracy and reliability mainly due to heterogeneity in imaging modality and small sample size. Semi-automatic segmentation exhibited moderate certainty of evidence in its reliability and scored very low in the accuracy due to the inadequate reference standard.

2.4 Discussion:

Summary of evidence

There are several reasons why accurate and reliable condylar segmentation from three-dimensional images has been difficult to obtain efficiently when compared to other mandibular structures. A relatively low bone density of condyles, complex overlapping with other skeletal structures including glenoid fossa, and intimate proximity with the articular disc has been suggested as reasons for the difficulty[18]. This systematic review results suggest that the three-dimensional volume of the condyles segmented from the CBCT images exhibit a moderate amount of variance in reliability and accuracy dependent upon the segmentation technique employed. Limited literature is available regarding the condylar segmentation technique in other imaging modalities such as multi-slice CT and MRI[21,22]. This is likely due to the relatively limited clinical usage of imaging modalities other than CBCT because of cost, limited availability and radiation exposure to patients in cases of medical CT scan[9].

The most commonly used condylar segmentation technique using CBCT images is a threshold-based volume segmentation in which an operator use a software's volumetric sculpting and segmentation tool to remove structures outside the volume of interest (Figure 2.2). This technique is highly dependent upon the variable threshold setting determined by the operator to best visually isolate the structure(s) of interest[28]. The results from two of the included studies suggest that the manual segmentation technique using variable threshold is least accurate in the condylar region and exhibits higher accuracy and reliability when completed by an experienced 3D technician in commercial laboratory compared to a clinician with 3 years of clinical experience[18,28]. Operator subjectivity in determining variable threshold is intrinsic with this method and may significantly influence the reliability and accuracy of condylar segmentation from CBCT images[21]. Although García-Sanz *et al.* reported excellent inter-observer reliability, the operator had access and superimposed the scanned surface model of condyle to aid in volume segmentation process thus likely resulting in substantially high inter-observer reliability[26]. Threshold-based volume segmentation is a comparatively convenient segmentation tool with a capability to accurately segment the mandibular condyle; however, clinicians must be careful interpreting the results using this method as the operator's experience can influence the validity of the outcomes.

The manual technique described by Bayram *et al.*[25] reduces the variability of the threshold by further sectioning the segmented condylar volume in the sagittal plane with the operator outlining the condyle borders for each slice (Figure 2.3). The results showed significant positive correlations between the observers, and no significant statistical difference was found between the segmented volume and physical volume; however, underestimation and overestimation were reported in some samples. Despite its apparent accuracy and reliability, the most relevant disadvantage may be that the technique is tedious and a time consuming process, which could be inviable when it is necessary to segment multiple condyles for morphological analysis.

Semi-automatic segmentation method described by Xi *et al.*[23,24] and da Silva *et al.*[27] aims to remove the operator subjectivity in threshold determination as its technique allows very limited operator involvement and the majority of the condylar segmentation is completed by the computer algorithm, independent of the operator (Figure 2.3). This is supported by the low intra-observer and inter-observer differences in condylar volume and distance maps of the condylar surface[23] and high intra-examiner reliability as demonstrated by da Silva *et al.* study[27]. However, the absolute mean differences in condylar volume using this method are substantially different between a group with extensive experience and a group with little experiencet[24]. This indicates that examiner experience does influence aspects requiring operator judgement, likely due to the operator variability in setting the global threshold values and any manual steps taken to correct the gross miscalculation of condylar outline from the software algorithm. This technique is similar to the manual technique by Bayram *et al.*[25] in that it determines condyle border in each slice, but this semi-automatic segmentation technique is likely to be more efficient and subject to less operator variability because it delegates most of this task to the software algorithm (Figure 2.3). Although the semi-automatic segmentation was reported to be a reliable and efficient method of condylar segmentation, it lacks accuracy data against an appropriate validated reference model. Accuracy data was absent in da Silva *et al.* study[27]. Furthermore, the reference model to validate the method presented in Xi *et al* study[23] was manual threshold-based condylar segmentation from CBCT image, which still is an imaging segmentation method rather than a direct measurement of the physical specimen or validated model such as laser-scanned 3D model. Manual segmentation has been found to have reliability and accuracy issues depending on the operator[18,28] . Nicolielio *et al.*[21] described another semi-automatic segmentation technique from both CBCT and multi-slice CT (MSCT) images using a global threshold algorithm and bone threshold values visually confirmed by the observer to remove any residual volume. Both CBCT and MSCT condylar semi-automatic segmentation exhibited a good to excellent intra and inter-observer agreement though inter-observer reliability was lower in CBCT segmentation (ICC=0.89-0.96 for MSCT; ICC=0.60-0.91 for CBCT). In terms of accuracy, micro-CT scan of the dry mandible condyle was used as validation reference. Unlike other studies measuring condylar volume by obtaining external condylar surface and calculating the volume based on this, this study evaluated the segmentation of internal mineralized bone within the condyle. This results in much lower condylar volume as any air space within condylar bone would not be considered in the resulting condylar volume. The part-comparison analysis result indicated that the average over-estimation of bone segmentation from CBCT and MSCT images were less than the voxel size. The resulting MSCT and CBCT total condylar bone segmentation volume was considerably higher when compared to bone segmentation done using high-resolution micro-CT; however, whether the discrepancy was statistically significant was not reported. The study suggested the discrepancy in the volume of interest (VOI) selection as the probable cause of this significant over-estimation. Despite the average over-estimation of bone segmentation through part-analysis being less than voxel size, the subsequent total condylar mineralized bone volume, which comprises of a large number of voxels, can be significantly affected. It indicates that the condylar bone segmentation using both CBCT and MSCT involving internal mineralized bone may result in high degree of inaccuracies when extended to total condylar volume. While the semi-automatic segmentation from CBCT images is a reliable condylar segmentation method, more studies comparing to the validated reference standard is needed to evaluate its accuracy.

When assessing a condyle volume, a reliable method to determine the condylar region of interest is crucial, specifically, the inferior border of the volume of interest, as other aspects of border are determined by the segmentation process. Any significant errors in repeatedly establishing this inferior border may significantly influence the resulting condylar volume. Bayram *et al.* established the inferior border at a line tangent to the distal slope of the coronoid process[25]. Although this method can work reliably in vitro when no other surrounding craniofacial structures are present as demonstrated by their reported high inter-observer reliability, this may pose a problem when used clinically because a small change in the position of mandible due to muscle tension can cause an increase in the coronoid process curvature as suggested by Torisu *et al.*[29], significantly affecting the tangent line thus the resulting condylar volume. In addition, this method would dramatically increase the posterior surface area of the condylar neck and ramus within the volume of interest, which undergoes intramembranous growth, whereas we need to limit our scope to primarily endochondral growth of the condylar head. Xi *et al.* introduced c-point, the most inferior point of sigmoid notch, and c-plane, a plane parallel to the Frankfurt plane at c-point similar to the method described by da Silva *et al.* study[23,24,27]. Location of c-points were repeated by the same observer and the percentage difference of resulting condylar volumes was 0.1%. Nicolielio *et al.*[21] study also investigated the reliability of their volume of interest determination method where a standardized sphere was created with its border passing through the most inferior point of sigmoid notch[23,24,27]. Intra- and inter-observer mean discrepancy in volume of interest was marginally larger than a voxel size, 0.5±0.5mm and

0.7±0.7mm, respectively. Its absolute effect on the resulting condylar volume was not reported; however, they were able to analyze solely on the segmentation process reproducibility without the influence of volume of interest selection by subtracting the borders difference before performing the part-comparisons to the reference model[21].

Only one study presented the condylar segmentation using UTE MRI imaging modality[22]. MRI, which is widely used to evaluate TMJ articular disc disorders[30] , could be used to segment and evaluate the condylar cortical bone surface by determining the interface of high tissue contrast between condylar bone and cartilage[22]. In this study, the segmentation from UTE MRI images was manually completed by experienced observers. Because of the limitations with this segmentation method, the region of interest assessed was limited to the articulating surface of the condylar head, which is substantially smaller than the typical condylar volume of interest assessed with CBCT images. Nonetheless, in contrast to CBCT, UTE MRI images allowed the segmentation and assessment of fibrocartilage. The study presented accuracy data comparing the data obtained from the micro-CT scan of the condyle, which was segmented semi-automatically. The mean deviation of bone surface from MRI to micro-CT scan was about the double the voxel size of MRI (0.19±0.15mm). ICC ranging from 0.892 to 0.972 between the UTE MRI and micro-CT segmented condylar curvature and volume, low percentage deviation (≤6.6±6.2), and an excellent inter-observer reliability (ICC≥0.997) of MRI indicates that UTE MRI appears promising in limited condylar segmentation with an acceptable accuracy and reliability. However, further studies are needed to assess its efficacy when a condylar volume of interest is extended to involve a more osseous region of the condyle, where the assessment capability of MRI is known to be limited[16] .

To summarize the selected studies, the condylar segmentation techniques from three-dimensional imaging are largely divided into three types, each with its own advantages and disadvantages: threshold-based volume segmentation, manual segmentation, and semi-automatic segmentation. There is a very limited number published of studies on the non-CBCT imaging modalities segmentation techniques. The accuracy of the linear measurements in CBCT image is well-established from the previous studies[31,32]; however, the accuracy of segmentation of mandibular condyle from CBCT image is uncertain due to the variances in segmentation techniques employed. Volume threshold-based segmentation from CBCT images is frequently used by clinicians and often completed by the commercial lab as the process is time-consuming and may not be economical for clinicians to perform[28] . While there is a moderate evidence to support the accuracy of the segmentation by experienced lab technicians (Table 2.3), the results from inexperienced observer may differ and thus the reliability of the method for non-commercial application is questionable. Utilization of semi-automatic condylar segmentation, relying heavily on the software algorithm rather than the observer's experience, has been increasing and the evidence supports its reproducibility[23,24,26]. Although this is a promising segmentation method with several advantages over the volume threshold-based segmentation and manual segmentation, a lack of comparison with appropriate reference standard inhibits making a conclusion on its accuracy. Additional studies focusing on the accuracy of semi-automatic segmentation, in particular, has a potential to provide the clinicians with another segmentation technique tool to consider when accurately and reliably examining mandibular condyle, which can further elucidate the condylar morphological changes associated with TMJ dysfunction, orthognathic surgery, and functional orthodontic appliances.

Limitations

There are potential risks of bias in the included studies including a failure to report the accuracy of the segmentation tools in 3 of the studies[23,24,27] , a failure to report the blinding of results, and non-randomization of sample in 7 of the studies[21-27]. At the systematic review level, lack of meta-analysis due to heterogeneity of the included studies limits the analysis of reliability and accuracy of segmentation techniques. Reported data varied greatly in measured parameters including condylar volume, linear measurements of the landmarks, distance maps of condylar surface and, surface curvature. It has been shown that surface area measurements on 3D mandible models are least accurate when compared to linear and volumetric measurements[33]. Additionally, one study reported statistical significance of accuracy data without providing the mean discrepancy values[25]. Reporting the numerical values of the mean differences would aid in establishing more homogeneity of the reported data from included studies for possible meta-analysis. Furthermore, mean difference data helps the reader interpret clinical significance. Very limited number of studies available for non-CBCT three-dimensional imaging modalities makes a thorough analysis of condylar segmentation techniques difficult.

2.5 Conclusion

Various condylar segmentation techniques have been used with three-dimensional imaging modalities to assess mandibular condylar morphology. Acceptable validity of manual thresholding condylar segmentation from CBCT images has been reported but its accuracy may be significantly influenced by the clinician’s experience with 3D segmentation. While the semi-automatic segmentation technique aims to minimize inter-observer errors, there is an inadequate reported data on its accuracy. A definitive conclusion with regards to which current technique is most reliable and accurate to efficiently segment the mandibular condyle cannot be made with currently available evidence. This is especially true in terms of non-CBCT imaging modalities with very limited literatures available. Further studies with more homogenous data sets are needed to perform a meta-analysis to analyze the available condylar segmentation techniques from three-dimensional images.

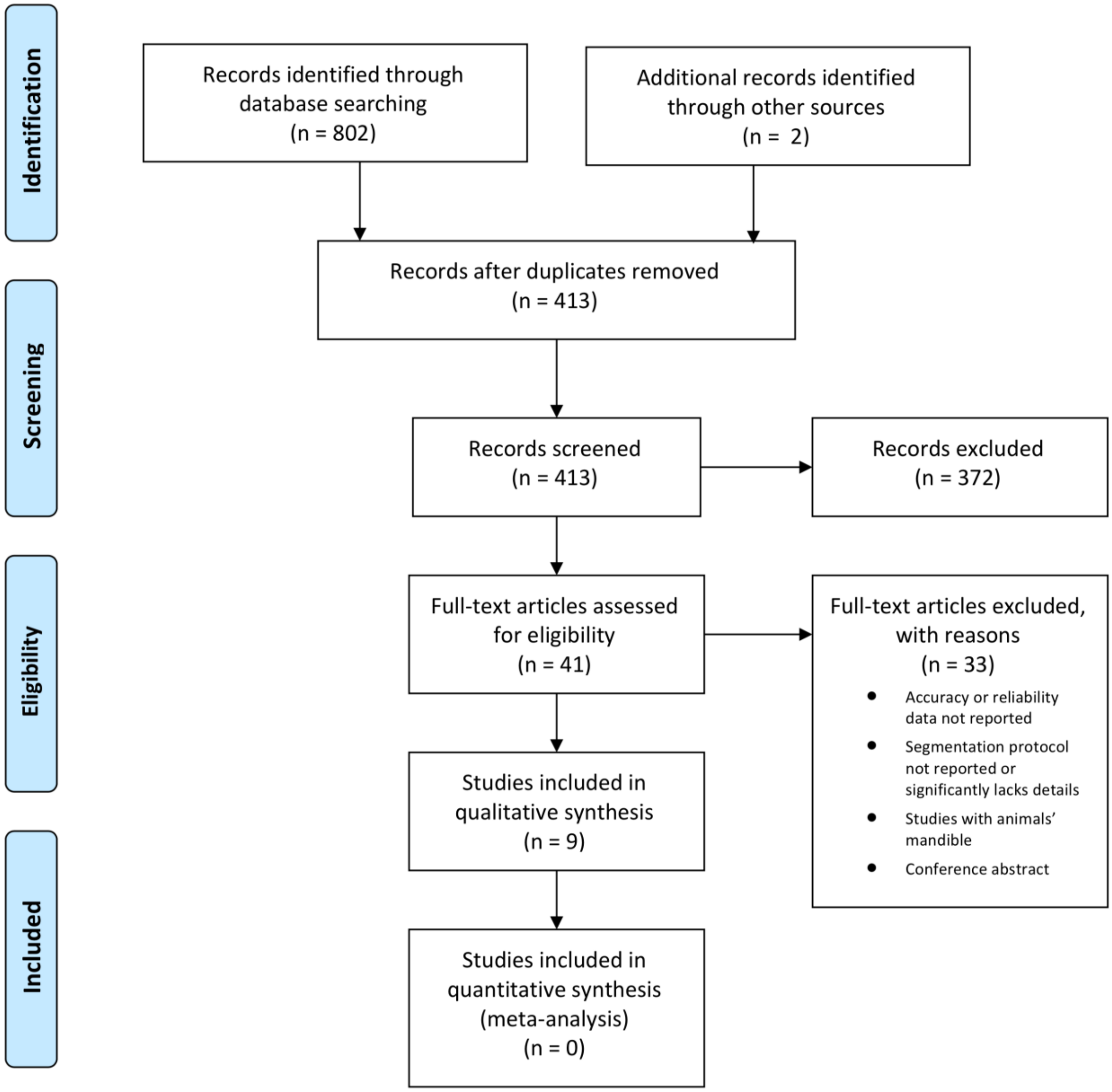

Figure 2.1: PRISMA Flow diagram of the article selection process

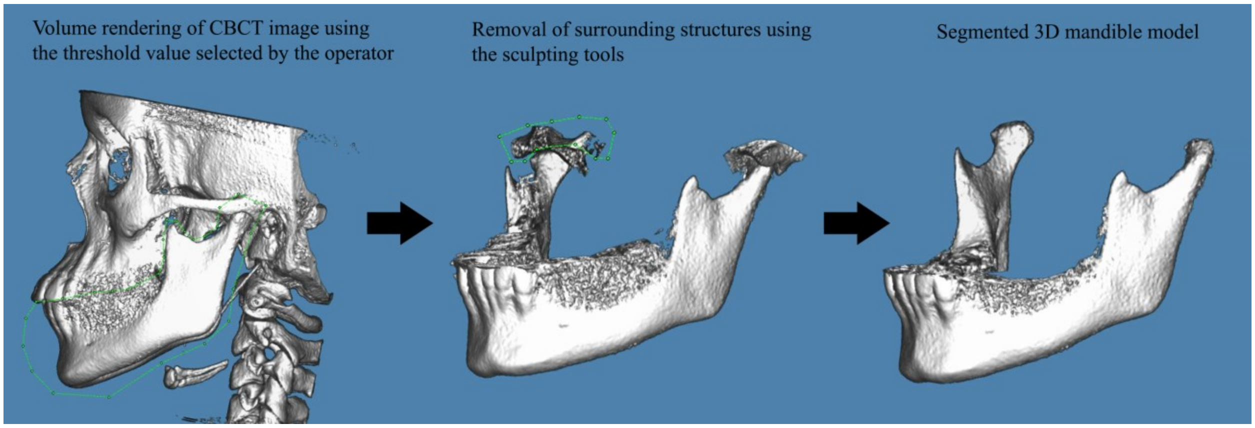

Figure 2.2: Schematic illustrations of threshold-based volume segmentation using Dolphin (Dolphin Imaging and Management Systems, Chatsworth, CA) software's volumetric sculpting tools

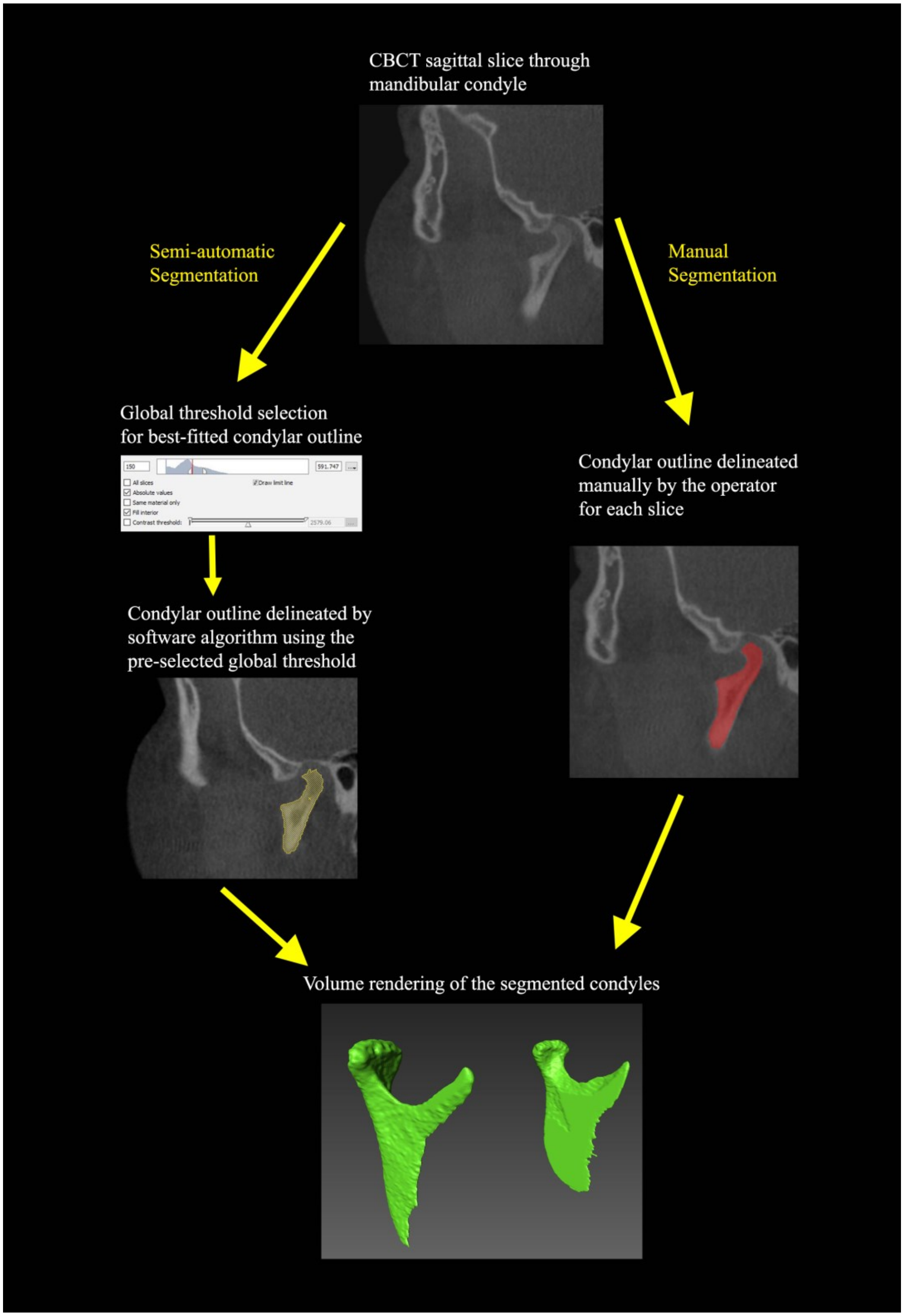

Figure 2.3: Steps illustrating semi-automatic segmentation (left) and manual segmentation (right) of mandibular condyles from CBCT image

Table 2.1. Summary of the study characteristics and data collected from the included studies

Authors (year)	Sample type and size	Imaging Modality and Protocol	Segmentation protocol (methods and software)	Measured parameters (eg. Volume, linear and angular measurements)	Reliability and Validation method	Reliability and Validation data
Xi et al. (2014)[24]	2 males, 8 females, randomly selected from CBCT database for oral and maxillofacial surgery patients	CBCT FOV: 16x22cm voxel size: 0.4mm scan time: 20s	Semi-automatic Segmentation: -Semi-automatic segmentation algorithm based on 3D region growing implemented in the Matlab software. Seed point selected by the observer once every five slides.	-Condylar volume (most inferior point of sigmoid notch identified and the plane through this point parallel to the Frankfurt horizontal plane determined as the inferior limit) -Median surface distance error	SG1- extensive clinical experience with segmentation of condyles based on CBCT data SG2-little clinical experience VG-Validation group used from previous study (used CBCT)	**Reliability** Mean differences in condylar volume: 18mm^3 between VG and SG1; 13.4 mm^3 between VG and SG2; 31.4 mm^3 between SG1-SG2, ICC of 0.97 within SG group Dice coefficients between three groups: 0.94-0.98 Average median surface distance error between VG-SG1 and VG-GS2 is 0.13mm
Engelbrecht et al. (2012)[18]	7 cadaver heads	CBCT FOV: 17cm; voxel size: 0.3mm	Threshold-based volume Segmentation: - Commercial segmentation done by experienced 3D technician (CS) -Clinician with 3 years experience in 3D CBCT imaging and segmentation using SimPlant Ortho Pro software sculpting tool (DS)	-Condyle width measurement (distance between right points condylion laterale and condylion medialie)	-Accuracy data presented -Laser surface scanned dry mandible after removal of soft tissue from cadaver heads used as a reference	**Reliability** Inter-observer agreement: ICC=0.97-1.00 (for all linear measurements in mandible) **Accuracy** Mean deviation of condyle width from the reference model 1.28±0.5 mm – 1.44±0.6 mm (CS) 1.79±1.17 mm - 1.93±0.91mm (DS)
Fourie et al. (2011)[28]	7 cadaver heads	CBCT FOV: 17cm; voxel size: 0.3mm	Threshold-based volume Segmentation: -Commercial segmentation done by experienced 3D technician (CS) -Clinician with 3 years experience in 3D CBCT imaging and segmentation using SimPlant Ortho Pro software sculpting tool (DS)	-Point-based landmarks including condylion laterale, mediale, condylion anterior, posterior, superior points	-Accuracy data presented -Laser surface scanned dry mandible after removal of soft tissue from cadaver heads used as a reference	**Reliability** Agreement between repeated measurement: ICC=0.98 Average method error = 0.05 (95% CI: 0.03-0.07) **Accuracy** mean linear deviation of landmarks location from the reference model -Condylion laterale: <0.75±0.06mm(CS); <1.03±0.27mm(DS) -Condylion mediale: <0.18±0.36mm(CS); <0.83±1.52mm(DS) -Condylion anterior: <0.43±0.27mm(CS); <1.27±0.58mm(DS) -Condylion posterior: <0.73±0.17mm(CS); <1.16±2.32mm(DS) -Condylion superior: <0.92±0.81mm(CS) <1.72±1.99mm(DS)
Bayram et al. (2012)[25]	5 dry mandibles containing nine condyles	CBCT FOV: 15cm voxel size: 0.2mm scan time: 10.8s	Threshold-based volume segmentation followed by manual segmentation: -Condyles isolated using various sculpting tools after making 3D reconstructions using Kodak Dental Imaging software; subsequently, the condylar volume sectioned in the sagittal plane with 0.3mm thick sections and 0.9mm intervals, and three observers independently manually adjusted density and contrast values to determine condyle borders	-Condylar volume (imaginary line created tangent to the distal slope of the coronoid process and part of mandible superior to this line determined for condylar volume)	-Volume of each reconstructed CBCT condyle calculated -Physical volume of the condyles calculated using water displacement method as the gold standard	**Reliability** -Pearson correlation among three observers in segmentation of condyles from CBCT: 0.990-0.997 **Accuracy** -No statistically significant differences between the physical measurements and observers' measurements (p>0.05) -No numerical results reported

Nicolielo et al. (2017)[21]	20 patients who underwent bimaxillary surgery 1 dry mandible	-MSCT FOV: 50x50cm slice thickness: 500µm 120kVp, 250mA, U75 kernel -CBCT FOV: 23x26cm voxel size: 0.4mm 96kVp, 5mA -Micro-CT Voxel size: 35µm 100kVp, 100µmA, 1mm aluminum Scan time: 9min	Semi-automatic Segmentation: -Semi-automatically delineated by using a global threshold algorithm using Mimics medical image processing software, and the bone threshold values were visually confirmed by the observer	-Condylar mineralized bone volume (standardized sphere with its border passing through the lowest point of mandibular notch created around the condyle and the condylar bone volume inside the sphere calculated)	-Intra-observer reliability and inter-observer reliability between two experienced radiologists on 10 randomly selected patients presented -Accuracy data presented by taking micro-CT (gold standard), CBCT and MSCT of one dry human mandible	**Reliability** Intra-observer: ICC=0.96 for MSCT; ICC=0.73 for CBCT Inter-observer: ICC=0.93 for MSCT; 0.60 for CBCT **Accuracy** (condylar mineralized bone volume) Micro-CT: 1167mm^3 MSCT: 1834mm^3 CBCT: 1732mm^3 Part-comparison analysis exhibited overestimation of the bone segmentation of 0.3 mm±0.2 mm for MSCT and 0.4 mm±0.3 mm for CBCT
Geiger et al. (2014)[22]	9 TMJ condyles from 6 cadaveric mandibles	-3D UTE MRI voxel size: 104micrometer -Micro-CT voxel size: 18micrometer	UTE MRI manual segmentation: done manually by two trained observers using open-source image processing software (ImageJ)	-Bone Gaussian curvature -Mean curvature -Bone volume	-Validation reported by using microCT scanned image as the gold standard	**Reliability** MRI vs MRI (inter-observer) -% deviation 1.8±1.8% for Gaussian curvature 0.6±0.5% for mean curvature 2.0±0.3% for bone volume -ICC ranged from 0.997-0.999 **Accuracy** MRI vs microCT: -% deviation from reference 5.7±6.5% for Gaussian curvature 5.0±7.1% for mean curvature 6.6±6.2% for bone volume -ICC 0.892 for Gaussian curvature 0.893 for mean curvature 0.972 for bone volume
Xi et al. (2013)[23]	10 adult patients with mandibular retrognathia undergone BSSO surgery	-CBCT FOV: 16x22cm voxel size: 0.4mm scan time: 20s	Semi-automatic Segmentation: -Semi-automatic segmentation algorithm based on 3D region growing implemented in the ImageJ software. Seed point selected by the observer once every five slides.	-Condylar volume (most inferior point of sigmoid notch identified and the plane through this point parallel to the Frankfurt horizontal plane determined as the inferior limit) -Surface distance maps	-Intra-observer reliability and inter-observer reliability presented -No accuracy data in comparison to gold standard was presented	**Reliability** Intra-observer mean differences in condylar volume = 8.62±24.67mm^3 Inter-observer mean differences in condylar volume = 6.13±14.16mm^3 Intra-observer mean discrepancy in distance maps of the condylar surface = 0.22mm Inter-observer mean discrepancy in distance maps of the condylar surface = 0.13mm
García-Sanz et al. (2017)[26]	6 cadaver heads	-CBCT FOV: 18x20cm voxel size: 0.2mm scan time: 18s	Threshold-based volume Segmentation: -Volumetric CBCT data reconstructed and condyles isolated using Dolphin Imaging software's sculpting tool using the surface models obtained from 3D scanner as reference	-Condylar volume (inferior plane of the segmentation defined as condylar neck) -Linear measurements from anatomical landmarks	-Intra-observer reliability and inter-observer reliability presented -Accuracy data presented using dry condyles after soft tissue removal	**Reliability** Volume: Intra-observer and inter-observer reliability, ICC=0.99 Linear measurements: Intra-observer, ICC=0.98~0.99, Inter-observer, ICC=0.95~0.99 **Accuracy** *(Mean differences between CBCT and reference)* Volume: -0.010±0.095 cm^3 Linear: -0.004±0.027~0.019±0.084mm
da Silva et al. (2018)[27]	23 condyles = 20% of 144 condyles used for volumetric assessment following orthognathic surgery	-CBCT FOV: 23x17cm Voxel size: 0.4mm Scan time: 40s	Semi-automatic segmentation using ITK-SNAP 3.0.0 segmentation software using region-growing algorithm following the volumetric cropping of condyle at VOI using Dolphin imaging software	-Condylar volume (inferior limit defined at a plane at the most inferior point of sigmoid notch with the skull oriented at Frankfurt horizontal plane parallel to horizontal axis)	-Intra-observer reliability -No accuracy data presented	**Reliability** Volume: Intra-observer reliability: ICC=0.94

Table 2.2. Summary of selected studies using the quality of assessment tool for diagnostic accuracy studies (QUADAS-2)

Study	Risk of Bias				Applicability Concerns		
	Patient selection	Index Test	Reference Standard	Flow and Timing	Patient selection	Index Test	Reference Standard
Xi et al. (2014)[24]	Low	Unclear	High	Low	Low	Low	High
Engelbrecht et al. (2012)[18]	High	Low	Low	Low	Low	Low	Low
Fourie et al. (2011)[28]	High	Low	Low	Low	Low	Low	Low
Bayram et al. (2012)[25]	High	Unclear	Low	Low	High	Low	Low
Nicolielo et al. (2017)[21]	High	Unclear	Low	Low	High	Low	Low
Geiger et al. (2014)[22]	High	Unclear	Low	Low	Low	Low	Low
Xi et al. (2013)[23]	Low	Unclear	High	Low	Low	Low	High
García-Sanz et al. (2017)[26]	Low	Unclear	Low	Low	Low	Low	Low
da Silva et al. (2018)[27]	Low	Unclear	High	Low	Low	Low	High

*Bias reported in high risk, low risk, or unclear

Table 2.3. GRADE's summary of findings. Accuracy and Reliability of three-dimensional condylar segmentation techniques. Meta-analysis was not performed due to the heterogeneity of imaging modalities and methods. A qualitative descriptive analysis was performed.

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)
Threshold-based Segmentation Accuracy	40 (3 RCTs)	⊕⊕⊕◯ MODERATE [a]
Threshold-based Segmentation Reliability	12 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]
Manual Segmentation Accuracy	22 (2 RCTs)	⊕⊕◯◯ LOW [c,d]
Manual Segmentation Reliability	22 (2 RCTs)	⊕⊕◯◯ LOW [c,d]
Semi-automatic Segmentation Accuracy	60 (2 RCTs)	⊕◯◯◯ VERY LOW [e,f]
Semi-automatic Segmentation Reliability	60 (3 RCTs)	⊕⊕⊕◯ MODERATE [f]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. CBCT Volume threshold-based segmentation accuracy results differ based on the experience of the operator
b. Segmentation completed while the operator had access to the reference model
c. Sample size too small
d. Different imaging modalities (CBCT and UTE MRI) with limited information provided on the UTE MRI segmentation technique
e. Inadequate reference standard
f. Different condylar volume of interest parameters: one study assessed surface condylar volume while the other assessed mineralized condylar bone volume

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Chapter 3: Accuracy and reliability of semi-automatic mandibular condylar segmentation from CBCT images

3.1 Introduction:

Advancement of three-dimensional imaging modalities have enabled clinicians and researchers to analyze various craniofacial structures to the extent that was not possible with two-dimensional radiographic images[1]. Of the available three-dimensional imaging modalities, cone-beam computed tomography (CBCT) has become increasingly popular in orthodontics with its ability to visualize and perform accurate linear measurements on three-dimensional skeletal models[2] while exposing the patients to a relatively low radiation when compared to conventional CT scan[3]. The ability to assess the dentofacial structures in three-dimensions using CBCT images has become one of the important adjunctive diagnostic tools in helping clinicians establishing accurate orthodontic diagnosis and treatment plans[1] .

Comprehensive assessment of a particular dentofacial structure from a CBCT image often requires an accurate and reliable segmentation to isolate the structure[4] . Mandibular condylar segmentation from CBCT images possess more difficulty in accurate segmentation when compared to other osseous structures[4] . Engelbrecht et al. suggests the relatively less dense osseous structure of mandibular condyle, various superimposing surrounding structures and close proximity to temporomandibular disc as probable reasons for difficulty in segmenting the mandibular condyle[5] . Furthermore, the varying bone densities and composition within the condylar structure and between individuals further complicates the segmentation process, where bone density and its resulting absorption value significantly impacts both its accuracy and reliability[6] .

Several condylar segmentation methods have been proposed and studied as discussed in Chapter 2. Volume threshold-based segmentation is most widely used and exhibits high accuracy and reliability when completed by an experienced technician or clinician; however, the result differs when completed by an operator with a limited experience[4] . It is this operator subjectivity in volume threshold-based segmentation that other segmentation methods aim to minimize. The manual segmentation technique achieves this objective by having the operator outline the condylar border for each CBCT slice[7]. Although the method described demonstrated high accuracy when compared to the physical measurements done on cadaveric mandible, this is a tedious process, likely inhibiting clinical viability when multiple condylar segmentations are required[7] .

Semi-automatic segmentation method is a similar method to manual segmentation with some level of automated process completed by the software using computer algorithm. In previous studies employing semi-automatic segmentation, the operator selects the global threshold range and the computer algorithm determines the volume of interest based on the pre-selected grayscale cut-off values[8-10]. Past studies demonstrated the efficiency and reliability of this method but lacked a comparison to a validated reference model[8-11].

To the best of our knowledge, there has not been any study examining both the reliability and accuracy using the validated physical model measurement of semi-automatic condylar segmentation technique with respect to condylar volume. The objective of this study is to develop and validate semi-automatic condylar segmentation technique from CBCT images.

3.2 Materials and Methods:

Fabrication and scanning of mandibular models

A well-preserved dry human skull was obtained from the Department of Orthodontics, University of Alberta. Ethics approval was not required as the acquired dry human skull was an anonymous biological material involving no identifier. Its mandible was isolated from the dry skull and scanned using i-CAT (i-CAT, Imaging Sciences International, Hatfield, PA) at 120kVp, 7mAs, 9.1 seconds image timing, and 0.25mm voxel size. The obtained CBCT 3D volume in Digital Imaging and Communications in Medicine (DICOM) format was converted to stereolithography (STL) file format using Dolphin imaging software (Dolphin Imaging and Management Systems, Chatsworth, CA). Three mandible models were 3D-printed using Objet Eden350V printer (Stratasys, Eden Prairie, MN) with Vero gray material at a resolution of 16 microns in the Z-axis. Six radiopaque markers were placed for each 3D-printed model at following locations: most superior point of coronoid

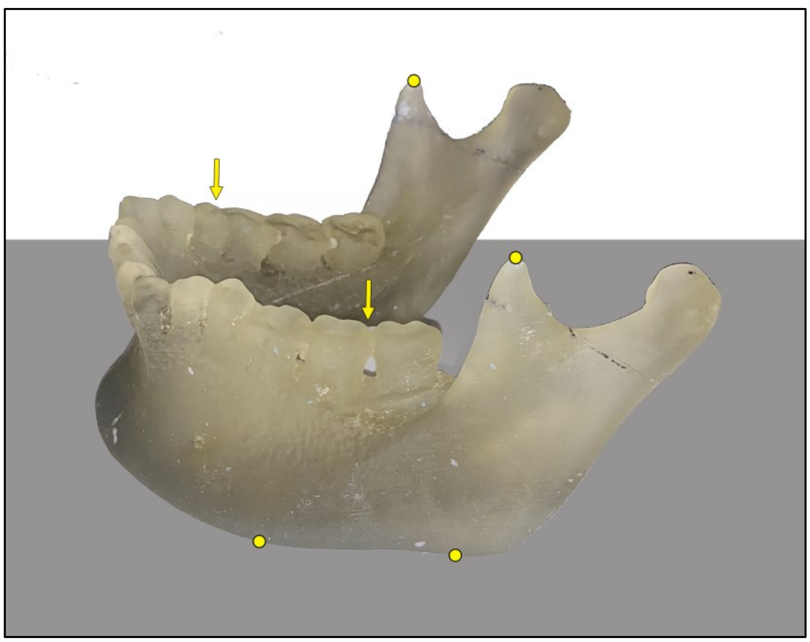

Figure 3.1: 3D-printed mandible with six radiopaque markers denoted by yellower circles and arrows

processes, right mental foramen, and three tripod areas along the inferior border of the mandible physically contacting the surface when model is placed on a flat surface (Figure 3.1).

For CBCT scans, 3D printed mandible models with the corresponding study skull were placed into a double layered Plexiglass box with water-filled compartments situated between two layers to simulate soft tissue attenuation (Figure 3.2).

Figure 3.2: 3D-printed mandible with the corresponding study skull in a double layered Plexiglass box

CBCT scanning was performed using i-CAT following the normal clinical full field of view CBCT protocol at 0.3mm voxel size, 8.9 seconds, and 640x640mm field of view to replicate the clinical scenario rather than a highest possible resolution, which is not commonly performed due to the increased patient radiation exposure. Images were then converted to DICOM (Digital Imaging and Communications in Medicine) format.

Semi-automatic segmentation of CBCT image using Avizo software

DICOM file of the scanned CBCT images was imported and analyzed using the Avizo software (Standard Edition, Version 9.1, Mercury Computer Systems Inc., Chelmsford, Mass). Avizo software was used over Dolphin, though it is one of the commonly used software in clinical settings to assess CBCT volume, because the Avizo software allows for the segmentation slice by slice and maintaining the raw voxels without any smoothing effect, of which may influence the resulting segmented condylar volume, whereas Dolphin's segmentation function is limited to the threshold-based volume segmentation using sculpting tools. Although other potentially more user-friendly segmentation tool software are available, the Avizo software's comprehensive feature sets allow all necessary analyses to be completed within one software rather than using multiple software. Once the Isosurface volume of scanned CBCT images is established, using the magic wand tool in segmentation window, threshold range is adjusted by the operator for the best-fit condylar outline in an axial slice through the condyle (Figure 3.3). Thereafter, a seed-point was selected by the operator for every axial slices through the condylar region. When an obvious addition of surrounding structures outside the volume of interest or omission of condylar structure occurred due to a diminished contrast in gray value, threshold range was manually adjusted or limiting line was used to correct the area of interest selection. A new surface model from the segmented volume was constructed with zero surface smoothing.

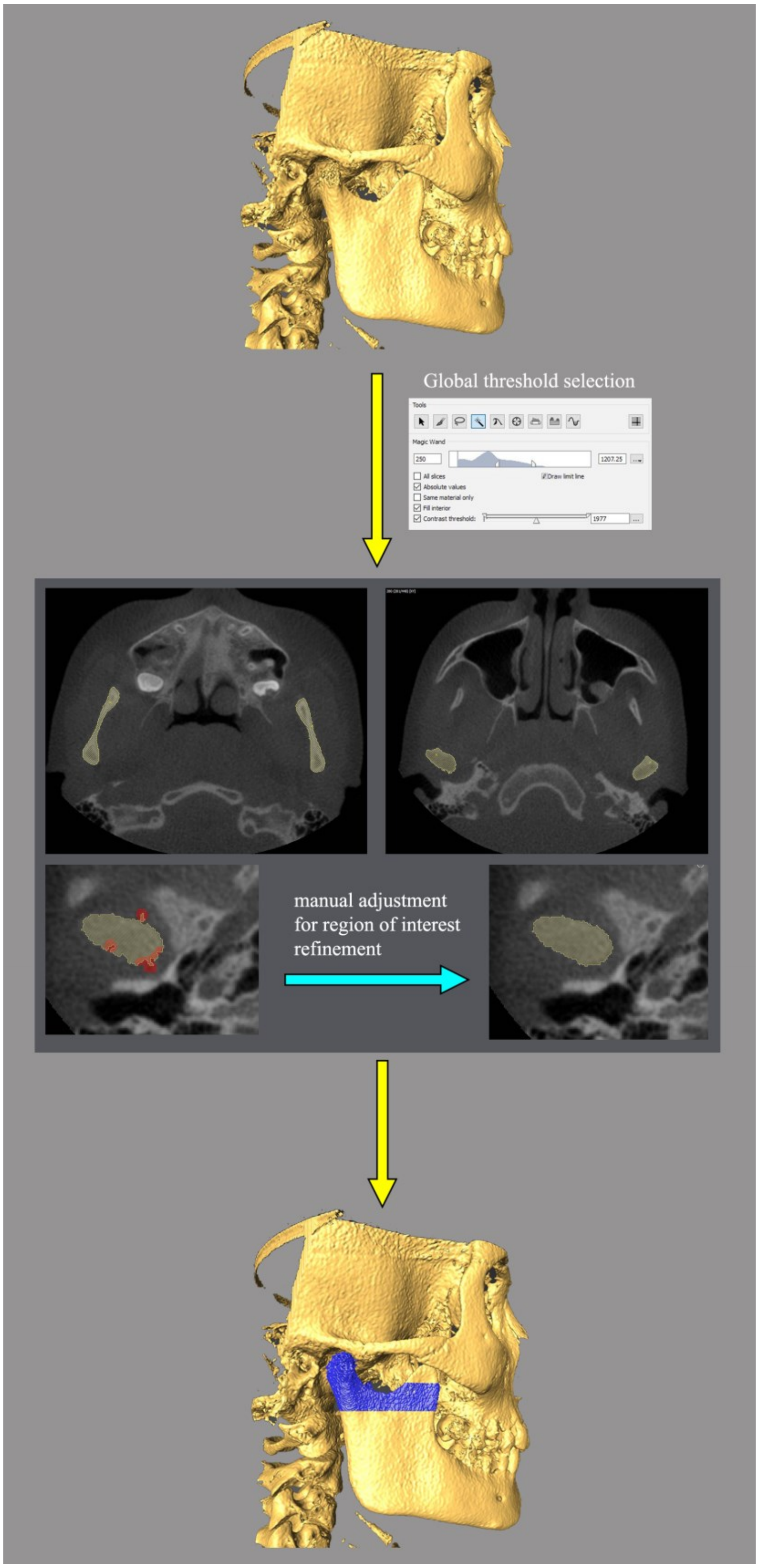

Figure 3.3: Schematics showing steps for semi-automatic segmentation of mandibular condyle

Volume of interest (VOI) determination in CBCT

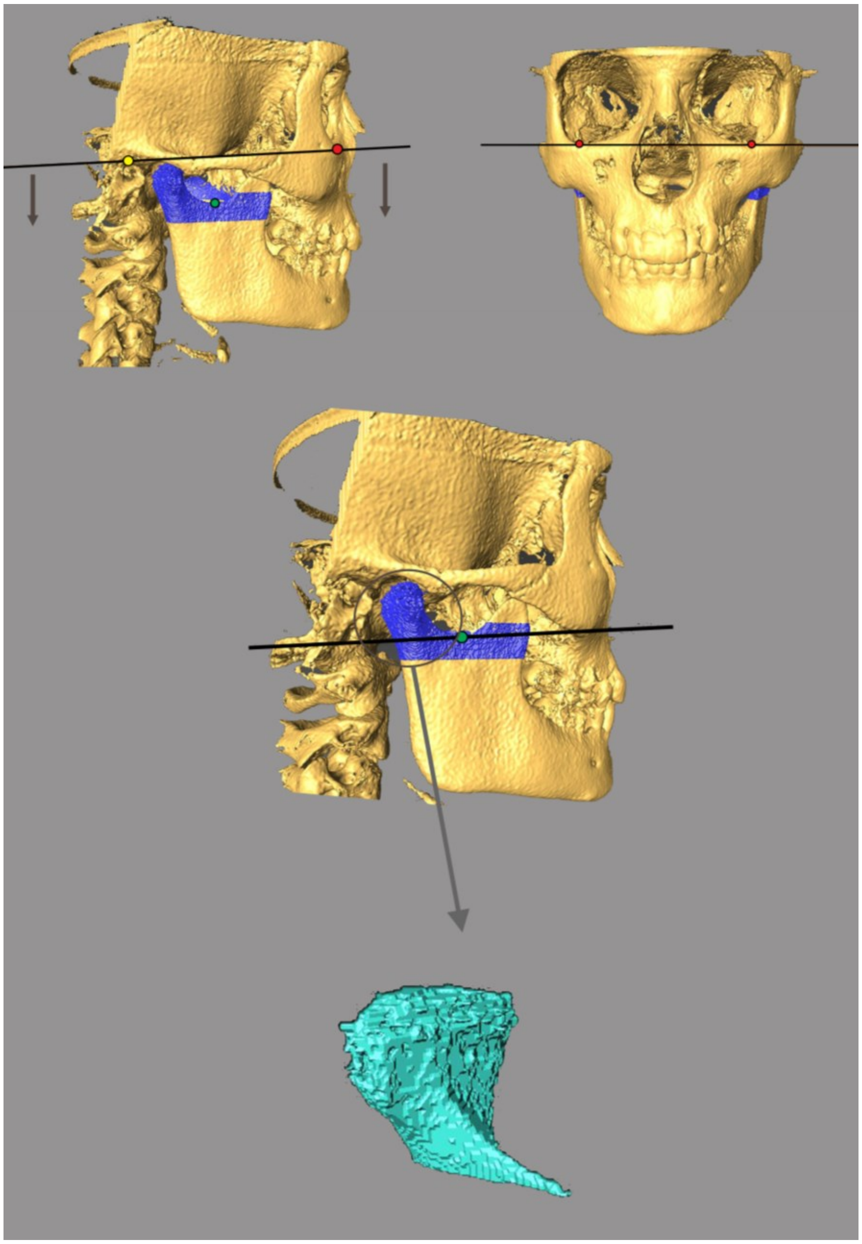

Figure 3.4: identification of Frankfurt 3D plane (top); translation of Frankfurt plane inferiorly to the most inferior point of sigmoid notch (middle); segmented condylar volume after determining VOI (bottom)

A three-dimensional Frankfurt-horizontal (FH) plane was constructed using three landmarks from craniofacial structure (Figure 3.4); left and right infraorbitale and porion (side that is closest to the condyle to be assessed). Condylar volume of interest (VOI) was determined by translating the FH plane inferiorly until it reaches the most inferior point of sigmoid notch, and the resulting condylar volume superior to this plane was analyzed for volume calculation. This process of CBCT condylar segmentation and VOI determination was repeated by the same operator three times, a week apart each for all six condyles, in a random order each time.

VOI determination in physical model

The inferior plane of condylar volume of interest, which is parallel to the FH plane at the most inferior point of sigmoid notch was transferred to the 3D-printed mandible model utilizing 12 linear distance measurements on each condyle using different radiopaque markers and landmarks (Figure 3.5). Reference markers included six radiopaque markers (red circles in Figure 3.6) and two anatomical marks (green circles), the most superior point condylar heads, per mandible model. To locate the most superior point of condylar head, three-radiopaque markers along the inferior border of the physical model were used to calibrate the orientation of mandible in CBCT volume. Subsequently, the most superior point of condyles was identified in CBCT volume and in physical models with the calibrated mandibular orientation.

Three points were identified along the inferior border of the VOI in CBCT volume, one in the anterior aspect of coronoid process, one at the most inferior point of sigmoid notch, and one in the posterior aspect of condylar neck (blue circles in Figure 3.5). Linear distances from each of the four reference markers to each of the three points along the inferior border of VOI were

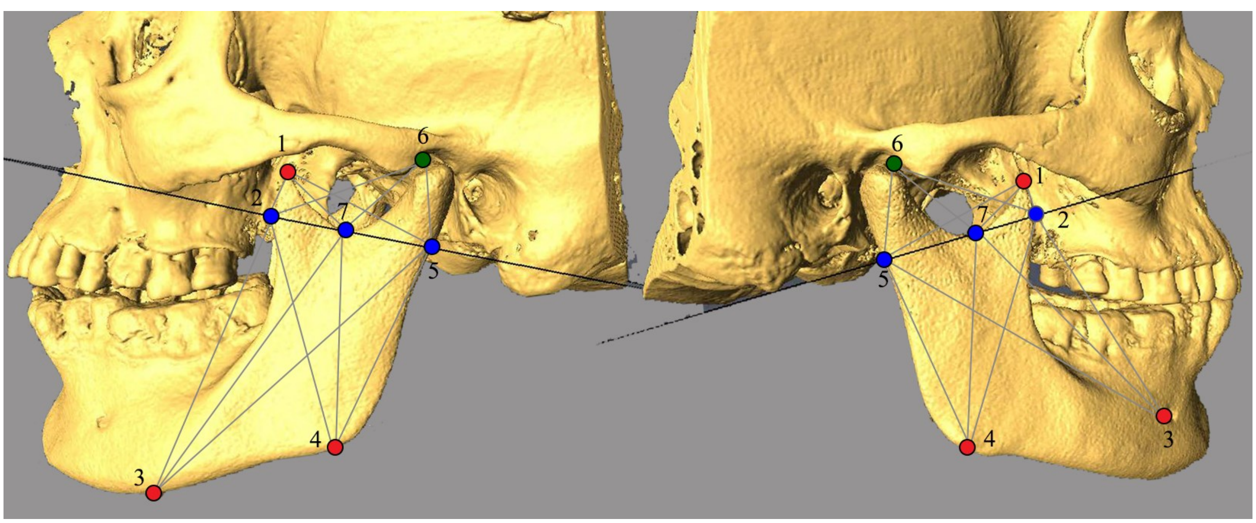

Figure 3.5: Reference markers including six radiopaque markers (red) and two anatomical landmarks, most superior point of condyle in calibrated mandibular orientation (green); Three points along the inferior border of VOI (blue); 12 linear measurements between reference markers and the three points defining the inferior border of VOI (grey lines); all points numbered for identifying measurements

measured in CBCT volume, totalling 12 linear measurements per condyle. Using the reference markers found in physical model and the linear measurements from CBCT volume, three points along the inferior border of VOI were identified and marked in the physical models using a digital caliper. Linear measurements between the identified points and reference markers on all six physical condyles were validated using FaroArm (FARO, Lake Mary, FL) by comparing to those obtained from CBCT image.

Condylar volume measurement in physical mandible models

Using the validated three marked points, the inferior border of VOI was marked and scribed on the physical models with 0.5mm depth indentation using a high-speed metal disc. Three impressions of each of physical condyles were obtained using the lab putty (Coltene/Whaldent Inc., Cuyahoga Falls, OH) and the excess material beyond the scribed plane was removed. Each impression was measured on an analytic balance (sensitivity=0.1mg) before and after being filled with the distilled water at 23°C (Density=0.9982 g/cm3). The final volume of the physical model of condyle was calculated using the weight difference and known density of water.

Simulation of errors in determining VOI

In order to assess the effect of operator errors in determining the inferior plane of VOI on the final volume of the condyle, the Frankfurt plane was rotated by the interval of 1 degree up to 3 degrees in both clock-wise and counter-clockwise direction and each plane was translated until the most inferior point of the sigmoid notch and the final condylar volume was calculated for each interval (Figure 3.6). Furthermore, the inferior plane was translated up to 0.9mm with the interval of 0.3mm superiorly and inferiorly and the resulting condylar volumes were calculated. This process was repeated for all 6 condyles.

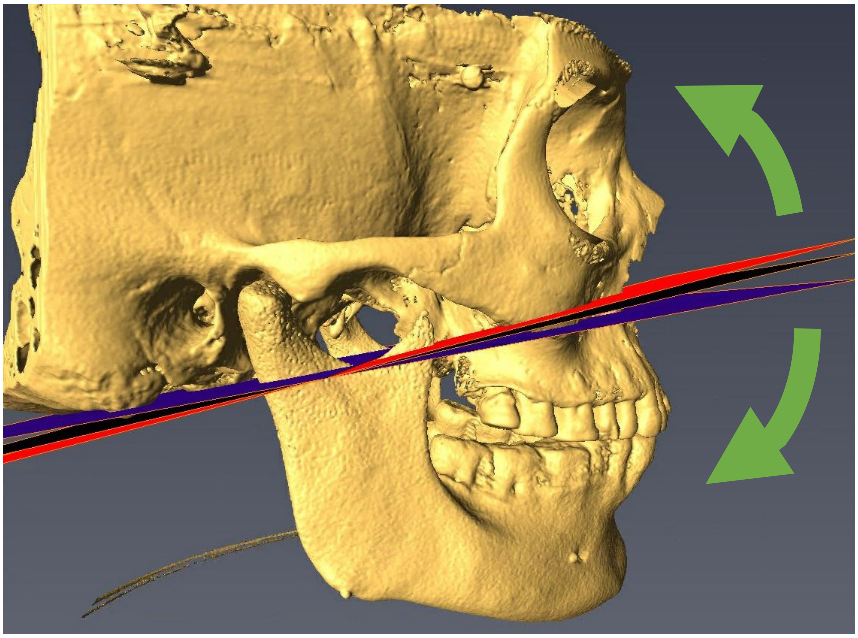

Figure 3.6: Original inferior plane of VOI (black) rotated 1-degree clock-wise and counter-clockwise to simulate the operator error in identifying 3D Frankfurt plane

Statistical Analysis:

Statistical analysis was performed using IBM SPSS Statistics software (version 23.0 for Mac, IBM Corp., Armonk, NY). A significant level of α=0.05 was chosen for all statistical analyses. Intraclass correlation coefficient (ICC) was used to compare the linear measurements values obtained from CBCT images to those obtained from the 3D printed mandible using FaroArm. Assessment the intra-rater reliability and the accuracy of condylar volume measurements using the semi-automatic segmentation compared to the physical volume was completed using ICC. Interpretation of ICC values were done per guidelines outlined by Koo and Li study[12] .

- ICC above 0.90: Excellent agreement
- ICC above 0.75: Good agreement
- ICC between 0.51 and 0.74: Moderate agreement
- ICC below 0.50: Poor agreement

3.3 Results:

Comparison of linear measurements obtained from CBCT images to those obtained from the 3D printed models using FaroArm with percentage error for each measurement is summarized in Table 3.1. The mean difference of linear distances between the two measurement modalities was -0.51±0.94mm. ICC result shows an excellent agreement between the two modalities at 0.998 [0.997, 0.999].

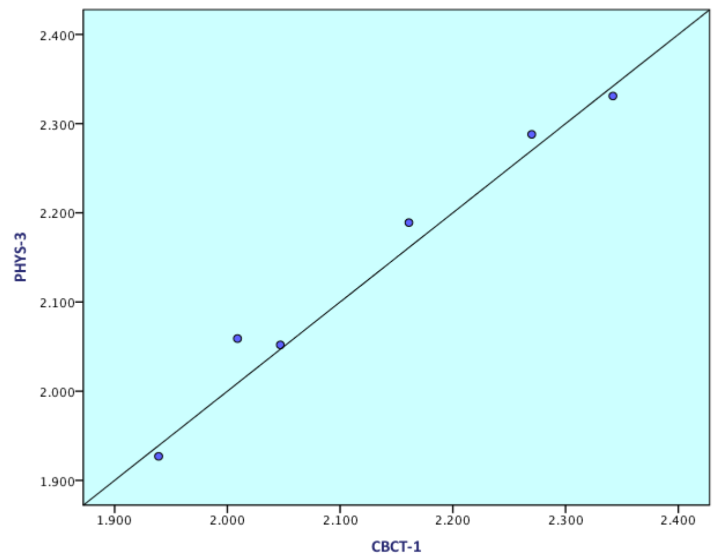

Figure 3.7: Plot presenting the agreement between the condylar volumes obtained from physical models and those obtained from CBCT using semi-automatic segmentation technique

ICC values of the three sets of volume measurements each from physical condylar models and CBCT images using semi-automatic segmentation technique from the same observer for intra-rater reliability is shown in Table 3.2. In terms of the intra-rater reliability for both physical and CBCT methods, the average error differences and standard deviations among the three sets of measurements were calculated as well: -0.89±25.42mm^3 for the physical volume and 4.56±17.17mm^3 for the CBCT volume. The mean difference between the physical volume and CBCT image volume was 4.83±11.89 mm^3. ICC value demonstrating the agreement between the resulting condylar volumes from the CBCT images using semi-automatic segmentation technique to those obtained from the physical condylar models is 0.988 (Table 3.2), and its corresponding plot is presented in Figure 3.7.

The sensitivity analysis (Table 3.3) demonstrates the change in resultant condylar volume in percentage difference and absolute difference values when the segmentation plane is rotated within sagittal plane and translated along z-axis. Mean average of absolute difference change in condylar volume per 0.3mm translation is 25.49±6.92mm^3 in inferior direction and -29.86±10.81mm^3 in superior direction. In regard to the rotation, the result showed 13.86±9.92mm^3 when segmentation plane rotated counter-clockwise by 1 degree and -12.67±3.08mm^3 when rotated clockwise by 1 degree. The graphs exhibit generalized linear relationship in changes in resultant condylar volume for both translation and rotation of segmentation plane.

3.4 Discussion:

Although there are various methods of segmenting mandibular condyles, which has been shown to be less reliable and accurate structure to segment compared to other craniofacial structures, each with its own advantages and disadvantages, semi-automatic segmentation technique showed a promise in effective and relatively convenient method of segmenting and analyzing condyles[8,9] . The results from this study demonstrates an excellent intra-rater reliability (ICC=0.990) and an excellent agreement between the condylar volume results obtained from the physical models and those obtained from CBCT images using the developed semi-automatic segmentation technique (ICC=0.988). This not only supports the high reproducibility of this segmentation technique, which has been shown in previous studies[8,13], but also reveals that it exhibits an excellent accuracy in assessing condylar volume when compared to the reference values, which has not been demonstrated before. The intra-rater reliability of the physical volume determination has a wider confidence interval [0.748, 0.989] than that of CBCT method and is explained by the possible errors introduced by the dimensional stability of the impression material and human errors in physical cutting along the segmentation line.

CBCT 3D model has an advantage of allowing the operator to conveniently select and move different planes through the specified anatomical landmarks[14] . This advantage aids in establishing a particular plane and thereby the condylar volume of interest utilizing Frankfurt plane. Contrarily, this is very difficult to perform in physical skull without out highly specific measurement tools. Accurate and reliable method to transfer this plane established in CBCT images to the physical model is essential to accurately compare the resulting condylar volumes. Using the radiopaque markers placed on the mandible model prior to CBCT scan, several linear measurements were calculated from the markers to the points along the segmentation plane. Once the plane has been initially transferred and marked using a digital caliper on the physical model, the location of the plane compared to the that of CBCT image was validated by utilizing FaroArm to quantify the linear distances between the points. FaroArm, which uses laser stripe triangulation, has been stated to have a point repeatability of 0.023 to 0.064mm, which is far below the voxel size of 0.3mm[15]. ICC result (0.998) supports an excellent agreement between the distances among the points measured using Avizo software from CBCT images and those measured using FaroArm while the mean difference found (-0.51±0.943mm) was slightly below that of two voxels size. This suggests that the method described to transfer the segmentation plane defined in CBCT volume to the 3D-printed mandible model is highly correlated to each other with minimal mean difference that is likely to be clinically irrelevant.

Accurate volume analysis requires a precise establishment of volume of interest[16]. In terms of mandibular condyle volume analysis, the reproducibility of the inferior plane segmenting the mandibular condyle has a substantial impact on the resultant condylar volume. The method presented in this study relies on a reliable determination of skeletal Frankfurt horizontal plane using three landmarks: left and right orbitale and left or right porion. Although the skeletal Frankfurt horizontal plane has been used as a reference plane for analysis from CBCT image volume[8,9,11,17] , sensitivity analysis was performed to observe the effect of possible operator error in locating landmarks or establishing the Frankfurt horizontal plane. First, the pre-determined inferior plane of volume of interest was translated by one voxel size interval (0.3mm) and the difference found ($25.49 \pm 6.92 mm^3$) was considerably large than the difference found when the plane was rotated by 1 degree ($13.86 \pm 9.92 mm^3$). Pure translational error is less likely to occur because once the Frankfurt plane is determined, the locating and moving the plane to the most inferior point within sigmoid notch is reasonably reproducible using the software. It is considerably more probable that the human errors are made while locating the points to determine Frankfurt plane. Mohsen et al. described the reproducibility of landmarks constituting Frankfurt plane[18] . Their study revealed that the porion z-axis coordinate exhibited the lowest inter-observer and intra-observer reliability relative to other axes of porion coordinates and all axes of orbitale coordinates. This is further supported by the results published by Hofmann study[19]. This relatively low reproducibility in z-axis coordinate of porion causes the changes in the rotation of the Frankfurt plane within sagittal plane thereby affecting overall condylar volume of interest. When the inferior segmentation plane was rotated by 1 degree, the mean difference in resultant condylar volume was approximately half of the change observed by one-voxel translation and less than 1.51% volume discrepancy. This 1-degree rotation of the inferior segmentation plane, using Pythagorean's theorem, equals to approximately 1.5mm vertical change in porion point in Frankfurt plane in a normal human cranium. This is well over the z-axis consistency of porion landmarks assessed by nine different assessors on CBCT volume of 0.59±0.42mm as demonstrated by Schlicher et al[20]. The same study also suggests that porion should be used for analysis of vertical and sagittal measurements but not for analysis consisting of transverse dimension due to a relatively high inconsistency in transverse dimension in locating porion. Result from this study suggests that possible human error in locating of porion, potentially less reliable landmark when establishing Frankfurt plane, has a minimal impact on the resultant condylar volume.

3.5 Conclusion:

Semi-automatic segmentation technique developed to segment mandibular condyle from CBCT image was highly reproducible. Condylar volume computed from the described segmentation technique was highly accurate when compared to the physical condylar volume measurements. Observer variability in locating landmarks constituting Frankfurt horizontal plane, which was utilized to determine condylar volume of interest, yielded minimal impact on the resultant condylar volume.

Table 3.1. Linear distance measurements obtained from CBCT images and from the 3D printed mandibular models using FaroArm in absolute values and the differences in percentage.

Mandible 1			
Points	**CBCT (mm)**	**FaroArm (mm)**	**%error**
2-1 (R)	9.42	9.77	3.57%
2-4 (R)	17.61	17.42	1.08%
2-6 (R)	34.94	36.53	4.35%
5-1 (R)	33.16	34.79	4.68%
5-4 (R)	21.50	20.69	3.89%
5-6 (R)	19.74	20.82	5.19%
7-1 (R)	63.08	62.74	0.55%
7-4 (R)	67.73	69.79	2.95%
7-6 (R)	76.25	77.81	2.01%
2-1 (L)	9.48	9.84	3.66%
2-4 (L)	16.44	16.51	0.44%
2-6 (L)	33.79	36.63	7.76%
5-1 (L)	33.98	33.34	1.92%
5-4 (L)	23.32	20.30	14.86%
5-6 (L)	20.80	21.04	1.13%
7-1 (L)	49.20	48.46	1.52%
7-4 (L)	46.43	46.95	1.12%
7-6 (L)	47.46	46.85	1.31%
Mandible 2			
1-2 (L)	9.20	9.43	2.39%
1-5 (L)	34.49	35.78	3.59%
1-7 (L)	17.91	17.92	0.07%
4-2 (L)	49.78	49.78	0.00%
4-5 (L)	47.04	48.73	3.46%
4-7 (L)	45.71	46.14	0.93%
6-2 (L)	32.95	33.88	2.73%
6-5 (L)	17.94	18.06	0.64%
6-7 (L)	19.68	19.40	1.47%
8-9 (R)	7.85	8.21	4.37%
8-12 (R)	33.66	35.03	3.90%
8-14	17.34	17.33	0.09%
11-9	49.37	50.53	2.29%
11-12	47.39	48.94	3.17%
11-14	46.56	47.14	1.24%
13-9	31.83	32.34	1.58%
13-12	18.30	19.08	4.09%
13-14	18.90	19.17	1.43%
Mandible 3			
1-2 (L)	8.72	8.80	0.90%
1-5 (L)	34.51	36.04	4.25%
1-7 (L)	16.96	17.09	0.75%

4-2 (L)	49.31	49.94	1.26%
4-5 (L)	44.58	45.15	1.27%
4-7 (L)	44.75	45.45	1.53%
6-2 (L)	32.93	33.90	2.86%
6-5 (L)	19.00	19.78	3.94%
6-7 (L)	20.50	20.63	0.61%
8-9	8.04	8.44	4.78%
8-12	15.09	15.86	4.82%
8-14	32.85	34.50	4.77%
11-9	50.31	50.39	0.16%
11-12	44.93	44.28	1.47%
11-14	43.65	45.87	4.85%
13-9	31.05	31.39	1.07%
13-12	19.62	20.48	4.21%
13-14	21.18	20.47	3.48%

Table 3.2. Intraclass coefficients values for the physical condylar models' volume determination, and semi-automatic condylar segmentation technique from CBCT images

	Intraclass Correlation	**95% Confidence Interval**	
		Lower bound	**Upper bound**
Physical	0.932	0.748	0.989
CBCT	0.990	0.959	0.999
Physical-CBCT	0.988	0.918	0.998

Table 3.3. Changes in the condylar volume resulting from translation and rotation of the inferior plane of VOI in percentage difference and absolute values

Changes	**Translation (%)**	**Rotation (%)**	**Translation (mm³)**	**Rotation (mm³)**
		Condyle_1R		
-0.9mm (-3deg)	2.76%	1.57%	56.71	32.19
-0.6mm (-2deg)	1.72%	0.74%	35.30	15.30
-0.3mm (-1deg)	0.88%	0.22%	18.03	4.51
0	0.00%	0.00%	0.00	0.00
+0.3mm (+1deg)	-1.65%	-0.52%	-33.98	-10.64
+0.6mm (+2deg)	-3.64%	-1.25%	-74.82	-25.75
+0.9mm (+3deg)	-4.56%	-1.72%	-93.67	-35.32
		Condyle_1L		
-0.9mm (-3deg)	5.19%	3.73%	99.63	71.70

-0.6mm (-2deg)	3.59%	2.66%	68.87	51.16
-0.3mm (-1deg)	1.77%	1.51%	33.96	28.97
0	0.00%	0.00%	0.00	0.00
+0.3mm (+1deg)	-1.06%	-0.49%	-20.43	-9.44
+0.6mm (+2deg)	-2.35%	-1.04%	-45.04	-20.02
+0.9mm (+3deg)	-3.59%	-1.60%	-68.94	-30.73
Condyle_2R				
-0.9mm (-3deg)	2.81%	1.80%	57.78	36.90
-0.6mm (-2deg)	1.90%	0.93%	39.09	19.19
-0.3mm (-1deg)	0.89%	0.15%	18.34	3.07
0	0.00%	0.00%	0.00	0.00
+0.3mm (+1deg)	-2.08%	-0.56%	-42.79	-11.47
+0.6mm (+2deg)	-3.72%	-1.16%	-76.54	-23.72
+0.9mm (+3deg)	-4.85%	-1.72%	-99.85	-35.28
Condyle_2L				
-0.9mm (-3deg)	4.85%	2.71%	93.98	52.46
-0.6mm (-2deg)	3.21%	1.94%	62.18	37.51
-0.3mm (-1deg)	1.47%	1.10%	28.53	21.23
0	0.00%	0.00%	0.00	0.00
+0.3mm (+1deg)	-1.06%	-0.59%	-20.50	-11.38
+0.6mm (+2deg)	-2.21%	-1.79%	-42.72	-34.62
+0.9mm (+3deg)	-3.98%	-1.92%	-77.08	-37.19
Condyle_3R				
-0.9mm (-3deg)	3.30%	1.86%	67.54	38.16
-0.6mm (-2deg)	2.02%	1.02%	41.50	20.92
-0.3mm (-1deg)	1.08%	0.67%	22.19	13.78
0	0.00%	0.00%	0.00	0.00
+0.3mm (+1deg)	-2.01%	-0.81%	-41.25	-16.58
+0.6mm (+2deg)	-3.59%	-1.70%	-73.63	-34.79
+0.9mm (+3deg)	-4.56%	-2.91%	-93.48	-59.69
Condyle_3L				
-0.9mm (-3deg)	4.18%	2.08%	81.57	40.70
-0.6mm (-2deg)	2.91%	1.20%	56.87	23.35
-0.3mm (-1deg)	1.63%	0.59%	31.89	11.61
0	0.00%	0.00%	0.00	0.00
+0.3mm (+1deg)	-1.03%	-0.84%	-20.20	-16.49
+0.6mm (+2deg)	-2.77%	-1.83%	-54.15	-35.71
+0.9mm (+3deg)	-3.97%	-2.89%	-77.43	-56.37

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Chapter 4: Condylar volume changes in growing patients treated with fixed Class II appliances using a semi-automatic mandibular condylar segmentation technique: A pilot study

4.1 Introduction:

The mandibular condyle is an essential center in the overall growth of the mandible[1] , thereby a crucial determinant of the antero-posterior position of the mandible[2] . For this reason, various types of functional appliances aim to take advantage of condylar growth and temporomandibular complex remodelling to maximize the overall mandibular length in Class II adolescent patients with retrognathic mandible[3-5]. However, the clinical effectiveness of these appliances continues to be controversial while the biomechanism has not been fully elucidated[6]. Multiple studies have shown that the treatment using Class II functional appliances, a Herbst appliance for example, affects all components of the temporomandibular joint complex including glenoid fossa, condyle, condylar position, and disc position[2,7-9]. In contrast to a large number of studies on condylar positional change in patients treated with functional appliance using both two-dimensional and three-dimensional imaging, a limited number of studies are available regarding the effect of fixed Class II appliances on the overall condylar volumetric change[10,11].

A Herbst appliance is a fixed functional Class II appliance (Figure 4.1) which aims to improve the anteroposterior relationship between maxilla and mandible through an orthopedic effect by maintaining the mandible positioned anteriorly[5,7,8]. Evidence suggests that this continuous anterior displacement of condyle triggers an adaptive response resulting in glenoid fossa remodelling[12] . Several studies suggest that the anterior positioning of condyle-fossa relationship is also due to the condylar growth in addition to the glenoid fossa remodeling through histologic and radiographic evidence[9,13,14]. Xbow appliance (Figure 4.1) is a type of fixed Class II appliance composed of Forsus springs that do not continuously posture the mandible forward as Herbst appliances do and thus the patient is able to seat the condyle into the normal relationship by overcoming the activated springs[15]. Cephalometric studies on Xbow appliance found that both skeletal and dentoalveolar changes were observed in patients treated with Xbow appliance[16]. Due to a lack of studies on the skeletal effect of Xbow appliance using three-dimensional imaging, the extent of the orthopedic effect that these appliances have on condylar growth in terms condylar volume, in particular, is not well understood.

Figure 4.1: Clinical photos of Herbst appliance (top), and Xbow appliance (bottom)

Three-dimensional imaging is capable of providing a considerable amount of additional data when compared to a traditional two-dimensional imaging with regards to a comprehensive evaluation of mandibular condylar morphological changes. Traditional radiographic analysis on condyles is limited to the condylar positional changes relative to another radiograph landmark in one plane; whereas, three-dimensional imaging potentially provides information on changes in condylar shape, volume, and position[17,18]. To accurately calculate the condylar volume, an accurate and reliable condylar segmentation from three-dimensional images and a reproducible approach of determining the volume of interest are necessary[19]. Condylar volumetric changes have been assessed in a number of previous studies considering the pathological changes in condyle and the effect of surgical and/or orthopedic manipulation of condyle or mandible[20-22], while the literature on condylar volumetric changes due to Class II appliances is limited. Yildirim et al. study evaluated the condylar volumetric changes in patients with a twin-block functional appliance using CBCT images[11]. The authors observed an increase in condylar volume but lacked a control group monitoring condylar changes resulting from growth[11]. Aciri et al. reported an increase in condylar volume in both the control group and the patients treated with a fixed Class II functional appliance (Forsus nitinol flat-spring, 3M Unitek Corp, Monrovia, Calif); however, the obtained condylar volume was approximated using a non-validated approach as the total condylar volume was estimated from only three transverse CT slices per condyle[10]. To best of our knowledge, the effect of fixed Class II appliances in overall condylar volumetric changes using a validated condylar segmentation technique has not been reported. The objective of this study is to assess the condylar volumetric changes in patients treated with Herbst or Xbow appliances compared to those not treated with Class II appliances using the developed semi-automatic segmentation technique form CBCT images.

4.2 Materials and Methods:

The sample consisted of a total of 30 healthy adolescent patients which were randomly assigned to one of three different groups (2 treatment, one control). Sixty CBCT scans (two per patient at different time points) were obtained from the included patients. Ethics approval was obtained from the University of Alberta, Health Research Ethics Board (Pro00045191).

All thirty patients, initially, exhibited ½ cusp to full cusp Class II molar relationship bilaterally, no significant maxillary transverse deficiency, no extraction or orthognathic surgery was planned as part of the comprehensive orthodontic treatment, and were in late mixed dentition or early permanent dentition. Summary of the sample patients including age and treatment time for all three treatment groups is listed in Table 4.1.

Table 4.1. Summary of the included sample patients

Tx Group	Sample size (Gender)	Age at T1 (mean)	Age at T2 (mean)	Tx time (mean)
Herbst	3(M) / 7(F)	12-14 (13.0)	13-15 (13.9)	8-11 (9.2)
Xbow	6(M) / 4(F)	11-14 (12.5)	12-15 (13.2)	9-10 (9.4)
Control (no CII appliance)	5(M) / 5(F)	12-14 (12.8)	13-15 (13.6)	9-10 (9.3)

*Tx=Treatment; Age in years; Treatment time in months; CII=Class II

Of thirty patients, 10 patients were treated with Herbst appliance, and another 10 patients were treated with Xbow appliance. Pre-treatment CBCT (T0) and post-treatment CBCT (T1), taken on the day of the fixed class II appliance removal, were obtained. Any activation of these fixed Class II appliances was completed bilaterally and partial fixed appliance in the upper arch (3M Victory Series Active Self-Ligating .022 slots brackets) was bonded on maxillary central and lateral incisors on the same day the fixed Class II appliance was placed.

Control group consisting of 10 patients were first treated with full fixed appliances (3M Victory Series Active Self-Ligating .022 slots brackets and 3M Victory Series bands on maxillary molars) for initial dental alignment using a sequence of NiTi wires to work up to either .019x.025 stainless steel or beta-titanium wires without any inter-arch mechanics followed by insertion of Forsus springs (3M Unitek, Monrovia, Calif) to correct the antero-posterior arch discrepancy. Tie-back module was placed from the rod end to the mandibular molar bracket hook. Pre-treatment CBCT (T1) and post-treatment CBCT scan (T2), which was taken at 9 to 10 months after initial bonding of full-fixed appliance prior to the placement for Forsus springs, were obtained.

All CBCT scans were taken using an i-CAT machine (i-CAT, Imaging Sciences International, Hatfield, Pa) at 120kVp, 7mAs, 8.9 seconds, 13cm x 16cm FOV, and 0.3mm voxel size. Images were converted to Digital Imaging and Communications in Medicine (DICOM) format and imported into the Avizo software (Standard Edition, Version 9.1, Mercy Computer Systems Inc., Chelmsford, Mass). Condyles for all sixty CBCT scans were segmented, the volume of interest determined, and the resulting condylar volume was calculated using the developed semi-automatic condylar segmentation technique as described in Chapter 3.

Three CBCT images from the sample were randomly chosen, and a total of six condyles were segmented and condylar volumes were calculated independently by three observers (JK, KC, AR) using the semi-automatic condylar segmentation technique to assess inter-rater agreement. The principle observer (JK) repeated the semi-automatic condylar segmentation process on three randomly chosen sets of CBCT images to calculate condylar volume for six condyles, with each trial a week apart, to assess intra-rater reliability.

Statistical Analysis:

Statistical analysis was performed using IBM SPSS Statistics software (version 23.0 for Mac, IBM Corp., Armonk, NY). A significance level of α=0.05 was chosen for all analyses. Mixed-design ANOVA and descriptive statistics was used to present the comparisons of condylar volume changes between the three groups: Herbst, Xbow, and control group. Intraclass correlation coefficient (ICC) was used to assess the intra-rater and inter-rater reliability. Interpretation of ICC values was done per guidelines outlined in Koo and Li study[23] .

4.3 Results:

Descriptive statistics was calculated for all variables as shown in Table 4.2.

Table 4.2. Descriptive statistics of condylar volume of all three treatment groups before (T1) and after treatment (T2) as assessed through semi-automatic segmentation from CBCT images

Time	Condyle	Treatment	Mean condylar volume (mm^3)	Std. Dev. (mm^3)
T1	Right	Xbow	1440.29	287.20
		Control	1265.24	167.05
		Herbst	1206.35	228.35

T1	Left	Xbow	1486.21	283.82
		Control	1292.36	120.42
		Herbst	1186.05	242.14
T2	Right	Xbow	1515.15	290.51
		Control	1290.14	113.99
		Herbst	1313.93	302.98
T2	Left	Xbow	1543.77	314.17
		Control	1351.86	135.77
		Herbst	1326.00	312.88

Mixed design ANOVA test result and pairwise comparison suggest a mean increase of 77.39mm^3 in condylar volume from before and after treatment (p=0.001). Although the patients treated with Herbst appliance exhibited nearly twice the mean percentage increase in condylar volume compared to those treated with Xbow and control group (Table 4.2), the interaction effect between condylar volume increases and treatment types was not statistically significant (p=0.303).

Table 4.3. Mean increases in condylar volume from T1 to T2 of different treatment groups

Treatment	Mean increase (mm^3)	95% Confidence Interval (mm^3)		Mean percentage increase (%)
		Lower bound	Upper bound	
Xbow	66.21	-10.77	143.19	4.59
Control	42.20	-34.78	119.19	5.63

Herbst	123.77	46.79	200.75	10.53
Average	77.39	32.95	121.84	6.88

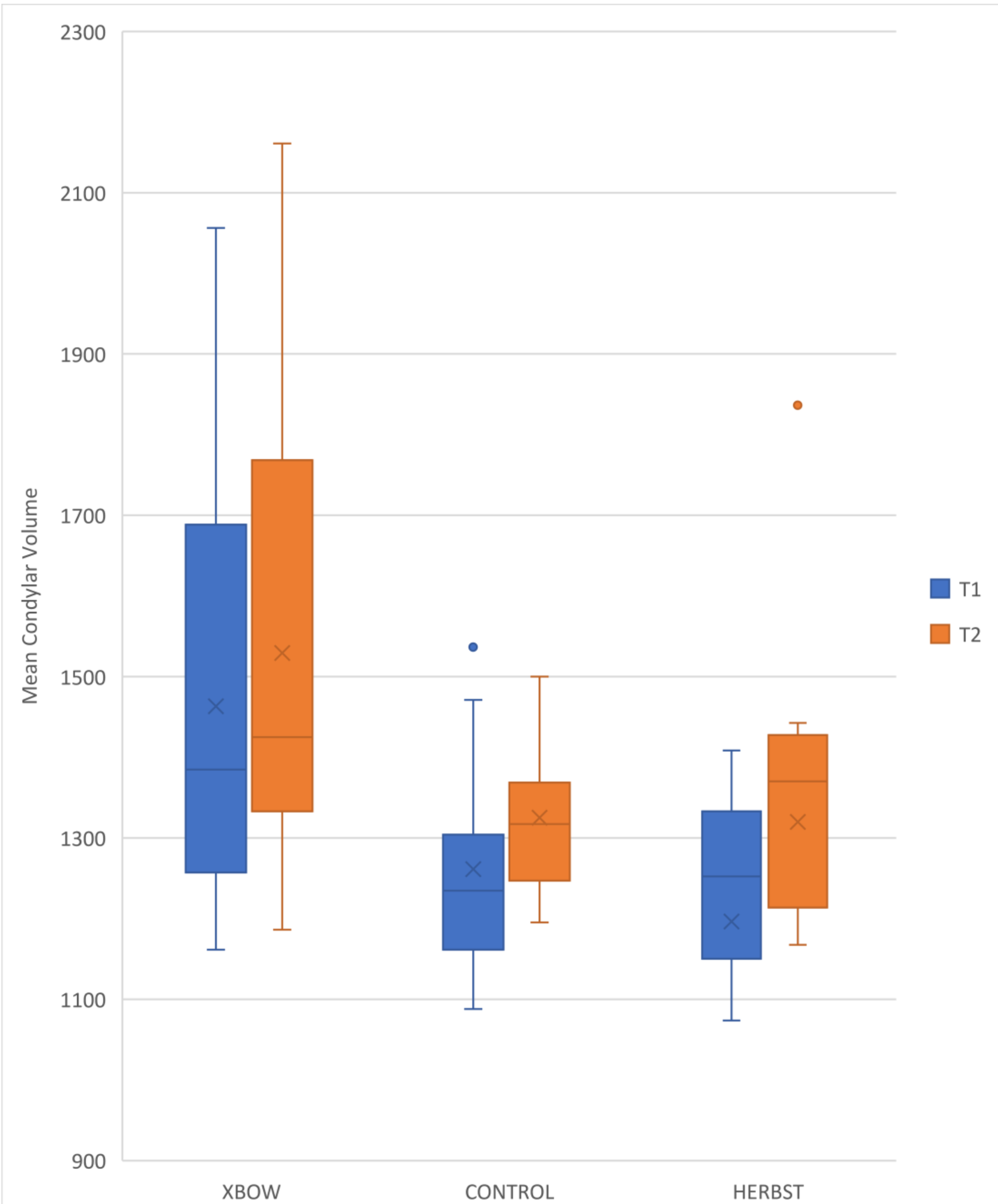

Figure 4.2: Box plots representing mean condylar volume for three groups at T1 and T2

Both intra-rater reliability and inter-rater reliability among three observers demonstrated an excellent agreement at ICC=0.998[0.992,1.000], and ICC=0.995[0.979,0.999], respectively. The mean difference among the three trials from the same observer was -8.00±5.30mm^3, and among three observers was 7.65±32.43mm^3.

4.4 Discussions:

The effects of a functional appliance on a temporomandibular joint complex has been extensively studied using various methods including CBCT[9,11,24], CT scan[10], magnetic resonance imaging (MRI) [2,25,26], histomorphometric technique[12], and, most comprehensively, using two-dimensional cephalometric data[5,9,14,26-28]. Although practical availability and low radiation dose of cephalometric radiograph allows for a relatively large amount of patient data for analyses, intrinsic limitations of lateral cephalograms including distortion and superimpositions severely limit an accurate assessment of temporomandibular joint complex including the condyle[18]. Three-dimensional imaging using CBCT allows to perform craniofacial analysis with a variable but relatively high degree of accuracy and permits analyses not possible with two-dimensional images including volumetric, shape, and multiplane positional assessment[29]. Comprehensive analysis of condylar structure requires an accurate and reliable method to segment the mandibular condyle from surrounding structures. Several segmentation methods from CBCT images are currently available. The developed semi-automatic segmentation technique described in Chapter 3 implements a level of software segmentation automation with a reduction in operator involvement while producing three-dimensional reproduction of condyles with a high degree of accuracy. In addition, this tool encompasses a method to reproducibly determine the condylar volume of interest, which significantly impacts the volumetric analysis. The reliability of the developed technique is further reinforced by an excellent intra-rater agreement (ICC=0.998) and inter-rater agreement observed in this study (ICC=0.995).

Three-dimensional imaging has been used to assess morphological and positional changes in mandibular condyle following functional appliance[11,24,30,31]. However, a limited number of studies exists in terms of evaluation of condylar volumetric changes observed in patients treated with fixed Class II appliances including Herbst and, especially, Xbow appliances. Results from this study demonstrate that there is an increase in condylar volume in growing patients regardless of presence and type of Class II appliances. A similar result was reported by Yildirim et al., where they compared condylar volume before and after treatment using Twin-block, a removable appliance, for an average of 7.4 months[11]. Although they concluded that Twin-block appliance increases condylar volume, there was no control group for an appropriate comparison. Our findings show that the control group, who were treated without any inter-arch appliance thus undergoing normal condylar growth without an intervention, had an increase in mean condylar volume. This finding is supported by Nota et al. where an increase in condylar volume was observed in normal growing patients through comparison of the main condylar volume of patients in different age groups: 11-16years, 17-21 years, and 22-26 years[1]. Furthermore, Aciri et al. found there was no statistically significant difference in condylar volume changes between the control group and the patients treated with fixed functional appliance with the similar interval between two time points (mean, 7 months), albeit using a non-validated segmentation method[10]. Therefore, it is possible that the reported increase in condylar volume in patients treated with Twin-block appliance may be primarily due to natural condylar growth in growing patients. This is significant because our results suggest that although there is a considerable increase in condylar volume in patients treated with Herbst fixed functional appliance, the magnitude of condylar volume increase when compared to the patients treated with Xbow appliance and control group, who were not treated with any inter-arch Class II appliances, is not statistically significant ($p=0.303$).

Herbst and Xbow appliances, though both are fixed Class II appliances, differ as the Herbst appliance consists of rigid arms that forcefully and continuously displace the mandible thus the condyle forward whereas Xbow appliance consists of Forsus springs thus permitting the patient to establish normal occlusion thereby repositioning condyle into normal condyle-glenoid fossa relationship. A previous study, using MRI, has demonstrated that Forsus springs do not cause a positional change between the condyle and glenoid fossa[32], while several studies support anterior condylar displacement and subsequent condyle-glenoid fossa remodelling in patients treated with the Herbst appliance[2,33,34]. Based on our findings, there seems to be no statistically significant difference in condylar volume changes between Herbst and Xbow groups, and both exhibited marginally higher, though not statistically significant, condylar volume increase when compared to the control group. Although Herbst group exhibited the largest mean increase in condylar volume at 123.77mm^3[46.79, 200.75], it is possible that the lowest mean condylar volume before treatment may have contributed to this largest mean condylar volume increase, indicating the greatest condylar growth potential. It is important to note that the findings from this pilot study is inherently limited by a relatively small number of patients assessed ($n=30$). Therefore, future studies with a larger sample size may help elucidate whether this factor has any significant impact on the mean condylar volume increase.

Measurement errors in condylar segmentation technique can certainly impact the interpretation of mean differences observed in condylar volume. It seems that the average measurement error of 4.56±17.17mm^3 reported in the validation of the segmentation technique explored in Chapter 3, which would equal to 0.34±1.27% of the average condylar volume assessed in this study, and intra-rater and inter-rater measurement errors of -8.00±5.30mm^3 and 7.65±32.43mm^3, respectively, would have a minimal impact on overall condylar volume increase that was observed, 77.39mm^3[32.95,121.84]. Nonetheless, the reported measurement errors can certainly have an implication in interpreting relatively small mean condylar volume differences seen among two study groups and a control group, especially if future studies with larger sample size finds a small but statistically significant difference between the groups. There have been few studies suggesting potential adverse effect in the condylar region including condylar flattening when treated with a functional appliance[35,36] ; however, our results indicate that, despite the possibility that morphologic changes may occur such as condylar flattening, there is no net reduction in condylar volume when compared to the patients not treated with Class II appliance. Despite a lack of detrimental effect on the overall condylar volume, there is a possibility that significant changes in condylar shape may occur without resulting in a reduction in the condylar volume. Future studies evaluating shape analysis of mandibular condyles can further clarify whether this occurs when being treated with orthodontic appliances. The developed semi-automatic condylar segmentation technique has a potential to be utilized for shape analysis as well as volumetric analysis that has already been validated.

4.5 Conclusion:

Condylar volumetric analysis using the validated semi-automatic condylar segmentation technique using CBCT images is a reliable approach to evaluate volume changes in mandibular condyles in growing patients treated with fixed Class II appliances. An increase in condylar volume was observed in all three groups: Herbst, Xbow and control group. However, the magnitude of condylar volume increase among Herbst, Xbow, and control group were not statistically significant. The results from this pilot study suggests that the condylar volume increase in growing patients is primarily due to the normal condylar growth and is not necessarily enhanced or impeded by the use of fixed class II appliances.

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Chapter 5: General Discussion

5.1 General discussion and summary of findings:

This study aimed to develop and validate a method to accurately and reliably segment the mandibular condyle from CBCT images, and utilize the developed method to evaluate the volumetric change in patients treated with fixed Class II appliance. Three research objectives were identified:

Objective #1:

- Systematically review the literature surrounding segmentation of the mandibular condyle using three-dimensional imaging modalities.

Objective #2:

- Develop a method to segment the mandibular condyle from CBCT images reliably and validate its accuracy.

Objective #3:

- Using the developed condylar segmentation method to evaluate volumetric changes in mandibular condyles in patients treated with different fixed Class II appliances.

The systematic review of the literature on the mandibular condyle segmentation from three-dimensional images found that several condylar segmentation techniques have been described with a varying degree of reported accuracy and reliability. Semi-automatic segmentation technique using CBCT images showed a promise in possibly minimizing inter-observer errors by designating a part of tedious work to the software algorithm but lacked adequate reported data on its accuracy.

Following the systematic review, a novel semi-automatic segmentation technique from CBCT images using Avizo software was developed. To assess the validity of the developed technique, condylar volumes calculated using the semi-automatic segmentation were compared to the reference values, which were obtained from the physical 3D-printed models of study skulls' mandible. Transferring method of segmentation plane, which establishes the volume of interest of condyle, from CBCT volume to physical models was verified for its accuracy using FaroArm. In addition, rotation and translation of the inferior plane of the volume of interest were introduced to assess the degree of discrepancy that may result from the possible errors in determining the volume of interest by the observer. The mean difference between the condylar volume obtained from the CBCT segmentation method and the physical model was 4.83±11.89 mm^3, exhibiting an excellent agreement (ICC=0.988). Excellent intra-rater reliability (ICC=0.990) was also reported. The sensitivity analysis indicated that a degree of inferior plane rotational change, which would equate to approximately 1.5mm of vertical discrepancy in location porion landmark when determining Frankfurt horizontal plane, would result in less than 1.51% of total condylar volumetric change.

Subsequent to validation of the developed condylar segmentation technique, CBCT images of patients treated with either Herbst appliance, Xbow appliance, or no inter-arch orthodontic appliance at pre-treatment and post-treatment time points were obtained to examine the volumetric changes in mandibular condyles using the semi-automatic segmentation method. Intra-observer and Inter-observer reliability of the segmentation method in clinical settings were measured and were shown to be excellent (ICC=0.998 and 0.995, respectively). A statistically significant increase in condylar volume was observed in all three groups with the mean increase of 77.39mm^3[32.95,121.84], but the differences in the magnitude of volumetric changes among the three groups were not statistically significant.

5.2 Limitations:

Chapter 3:

There is a number of factors that need to be considered in interpreting the data. The most significant factor may be the use of CBCT scans of the 3D-printed model of study skull to perform semi-automatic segmentation. CBCT scans of 3D-printed model understandably have a substantially different greyscale value when compared to the human mandibular condyles in clinical settings, and this can influence the segmentation process carried out by the software algorithm. Although this was done to prevent irreversible damages required on physical specimens to accurately measure the physical condylar volume, it is important to note that this study design can potentially result in a meaningful difference when segmentation performed in vivo. However, this unlikely has much influence on our findings regards to the effect of volume of interest changes in condylar volume.

This study included 10 patients per study group of which Herbst group had the smallest initial mean condylar volume at T1. A larger sample size would be advantageous to normalize the initial mean condylar volume for all study groups to better understand if a smaller initial mean condylar volume has an effect on the mean condylar volume increase.

Avizo software is not widely available in typical clinical settings, and extensive training and experience may be needed to become familiar with this software. Although the developed semi-automatic segmentation is expected to be less time-consuming than fully manual condylar segmentation, further investigations can reveal the extent of time-saving when compared to various other segmentation methods.

Chapter 4:

There was an inadequate number of subjects assessed (n=30, 10 in each group) to draw a definitive conclusion on the effect of different fixed Class II appliances in a change in the condylar volume. This study was limited to volumetric changes in the mandibular condyle, but the segmentation process allows for possible shape analysis to evaluate any morphological changes that may not necessarily affect the net change in the volume. Further analyses in shape and spatial relationship using the developed method may be of more interest to the researchers and clinicians to understand condylar growth and changes. All the limitations in chapter 3 apply in this chapter as well because the semi-automatic segmentation method used was developed and described in chapter 3.

5.3 Future recommendations:

Based on the findings in this study and the described limitations, the following recommendations for future studies are proposed:

- Further validation of the developed semi-automatic segmentation using cadavers to compare the segmented condyle from CBCT scans obtained with intact soft tissues and physical condylar volume obtained from cadaveric mandible void of all soft tissues.
- Evaluation of condylar volumetric changes in various fixed/removable Class II appliances with a larger sample size.

- Assessment of time required to train and perform the developed semi-automatic condylar segmentation process and comparisons with other available segmentation techniques.
- Using the developed condylar segmentation technique to perform shape analysis to evaluate the changes in condylar morphology that may not be detected in volumetric analysis.
- Integration of condylar segmentation technique with superimpositions of surrounding structures to assess the changes in the spatial relationship of temporomandibular joint complex, specially the between the condyle and glenoid fossa, observed during condylar growth and remodeling.

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Appendix

Search strategy for PubMed, MEDLINE, and EMBASE

PubMed:

Search	Add to builder	Query	Items found	Time
#8	Add	Search **((((CT) OR computed tomograph*)) AND (((TMJ) OR temporomandibular)) OR ((Condyl*) OR mandibular condyl*))) AND ((((segment*) OR isolat*)) OR ((3d analy*) OR three dimensional analy*))**	281	15:20:21
#7	Add	Search **(((segment*) OR isolat*)) OR ((3d analy*) OR three dimensional analy*)**	2239775	15:19:53
#6	Add	Search **(((TMJ) OR temporomandibular)) OR ((Condyl*) OR mandibular condyl*)**	50892	15:19:28
#5	Add	Search **(3d analy*) OR three dimensional analy***	2576	15:18:53
#4	Add	Search **(segment*) OR isolat***	2237548	15:18:03
#3	Add	Search **(Condyl*) OR mandibular condyl***	29498	15:17:44
#2	Add	Search **(TMJ) OR temporomandibular**	27747	15:16:54
#1	Add	Search **(CT) OR computed tomograph***	520258	15:16:13

MEDLINE and EMBASE (Ovid SP)

# ▲	Searches	Results	Type
1	(CT or computed tomograph*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	409340	Advanced
2	(TMJ or tempormandibular*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	7563	Advanced
3	(Condyl* or Mandibular Condyl*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	28406	Advanced
4	(Segment* or Isolat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1519625	Advanced
5	(3d analy* or three dimensional analy*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2409	Advanced
6	2 or 3	33445	Advanced
7	4 or 5	1521727	Advanced
8	1 and 6 and 7	202	Advanced