Received: 28 June 2020 | Revised: 13 September 2020 | Accepted: 15 October 2020

DOI: 10.1111/ocr.12434

ORIGINAL ARTICLE

Orthodontics & Craniofacial Research WILEY

Reference values of mandibular condyles metabolic activity: A study using ^{99m}Tc-MDP single-photon emission computed tomography

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Abstract

Objective: To assess the condylar bone metabolic activity in patients with temporomandibular joint health by measuring ^{99m}Tc-MDP uptake using a single-photon emission computed tomography (SPECT) to establish reference values of the uptake difference between condyles and the ratio with respect to the clivus.

Setting and sample population: Eighty consecutive patients of both sexes who were admitted to a Nuclear Medicine Centre between 2017 and 2019 were included in the study.

Method: This was an observational cross-sectional study in patients with SPECT indications to evaluate pathologies other than those of the temporomandibular joint. The values of the total and normalized counts in a fixed region of interest of five trans-axial slides were obtained to assess the percentage difference between the sides and the uptake ratio. The reference values are expressed as median and 5th and 95th percentiles.

Results: The sample included 53 women (66.25%) and 27 men (33.75%) aged 15-55 years. The percentage of uptake difference between condyles was 5.04% (0.46-14.78) for men and 5.17% (0.27-13.21) for women (difference not significant, $P = .9$). The uptake difference was below 10% in 85% of the subjects (n = 68). The ratio values for total counts in women (0.87, 0.46-1.33) were significantly different ($P = .0030$) from those in men (1.08, 0.61-2.09). No significant correlation with age was found.

Conclusions: These new reference ranges are applicable to the diagnosis of unilateral and bilateral condylar hyperplasia.

KEYWORDS

^{99m}Tc-MDP. SPECT, bone metabolism, condylar hyperplasia, mandibular condyle, reference values

1 | INTRODUCTION

Facial asymmetries, either congenital or acquired, according to their aetiology, involve the upper, middle or lower facial third causing alterations in the three planes of space with aesthetic, functional and psycho-emotional implications. They can appear during different stages of craniofacial growth, causing sequelae in adulthood if not timely treated. Asymmetries due to exaggerated, disproportionate and progressive growth of the mandibular condyle (condylar hyperplasia, CH) are different from those originating from alterations of the cranial base, the development of malocclusions or temporomandibular disorders and those that are part of existing craniofacial syndromes.[1]

Condylar hyperplasia may be unilateral (UCH) or bilateral (BCH).[2,3] UCH is the first cause of facial asymmetry, which develops when the UCH is not diagnosed early and evolves to produce aesthetic, occlusal and functional sequelae. Asymmetry occurs due to a difference in the growth rate of the mandibular condyles, affecting the position and size of the mandible and leading to different occlusal changes.[4] UCH is usually active between the ages of 10 and 30 and is more frequent in women and in the right condyle.[5-7] BCH is less frequent than UCH, producing severe mandibular prognathism but no significant asymmetry.

The diagnosis of CH depends on an accurate and a detailed correlation between clinical extraoral and intraoral radiographic and/or tomographic signs. Immediately a suspected active phase is established, it is necessary to conduct a nuclear medicine test such as a single-photon emission computed tomography (SPECT) to evaluate the bone metabolic activity in both condyles and in reference structures such as the clivus. This gammagraphic test uses an intravenous radiotracer, 99mTc methylene diphosphonate (^{99m}Tc-MDP), which is distributed according to the blood flow and bone metabolic activity of the osteoblasts.[1,8]

If the SPECT result is positive for UCH, the indicated treatment is a condylar surgery to eliminate the condylar portion presenting the overgrowth, followed by an orthodontic treatment for dentoalveolar compensation[9] or to prepare the patient for orthognathic surgery in order to correct the sequelae of the disease. By histopathology, active overgrowth is confirmed through the increased thickness of the soft condyle layers and the presence of chondrocyte islands in the subchondral trabecular bone referred to the age.[10]

The timing and surgical approach for this type of pathology varies depending on the aetiology of the asymmetric growth. Partial condylectomy is performed during the active phase of the overgrowth. However, if the asymmetry is due to a currently an active CH, orthognathic surgery is performed to correct the asymmetry.[1] Therefore, the therapeutic decision depends on the quantitative information obtained by bone SPECT.[5,6,11]

Although bone SPECT is very useful, there are no reference values for the uptake percentage or ratio in normal populations necessary to establish the risk and pathologic ranges and to decide regarding the difference between condyles to be considered as significant. The detection of bilateral CH, a condition described in the literature,[2] is not detectable without calculating the ratio between uptake for each condyle, with respect to the clivus.

The objective of the present study was to compare the bone metabolic activity measured in the mandibular condyles of subjects without condylar hyperplasia and signs of articular disorder, calculating the percentage and ratio of ^{99m}Tc-MDP uptake obtained by SPECT to establish normal reference values according to sex.

2 | METHOD

This study was carried out according to the requirements of the Declaration of Helsinki and was approved by the Institutional Ethics Committee. The study design was observational, descriptive and cross-sectional. The subjects (n = 80) were recruited at a Nuclear Medicine Centre from 2017 to 2019. The inclusion criteria were as follows: subjects without facial asymmetry, who signed the informed consent to participate in the study and who had medical indications to undergo a bone scan with ^{99m}Tc-MDP to evaluate benign and malignant bone pathologies other than CH and/or TMJ disorders.

Patients with antecedents of disease or surgery of the TMJ, orthognathic surgery, trauma or mandibular fracture, craniofacial syndromes, tumours or maxillary bone lesions, metastases or any kind of arthritis were excluded.

To rule out a temporomandibular dysfunction (TMD), all the patients underwent clinical assessment by a single specialist and were followed up through a survey based on the Research Diagnostic Criteria for TMD.[12]

SPECT was performed 2 hours after the endovenous administration of Tc99m-MDP (15 mCi in patients older than 18 years and a normalized dose indicated in the Paediatric Dosage Card of the EANM in those less than 18 years old). The images were acquired with a double head gamma-camera (GE Infina$^{(R)}$), using low-energy and high-resolution collimators, with a 128 × 128 matrix, obtaining 45 images for each 180° scan, each one for 18 seconds.

The data were obtained as radioactive counts from the SPECT and reconstructed in the Xeleris 3 (General Electric, Milwaukee, USA) processing station with the programme Volumetrix MI Evolution for Bone, OSEM iterative, with 4 iterations and 8 subsets, applying a Butterworth 0.45 filter and a power level 12, with correction for the recovery of the resolution. From this reconstruction, trans-axial images were used for quantification.

The tomographic images were processed to add five trans-axial images of both condyles to obtain total counts and normalized counts in fixed regions of interest (ROIs) of 1,76 cm^2 in the condyles, counts in the clivus and the background in the posterior fossa cerebellum. This method of quantification was previously validated and is highly reproducible.[13]

The SPECT data for total and normalized counts for each ROI were used to calculate the percentage of uptake and the uptake ratio between the condyles and clivus using the following equations:

$$\text{Number of normalized counts} = \text{Condylar counts} / \text{Number of pixels}$$

$$\text{Uptake \% right condyle} = \text{right condyle counts} / \text{right} + \text{left counts} \times 100$$

$$\text{Uptake \% right condyle} = \text{left condyle counts} / \text{right} + \text{left counts} \times 100$$

The uptake ratio between each condyle and the reference anatomic structure was calculated as:

$$\text{Ratio} = \text{counts per ROI (condyle)} - \text{background counts} / \text{Clivus counts} - \text{background counts}$$

The background counts indicate the uptake in a nearby structure; in this case, an equal ROI in the posterior fossa of the brain (cerebellum).

The statistical analysis included absolute and relative frequencies for qualitative variables and calculation of the median and 5th/95th percentiles Md (p5-p95) to obtain the reference interval. The Mann-Whitney U test was used to compare sex differences; the Kruskal-Wallis test was used for age range comparison. The use of non-parametric statistics was selected because, according to previous studies, radionuclide counts do not follow a normal distribution and the percentages and ratios are non-parametric data.

3 | RESULTS

A sample consisted of 80 subjects including 53 (66.25%) women. The median age was 44.5 years. The youngest subjects were 15 years old and the oldest 55 years old. The percentage difference between the condyles was lower than 10% in 85% of the subjects (n = 68) (Table 1).

The difference between the sides (left-right condyle) is important for diagnostic purposes and is presented in Table 2 in terms of uptake percentage and ratios for total and normalized counts. The intercondylar differences were not statistically significant ($P > .05$). Sexual dimorphism was significant for the general ratio in total and normalized counts, with a median higher in men than in women for total counts (1.08 vs. 0.87; $P = .003$) and for normalized counts (1.03 vs. 0.84; $P = .002$). However, the condylar difference in uptake % between the condyles according to sex was not significant ($P = .931$ and $P = .955$, respectively). (Table 3).

TABLE 1 General description of the group of subjects

Variable	
Sex	n (%)
Female	53 (66.25)
Male	27 (33.75)
Age	Median: 44.5; range: (15-55)
≤22	8 (10)
23-44	32 (40)
>44	40 (50)
Uptake %	n (%)
<10	68 (85)
Equal or > 10	12 (15)

TABLE 2 Results in total counts and normalized counts per condyle (Median and p5-p95 values)

Variable	Total counts	Normalized counts
General Ratio	0.90 (0.47-1.79)	0.91 (0.47-1.71)
Right condyle ratio	0.93 (0.44-1.91)	0.90 (0.44-1.74)
Left condyle Ratio	0.87 (0.48-1.81)	0.88 (0.48-1.62)
% Difference in general uptake	5.11 (0.33-13.91)	4.27 (0.35-11.54)
% Right condyle uptake	50.1 (44.1-55.2)	50.3 (45.4-55.1)
% Left condyle uptake	49.9 (44.8-55.9)	49.7 (44.9-54.6)

The age distribution for ratio and uptake % for total and normalized counts (Figure 1) is characterized by a high dispersion and absence of significant linear correlation ($P > .05$). According to the age groups, no significant differences ($P > .05$) were found between the youth, young adults and adults for all the measurements (Table 4).

4 | DISCUSSION

The aim of this study was to obtain quantitative data regarding the uptake of ^{99m}Tc-MDP using the SPECT test in the condyles of subjects with no signs of facial asymmetry or articular disease. Determining the normal reference values for this test is useful to guide clinicians in the detection of UCH from the data of the uptake difference between condyles and in cases of BCH, from the data of the uptake ratio with respect to the structure of the reference and the background.

Regarding the quantitative difference expressed as a percentage between healthy condyles, Hodder et al,[7] in a sample of 11 subjects; Kaban et al,[5] in 38 subjects; Fahey et al,[1] in 32 subjects and Fernandes et al,[14] in 44 subjects, found maximum differences of 6%, 6,2%, 6.7% and 8,7%, respectively. In the present study, with a higher group (n = 80), the median uptake difference between condyles was similar (5.04%), but the maximum value was 14,78%. Only Robinson et al,[15] reported maximum values of 12% between healthy condyles. The ROIs measured are different among the studies that have in common only the lack of articular pathology in the subjects. The difference in uptake for normal condyles is usually explained by the differences in growth and remodelling of the articular tissues, likely due to mechanical, anatomical and functional differences, but may also be related to differences in methodology. The comparison among studies in different populations also indicates the need to have local reference values, same as for any other clinical parameter.[16]

Regarding the uptake ratio with respect to the clivus, Chang et al,[17] Fahey et al,[1] and AlSharif et al[18] reported ratios for normal condyles of 0.68-1.44, 0.73-1.88 and 0.67-2.06 in samples of 16, 11 and 16 subjects, respectively, without differentiation by gender. In the present study, the ratio was significantly higher in men than in

TABLE 3 Statistical Results-Sexual dimorphism differences (Average and range)

Variable	Male	Female	*P* value
Ratio total counts	1.08 (0.61-2.09)	0.87 (0.46-1.33)	.0030*
Ratio normalized counts	1.03 (0.62-1.85)	0.84 (0.44-1.39)	.0023*
Uptake % difference between condyles (total counts)	5.04 (0.46-14.78)	5.17 (0.27-13.21)	.9311
Uptake % difference (normalized counts)	4.22 (0.54-11.78)	4.11 (0.24-11.51)	.9554

Note: Mann-Whitney U test.

*$P < .05$.

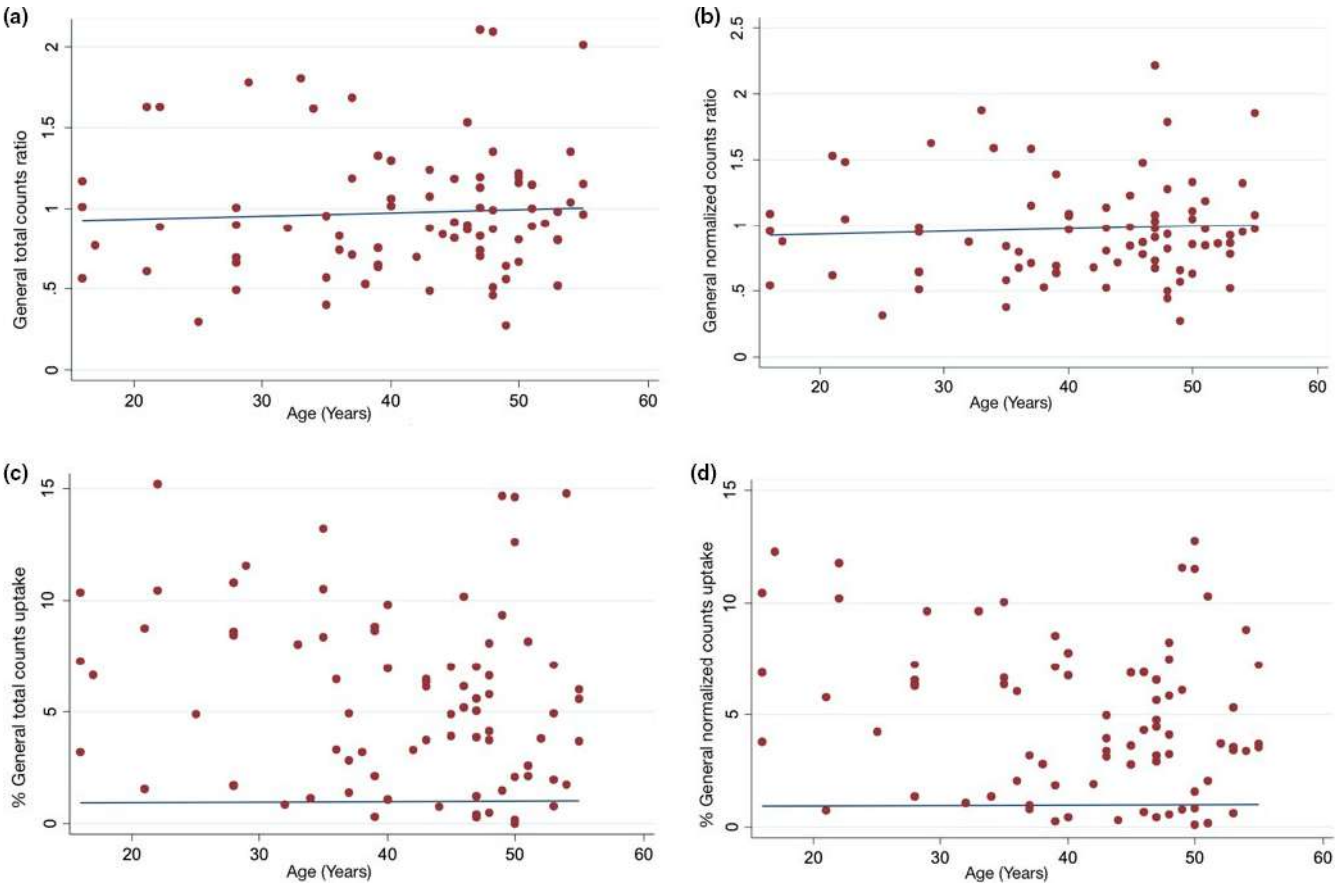

FIGURE 1 Age correlation graphs. A, Ratio, general total counts; B, ratio, normalized counts; C, general counts uptake %; D, normalized counts uptake %. The age distribution for ratio and uptake % for total and normalized counts is characterized by a high dispersion and absence of significant linear correlation ($P > .05$)

TABLE 4 Results in total counts and normalized counts according to age distribution (median and p5-p95 values)

Variable/Age(years)	≤22	23-44	>44	*P* value*
Ratio total counts	0.94 (0.56-1.63)	0.86 (0.40-1.78)	0.94 (0.48-2.05)	.5801
Ratio normalized counts	1.00 (0.54-1.53)	0.80 (0.38-1.63)	0.93 (0.47-1.82)	.4017
Uptake % difference between condyles (total counts)	8.01 (1.55-15.20)	5.50 (0.74-11.55)	4.89 (0.22-14.65)	.1748
Uptake % difference (normalized counts)	8.53 (0.72-12.28)	4.08 (0.29-9.63)	3.71 (0.30-11.54)	.926

Note: Kruskal-Wallis test.

*$P < .05$.

women ($P = .003$ for total counts), and only the present values for men coincide with the values reported by AlSharif.[18]

The lack of correlation with age in the current predominantly adult population (only eight subjects between 15 and 22 years) was also found in samples including more growing patients.[7,14,18] However, Fahey et al[1] and Karssemakers et al[19] in a group with a mean age of 14 and 19.9 years, respectively, found differences by age, suggesting a greater absorption in growing patients, although they used different methods than in the present study. The age subgroups in the present study were established considering that the residual growth ends only after 22 years of age,[20] and there were no infant or elderly patients.

Bilateral CH according to Obwegeser and Makek[3] and Wolford et al[2] is described as a less frequent entity with no family antecedents and clearly characterized by rapid, aggressive mandibular growth causing Angle Class III malocclusion and severe mandibular prognathism with bilateral condylar elongation. The clinical and radiographic characteristics are well described; however, there is no test to confirm the increased osteoblastic metabolic activity in both condyles, which will suggest the cause of the overgrowth and thus guide its treatment. The results of the present study provide a normal p5-p95 ratio of 0.46-1.33 for women and 0.61-2.09 for men, which is useful in suspecting an overgrowth of condylar origin as the cause of the mandibular prognathism when this range is exceeded. The ratio is taken with respect to the clivus because it is a metabolically stable structure[21] that does not support loads and is not articulated, but it contains the spheno-occipital synchondrosis that is completely closed from 15 to 18 years in women and 15-20 years in men.[22] Therefore, it must be considered that while there is metabolic activity in the clivus, age should be considered in the evaluation of the ratio.

Regarding UCH, the accepted cut-off is 10% for the difference in condylar uptake,[5,23] which is higher in the suspected condyle, and indicates an active pathology that should be treated by resection of a portion of the condylar head.[24]

According to the quantitative evaluation by SPECT, some therapeutic algorithms have been developed by Hodder et al,[7] Elbaz et al,[25] Rushineke et al[26] and Nolte et al,.[27] They coincide with the surgical decision for cases with different levels of asymmetry, when the difference in uptake is equal to or greater than 10%. In the present study, it was found that 15% of the subjects with no TMJ disease presented differences between 10% and 15%. Therefore, a higher cut-off should be considered in cases that are clinically doubtful.

Given that CH is a pathology that must be diagnosed on the basis of the correlation between the extraoral and intraoral clinical features with radiographic and/or tomographic findings,[4] the SPECT test is important because it is the only test that provides us with information about osteoblastic-type cell metabolism in the condyle or the suspected condyles in order to differentiate the active state of the pathology from an inactive state or other entity. Therefore, it is of paramount importance to select a cut-off threshold for each population, and to determine the normal reference value, the values indicate those at risk of the pathology and those that confirm the entity.

The existing therapeutic algorithms do not include orthodontic intervention as part of the treatment and do not evaluate the risk for bilateral cases based on ratios. Therefore, the authors suggest a new therapeutic algorithm (Figure 2), which involve the different entities related to non-syndromic facial asymmetries, including asymmetric mandibular prognathism, glenoid fossa asymmetry, functional laterognathism and unilateral condylar resorption.[4] Once the diagnosis is established, and if the pathology is suspected to be active, a SPECT/CT is requested to obtain information on bone metabolism and to correlate it with the anatomy of the condyles under study. Based on the present results, uptake difference values between 10% and 15% are considered as risk indicators, and clinical follow-up of the asymmetry and occlusal changes is mandatory. Values equal to or greater than 15% (the new suggested limit) are considered pathological and must be treated with condylectomy independent of the severity of the asymmetry. The surgical approach can be condylar shaving, high condylectomy or low/proportional condylectomy, depending on the severity of the asymmetry, age of the patient, skeletal discrepancy and the clinician's preferences for post-surgical interventions.[4,28-30]

If the diagnosis was made when the patient already had moderate or severe sequelae in the three planes of space (late diagnosis), the orthodontic treatment aims to obtain dentoalveolar decompensation to prepare the patient for an orthognathic surgery. However, if the compromise in the three planes of space is mild, the treatment is for dentoalveolar compensation with vertical management to recover the altered vertical dimension and to correct the occlusal plane.[31-34]

Finally, if the diagnosis is made very early, post-condylectomy orthodontic treatment is corrective as secondary bone remodelling occurs after early condylectomy, allowing the outcome of an ideal symmetry with no need for other interventions.[35-37] Otherwise, if the clinical evaluation suggests active bilateral hyperplasia and the uptake ratio is over the reference range, the clinician must decide if bilateral condylectomy is necessary to stop the condylar overgrowth and/or orthognathic surgery must be considered to correct the skeletal deformation. On the other hand, when the CH is in an inactive state, the type of surgical correction must be decided based on the sequelae caused by the pathology.

Taking into account the technical factors of the SPECT test, including the dose of the radiopharmaceutical, gamma camera calibration and individual factors such as the presence of a bone metabolic disease, renal function, body weight and food intake that may influence the results,[38-40] the uptake was measured in a fixed ROI, adding five trans-axial tomographic slides representing the total size of the condyle. This technique reduces intra-operator and inter-operator variability.[13] Additionally, the information was obtained from total and normalized counts, as both methods are used in nuclear medicine centres to present the results.

Given that some of the pathologies related to the increased bone metabolic activity of condyles occur in the growth and development stages, a limitation of the present study is that it did not have a large population of growing subjects, as only eight subjects were between 15 and 22 years of age. This limitation is difficult to overcome because

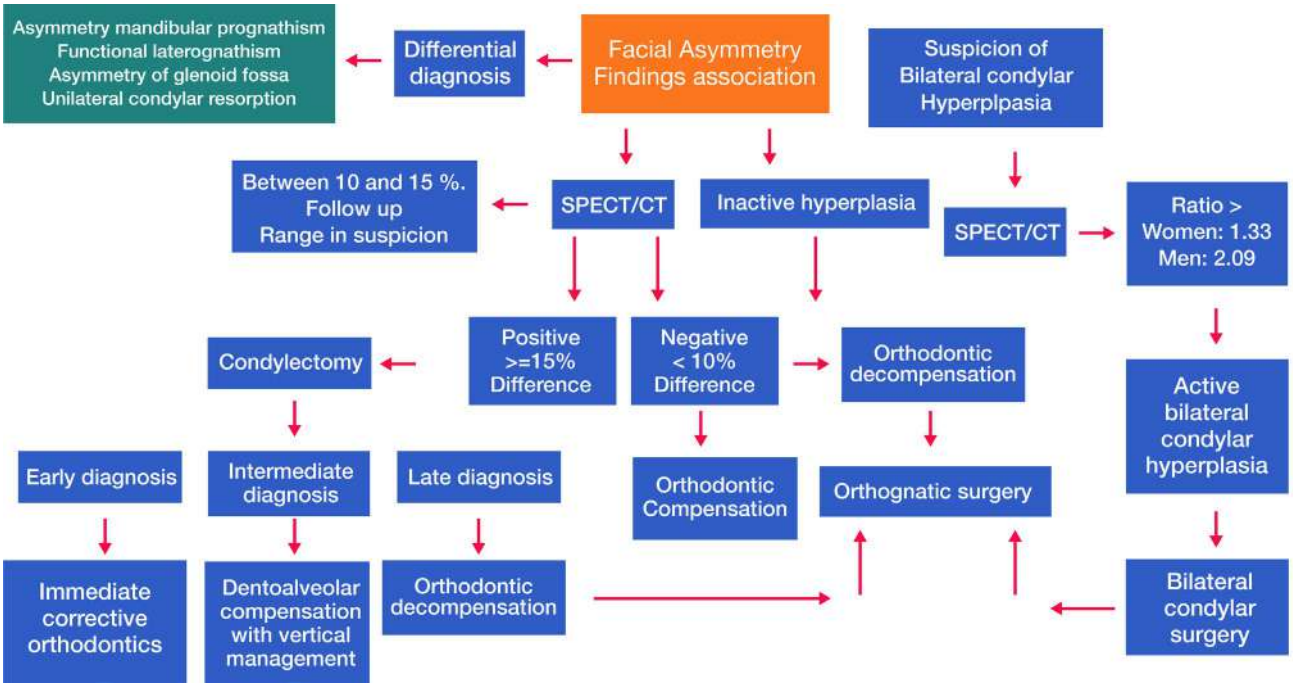

FIGURE 2 Therapeutic algorithm for the evaluation and treatment of unilateral and bilateral condylar hyperplasia, considering the percentage and the ratio of uptake of the radiopharmaceutical by each condyle. New cut-off points are suggested for the risk of the pathology (10%-15%), active state (>=15%) and inactive state (<10%)

nuclear medicine tests are not often requested for young patients, but for adult patients.

To overcome this limitation and provide an adequate sample size, it is suggested for further studies to use a multicentric design aiming to establish reference values for growing populations. It is also suggested to calculate the relative operation characteristic curves (ROC curves) based on data using different cut-off values.

5 | CONCLUSIONS

The median and percentile range Md (p5-p95) of ^{99m}Tc-MDP uptake difference between the condyles for the normal population attended was 5.04 (0.46-14.78) for men and 5.17 (0.2-13.21) for women (data based on total radioactive counts). This difference was not statistically significant ($P = .9$). Additionally, the ratio values with respect to the clivus were 1.08 (0.61-2.09) for men and 0.87 (0.46-1.33) for women. This difference was statistically significant ($P = .003$). No significant correlation with age was detected.

Considering that these percentile ranges for subjects without TMJ disease and without condylar hyperplasia consist of differences in condylar uptake values of up to 15%, the frequently accepted cut-off point (10%) could be reconsidered.

ACKNOWLEDGEMENTS

The authors wish to express their sincere acknowledge to the Imbanaco Medical Center, Research Institute staff for their support during the development of this study.

CONFLICT OF INTEREST

The authors state that they had no conflict of interest during the conduct of the study.

AUTHOR CONTRIBUTIONS

Diego Fernando López B.: Elaboration, planning, design, analysis of results and writing of the article. María Angélica Castro: Preparation, data collection and writing of the article. Juan Manuel Muñoz: Thematic advisor in nuclear medicine. Image acquisition and analysis. Rodrigo Andres Cardenas P: Thematic advisor in nuclear medicine. Image acquisition and analysis.

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How to cite this article: López DF, Castro MA, Muñoz JM, Cárdenas-Perilla R. Reference values of mandibular condyles metabolic activity: A study using ^{99m}Tc-MDP single-photon emission computed tomography. *Orthod Craniofac Res*. 2020;00:1–7. https://doi.org/10.1111/ocr.12434