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Systematic Review
Clinical Pathology

Histologic findings and related diagnostic methods in condylar hyperactivity

S. Espinosa[1,2,a], E. Covarrubias[3], R. Díaz[3], K. T. Díaz[4], E. A. Cafferata[5,6,a]

[1]Oral and Maxillofacial Surgery Department, Hospital Sótero del Río, Santiago, Chile; [2]Oral and Maxillofacial Surgery Service, Clínica Indisa, Santiago, Chile; [3]Private Dental Practice, Santiago, Chile; [4]Postgraduate School, Stomatology Second Speciality, Universidad Privada San Juan Bautista, Lima, Peru; [5]Periodontal Biology Laboratory, Faculty of Dentistry, Universidad de Chile, Santiago, Chile; [6]Department of Periodontology, School of Dentistry, Universidad Científica del Sur, Lima, Peru**Address: Emilio A. Cafferata, Periodontal Biology Laboratory, Faculty of Dentistry, Universidad de Chile, Sergio Livingstone Polhammer 943, Independencia, Santiago, Chile.

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Abstract. Condylar hyperactivity (CH) is a rare condition that entails a progressive deviation and deformation of the mandible. There is no consensus regarding characteristic histopathological features or a standardized diagnostic process; thus, histopathological analysis of the condyle cannot confirm or exclude an active CH after condylectomy is performed. An electronic search was performed in Medline, Embase, Web of Science, LILACS and grey literature up to December 2019. Additionally, a manual search was performed. Risk of bias of the included studies was assessed using the Newcastle–Ottawa Scale and the Institute of Health Economics Quality Appraisal. All analyses were performed independently and in duplicate. Seventeen articles from 660 were included. Six articles were cross-sectional studies and 11 were case series. Almost all the articles (14) described an augmented thickness of the cartilage layer associated with cartilage islands within the subchondral bone in patients affected by CH. Histological findings seem to be mostly related to the age of the sample rather than a characteristic description of CH. No clear association was found between SPECT/scintigram uptake and a specific histological finding. Hence, there is a necessity for the development of specific tools for evaluating and reporting studies where histology is needed for diagnosis confirmation.

Key words: review; bias; condylar hyperplasia; histology.

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Condylar hyperactivity (CH), also referred as condylar hyperplasia, is a pathological condition of the temporomandibular joint characterized by abnormal non-neoplastic growth of one of the condyles, which can cause facial asymmetry, deviation of the jaw, alterations in the occlusion, and less frequently, pain and dysfunction[1].

Despite being first described in 1836 by Robert Adams[2], there is still no agreement on a gold standard method for CH diagnosis[3]. Little is known about its aetiology, clinical development, and particularly, there is no consensus regarding its histological features[4–6]. Hovell[7] stated that normal histologic features were seen in CH resected condyles. Others[3,8], found augmented thickness of the cartilage in CH. Slootweg and Müller[9] found different types of histological descriptions, from which they proposed a classification comprising three different types of condyles. Type I condyles exhibit a broad prolifera-

[a] These authors contributed equally to this work.

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tion zone that gradually merges with an underlying thick layer of hyaline growth cartilage; then, this latter layer at its undersurface is resorbed and replaced with bone. Type II condyles are characterized by a proliferation zone that exhibits a patchy distribution, which consists of broad cell-rich areas alternating with cell-poor areas or areas without any cellular proliferation. Apart from that, it was observed that there was a replacement of hyaline growth cartilage by fibrocartilage in patients older than 20 years, which was associated with the expected condylar maturation histological characteristics[10]. Moreover, type I and II condyles presented clinical excessive growth without altering the natural evolution of the expected condyle maturation and the presence of hyaline cartilage occurred by virtue of the age at which the condyle was removed. Finally, Type III condyles present a completely distorted architecture associated with the appearance of symptoms and suggests the presence of a reactive hyperplasia with arthritic signs rather than a genuine condylar hyperplasia[9].

Many diagnostic tools and criteria have been proposed[9,11–13] to determine an appropriate and opportune treatment for CH[14]. Complete facial examination, radiographies, model casts and different nuclear medicine techniques such as planar scintigraphy (PS)[15–17], single photon emission computed tomography (SPECT)[13,18,19], SPECT combined with computed tomography (SPECT-CT)[20–22] and positron emission tomography (PET)[23] have been proposed to assess the presence of CH, in order to prevent the continuous deformation of the jaw or mandibular asymmetry relapse after orthognathic surgery[19].

Nuclear medicine could play an important role in CH because it can assess changes in the condyle physiologic function as a direct result of the bone metabolic alterations within the cellular level[20]. In fact, radionuclide bone scanning is capable of comparing the differential metabolic activity between the normal and abnormal condyles, reflecting their real-time relative growth rates[24]. A detectable scan uptake difference (in PS or SPECT) of more than 10% between the left and right condylar regions, is suggestive of CH in active phase and consequently, condylectomy should be indicated[25]. Some authors suggest that SPECT is the best indicator for the levels of bone activity in CH[13,26]; therefore, SPECT has been proposed as a viable gold standard method to assess the CH associated with excessive cellular activity[27]. Wen et al.[3] showed that a high SPECT uptake could be related to specific histological features of the affected condyle in CH. However, other authors[4,5,28,29] found no association between the histologic features of CH and SPECT.

Another alternative diagnostic tool proposed for CH is PET[14,30], due to its high diagnostic sensitivity compared with SPECT and PS. Nevertheless, it is important to consider that bone scintigraphy exams have a low diagnostic specificity, because it is difficult to differentiate growth activity from other conditions such as bone healing, growth, infections, or arthritic changes[20]. Other approaches have been proposed to establish the growth activity of the mandibular condyle, using only clinical follow-up, serial radiographs and plaster models[31]. Although, these tools are not sufficiently accurate and may cause unnecessary delay in the CH treatment[19].

Hence, it is necessary to clarify whether there are characteristic histological patterns in CH, and whether there are diagnostic tools that allow a reliable CH diagnosis. Therefore, the aim of this systematic review is to report the histological features and their corresponding diagnostic tools for CH in the literature.

Material and Methods

This systematic review was conducted according to the PRISMA guidelines[32] and the PICO question was: for patients affected by CH (P), are histological (I) or clinical/imaging diagnostic tools (C) able to describe a characteristic disease pattern (O)?

Eligibility Criteria

Publications that met the following inclusion criteria were included: prospective or retrospective cohorts, case–control or case series studies that evaluated patients with condylar hyperplasia/hyperactivity clearly diagnosed by means of extraoral/intraoral exam and/or an imaging study, such as computerized tomography (CT), micro-computerized tomography (micro-CT), cone beam computerized tomography (CBCT) or nuclear medicine exams that included biopsies described by histomorphometric/immunohistochemistry techniques. Systematic or comprehensive reviews, conference abstracts, books, letters to authors and personal opinion publications were not included. Articles in languages other than English, Spanish, or French were not included. There were no publication date or status restrictions for inclusion.

Literature Search

Two authors (E.C., R.D.) performed the electronic database survey independently and in duplicate up to 1 December 2019; in Medline, Embase, Web of Science and LILACS. In addition, Proquest Dissertations and Theses (PQDT) and ProQuest were searched for potential 'grey literature' inclusion. References lists of included articles were also checked for further literature.

Data Selection and Extraction

Two reviewers (E.C., R.D.), independently and in duplicate selected the studies for their potential inclusion. When disagreements occurred, inclusion was discussed with a third author (S.E. or E.A.C.). Then, two independent reviewers (E.C., R.D.) extracted the data from the final full-text selected studies including mainly: diagnostic methods, histological analyses, histological findings and imaging analyses if available (Table 1). Disagreements were solved by discussion and a third author (S.E. or E.A.C.) examined all extracted data, in order to capture all relevant information.

Risk of Bias Assessment

The Newcastle–Ottawa Scale (NOS) for cross-sectional studies[33] and the Institute of Health Economics Quality Appraisal (IHEQA) checklist for case series[34] were chosen to assess the risk of bias (RoB) of the included studies. Studies evaluated with the NOS can be awarded a maximum of five stars for its selection domain, two for the comparability domain and three for the outcome domain. The obtained cumulative scores were expressed in percentages.

In order to determine a quality score for the case series evaluated with the IHEQA checklist, one point was given for each 'yes' answer, and each article could achieve a maximum of 20 points. Although, the 'yes' answers were determinants for the quality score, 'partial/unclear' and 'no' answers were additionally described for the discussion of the studies. The obtained cumulative scores were expressed in percentages. The whole RoB assessment was performed by two calibrated reviewers independently (K.D., E.A.C.) and any disagreement was resolved by discussion.

Results

An initial source of 660 articles was identified after duplicates removal ($\kappa = 0.78$).

Table 1. Description of the main characteristics of the included studies.

Author (s)	Participants	Affected side	Diagnostic method	Augmented Thickness of Cartilage Layer	Layers with Augmented Thickness	Presence of cartilage Islands in trabecular bone	Histologic correlation with age	Histologic correlation with Scintigrams/ SPECT
Norman & Painter[35]	"Inactive" hyperplasia: 6 cases - Females: 6 - Males: 0 - Mean age: 28.5 years (22 - 39 years) "Active" hyperplasia: 6 cases - Females: 4 - Males: 2 - Mean age: 18.1 years (17 - 23 years) Osteocondroma: 2 cases - Females: 1 - Males: 1 - Mean age: 46 years (21 - 71 years)	"Inactive" hyperplasia: - Right: 1 - Left: 5 "Active" hyperplasia: - Right: 2 - Left: 4 Osteocondroma: - Right: 0 - Left: 2	History Clinical examination Imaging study: Radiographs	+	N/A	+ (in active cases)	N/A	N/A
Gray et al.[11]	20 cases - Females: 15 - Males: 5 - Mean age: 25.8 years (15 - 55 years)	- Right: 11 - Left: 9	Clinical diagnosis Transcranial radiographs Planar scintigraphy	+	N/A	+	+	+
Gray et al.[17]	12 cases - Females: 8 - Males: 4 - Mean age: 21.5 years (15 - 55 years)	- Right: 9 - Left: 3	History Clinical examination Supportive radiological and scintigraphic exams	N/A	N/A	+	N/A	-
Eslami et al.[36]	9 cases 13 controls Mean age: 21.7 years (range N/R) Gender: N/R	N/R	Planar scintigraphy	+	Δ	+	N/A	N/A
Saridin et al.[4]	47 cases - Females: 29 - Males: 18 - Mean age: 21.6 years (range N/R)	- Right: 21 - Left: 26	Clinical examination: facial and dental analyses (not described in the paper, personal communication with the author) SPECT	+	O □ (Proportional to number of cartilage islands)	+	+	-
Fariña et al.[5]	8 cases - Females: 4 - Males: 4 - Mean age: 18.1 years (11 - 36 years)	- Right: 4 - Left: 4	Clinical examination confirming progressive deformation in time SPECT	+	□ Δ (Proportional to cartilage islands depth)	+	+	-
Meng et al.[8]	20 cases - Females: 9 - Males: 11 - Mean age: 22.4 years (14 - 20 years)	- Right: 9 - Left: 11	Clinical examination Orthopantomography, posteroanterior and lateral cephalograms. Cintigrams Follow-up for at least 1 year	+	Not specificied	+	+	N/A
Elbaz et al.[29]	28 cases - Females: 22 - Males: 6 - Mean age: 25.8 years (12 - 50 years)	- Right: 17 - Left: 11	Clinical examination Radiography SPECT	+	□ Δ	+ (6 of 28)	-	-
Wen et al.[3]	105 cases - Females: 63 - Males: 42 - Mean age: 21.5 years (13 - 33 years) - Just 58 cases were submitted to histopathology. 44 controls (just with SPECT) - Females: 22 - Males: 22 - Mean age: 22.6 years	- Right: 52 - Left: 53	Clinical examination Plaster models Radiography CT scan SPECT	+	O □ Δ	N/A	N/A	+

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Table 1 (*Continued*)

Author (s)	Participants	Affected side	Diagnostic method	Augmented Thickness of Cartilage Layer	Layers with Augmented Thickness	Presence of cartilage Islands in trabecular bone	Histologic correlation with age	Histologic correlation with Scintigrams/ SPECT
Guo et al.[37]	6 cases - Females: 4 - Males: 2 - Mean age: 22.5 years (18 - 27 years) 3 controls - Females: 1 - Males: 2 - Mean age: 31 years	Cases - Right: 3 - Left: 3 Controls: - Right: 1 - Left: 2	SPECT	+	□ Δ	+	N/A	N/A
Vásquez et al.[6]	5 cases - Females: 3 - Males: 2 - Mean age: 16.6 years (15 - 18 years)	- Right: 3 - Left: 2	Clinical examination: facial and dental analyses Imaging study: CBCT + SPECT	+	Different levels of involvement	+ (4 of 5)	N/A	N/A
Ji et al.[39]	CH: 12 cases - Females: 8 - Males: 4 - Mean age: 25.3 years (20 - 34 years) CO: 15 cases - Females: 8 - Males: 7 - Mean age: 24.1 years (19 - 32 years) Controls: 6 - Females: 2 - Males: 4 - Mean age: 24.3 years	CH: - Right: 5 - Left: 7 CO: - Right: 9 - Left: 6 Controls: - Right: 3 - Left: 3	Orthopantomography CT scan Follow-up for at least 1 year	+	□ Δ	+	N/A	N/A
Martin-Granizo et al.[26]	28 cases - Females: 20 - Males: 8 - Mean age: 24.4 years (14 - 42 years)	- Right: 19 - Left: 9	SPECT SPECT-CT	+	□ Δ	+ (13 of 28)	N/A	+
Vásquez et al.[38]	5 cases - Females: 3 - Males: 2 - Mean age: 16.8 years (15 - 18 years)	- Right: 2 - Left: 3	Clinical examination: facial and dental analyses CBCT + SPECT	+	□ Δ	+	N/A	N/A
López et al.[27]	27 cases - Females: 14 - Males: 13 - Mean age: 20.3 years (12 - 42 years)	N/R	Clinical examination: facial SPECT	+	O □	+	+	+
Karssemakers et al.[40]	17 cases - Female: 10 - Males: 7 - Mean age: 22 years (10 - 39 years)	- Right: 6 - Left: 11	History Clinical examination SPECT	N/A	N/A	N/A	-	N/A
Karssemakers et al.[41]	20 cases - Female: 12 - Males: 8 - Mean age: 22.8 years (10 - 39 years)	- Right: 8 - Left: 12	History Clinical examination (dentals casts, 3D photography, or cone-beam CT scans) SPECT	N/A	N/A	N/A	N/A	-

SPECT:, Single photon emission computed tomography; CT, Computed tomography; CBCT, Cone beam computed tomography; H&E, Hematoxylin and Eosin taining; N/A, Not analyzed; N/R, Not reported; CH, Condylar hyperactivity/hyperplasia; CO, Condylar osteochondroma.
O: Articular or Fibrous Layer; □: Proliferative Layer (undifferentiated mesenchymal cells); Δ: Hiperplastic/Hypertrophic Layer (Hyaline growth cartilage); bSUV, bone SPECT standard uptake value.

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Of these, 579 were dismissed after revising titles/abstracts, resulting in 81 articles eligible for full-text analysis ($\kappa = 0.8$). Then, 64 articles were excluded when revised against the inclusion criteria. Finally, 17 articles (Fig. 1) were included in the review ($\kappa = 0.8$)[3–6,8,11,17,26,27,29,35–41]. Eleven articles were case series and six were cross-sectional studies. The data extracted from the final 17 articles is summarized in Table 1.

The patient sample size in the included articles ranged from five to 149 patients, mainly including samples from young patients (23 ± 3.8 years old).

In relation to the diagnostic methods described, 13 articles[3–6,8,11,17,27,29,35,38,40,41] used clinical examination; however, none of them provided a detailed description of this process for diagnosing CH. Four articles[26,36,37,39] used only imaging methods, such as orthopantomography, PS, CT, SPECT or SPECT-CT, with no mention of clinical examination. Most of the articles (11)[3–6,8,11,17,27,29,35,38,40,41] used the combination of clinical and imaging tools for their inclusion criteria, being planar scintigrams[8,11,17,36], planar radiographs[3,8,11,17,29,35,39], CT[3,6,38,39], SPECT[3–6,26,27,29,37,38,40,41], and SPECT-CT was the most frequent[26].

Histological descriptions

The most common feature observed in CH condyles was augmented thickness of the cartilage (14 articles)[3–6,8,11,26,27,29,35–39]. Although almost all of these articles described the presence of cartilage islands in their results, three articles did not find any in their whole sample[6,26,29]. In relation to the augmented thickness of the cartilage, there were differences among the studies regarding which specific layers of the cartilage were affected, which are described below.

Cartilage augmented thickness: Proliferative and Hyperplastic/ Hypertrophic layer

Six articles[3,5,29,37–39] found that both the proliferative layer and the hyperplastic layer had augmented thickness. Wen et al.[3] found that condylar cartilage with active growth showed a thicker proliferative zone and hypertrophic layer, characterized by the presence of a marked hyperplasic zone of undifferentiated mesenchymal cells (proliferation layer) and hyaline chondrocytes (hypertrophic layer). Guo et al.[37] showed an upregulation of proangiogenic factors, including fibroblast growth factor-2 (FGF-2) and vascular endothelial growth factor (VEGF), associated with a thickened hypertrophic cartilage layer, a proliferating layer and scattered cartilage islands within the subchondral trabecular bone in CH joints. Vasquez et al.[38] found that all the observed condyles presented proliferative and fibrocartilaginous layers; however, their extension and thickness varied across the condylar surface.

Cartilage augmented thickness and other findings

Six articles described that the whole cartilage was augmented in thickness, with no further details[4,6,8,11,26,35]. Norman and

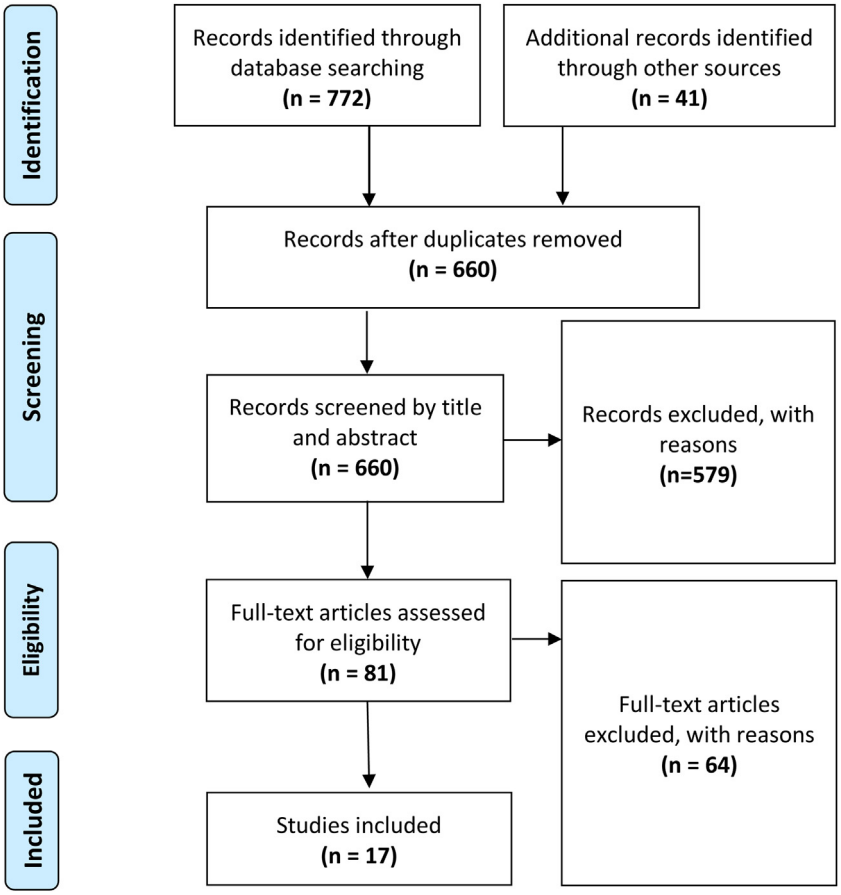

Fig. 1. PRISMA flowchart.

Painter[35] found augmented thickness of the cartilage in the cases that were classified as 'active CH', including cartilage islands surrounded by bone. Besides, Gray et al.[11] observed that all the included patients (20) presented a layer of mesenchymal cells. A marked association was found between the frequency and the depth of the cartilage islands. Saridin et al.[4] found a positive association between the thickness of the cartilage layer and the number of cartilage islands; thus, both histologic features could be associated with excessive bone formation in some patients affected by CH, especially in the younger ones. However, no uniform or characteristic histologic patterns were found in patients affected by CH. Vasquez et al.[6] described the presence of connective tissue islands at the bone level with different levels of aggressiveness of CH or differences regarding the duration of disease activity. Martin-Granizo et al.[26] found that the proliferative layer had a thickness 2.5 times greater in the high-uptake condyle compared with the low-uptake one.

Bone Cortical and Trabecular characteristics

Karssemakers et al.[40] found that condyles affected by CH analysed by micro-CT presented increased cortical porosity, higher bone volume fraction, greater trabecular thickness, separation and number, and less mineralization levels, when compared with known condylar healthy parameters.

Histological Findings and Age

Seven articles evaluated their histological findings according to the age of the patient from which the sample was taken[4,5,8,11,27,29,40]. From these, five articles[4,5,8,11,27] found that the histologic appearance varied according to the age of the patients. Gray et al.[11] described the presence of a persistent layer of undifferentiated mesenchymal cells and elements of overlying osteoarthritis in areas of CH of older patients (39–55 years). They hypothesized that osteoarthritis appeared as a consequence of the resulting pressure from the condylar overgrowth. Saridin et al.[4] found a significant association between age and cartilage thickness. Based on this, younger patients had a thicker cartilage layer than older ones, and tended to have greater number of cartilage islands. Fariña et al.[5] found a significant association between age and cartilage thickness, where older patients had less cartilage thickness, and between age and Ag-NOR counts, where older patients had lower Ag-NOR counts. Meng et al.[8], according to the Slootweg and Müller classification[9], found a strong association between age and the histological type, where type I condyles belonged to significantly younger patients and type III, belonged to the oldest patients. Indeed, a bivariate correlation analysis revealed a significant association between age and cartilage thickness; therefore, histological appearance of condylar hyperplasia could vary according to age. Lopez et al.[27] also confirmed that the presence of cartilage islands is significantly associated with age ($\leq$22 years old). Only two articles[29,40] did not find any association between histologic features and age in CH condyles. Elbaz et al.[29] stated that this absence of association reflected the lack of hormonal control during the post-pubertal period from which the samples were taken. Karssemakers et al.[40] found that there was no significant difference in the age of the CH condyles with increased cortical porosity and those with intact cortical bone.

Histological Findings and PS/SPECT

Nine articles[3–5,11,17,26,27,29,41] evaluated the association between histological findings and PS/SPECT; from which, five articles did not find a positive association. Gray et al.[17] evaluated the association between depth of cartilage islands, trabecular bone volume, percentage of resorption surfaces, osteoid volume surfaces, and PS; though, no association was found between the scintigraphic uptake and the depth of cartilage islands. Saridin et al.[4], using SPECT, found no significant differences between the mean bone uptake on the CH side and the relative thickness of the cartilage layer or with the amount of cartilage islands. Moreover, Fariña et al.[5] and Elbaz et al.[29] could not find an association between the histologic characteristics and SPECT. Karssemakers et al.[41] explored the association between condylar bone volume and measured condylar activity. They did not find any significant association between bone volume fraction assessed by micro-CT with condylar activity measured with SPECT in CH affected condyles.

Conversely, four articles found a positive association between PS/SPECT and their histologic findings. Gray et al.[11] observed that the patients with marked uptake on the scintigraphy had a higher frequency and depth of the cartilage islands. Wen et al.[3] showed that the relative uptake of the affected condyle was not related to the thickness of cartilage layers but was affected by the proliferation of undifferentiated mesenchymal cells and hyaline chondrocytes. Martin-Granizo et al.[26] found that the maximum size of the cartilage islands was the only statistically significant difference between low and high SPECT uptakes in a sample of 28 patients. Lopez et al.[27] found qualitative association between SPECT-positive results and histological findings, i.e. a significant increment in the proliferative layer thickness and the total thickness of the whole soft tissue.

RoB Assessment

Six articles[3,8,27,36,37,39] were described as cross-sectional studies and were analysed with NOS. Two studies[8,36] achieved the highest score; with seven and six stars, and a 77.8% and 66.7% degree of quality, respectively. Two studies[3,37] got five stars, with a 55.6% degree of quality. Finally, two studies[27,39] had the lowest score with four and three stars, corresponding to a 55.6% and 33.3% degree of quality, respectively. All of the studies scored positively for 'ascertainment of exposure', 'comparability' and 'clearly described statistic test'. Though, none of the studies showed a detailed description of the derivation of the exposed group or determination of the sample size, and only few of them were explicit regarding to the outcome assessment.

Apart from that, 11 articles[4–6,11,17,26,29,35,38,40,41] were described as case series studies and were evaluated using the IHEQA checklist. The maximum score was 12 points, achieved by two studies[40,41], five of them achieved 9 points[5,6,11,17,38], three achieved a score of 8 points[4,26,29], and the other one achieved 7 points[35]. All the case series reported that the objective of study was clearly stated, the intervention of interest was clearly described, and that relevant outcome measures were established *a priori*, using appropriate methods. Nevertheless, none of the studies clearly described additional interventions (co-interventions), or relevant outcome measures considered before or after the intervention. Also, all publications scored 'partial/unclear' regarding the patients' inclusion at a similar time point during the development of the disease and to the appropriate follow-up time for important events and outcomes to occur.

In particular, cross-sectional studies failed to describe the representativeness or the origin of the exposed cohort, and blinding during outcome assessment was

frequently not reported, leading to unsatisfactory scores and consequently a high/unclear RoB. In relation to the case series studies, similar results were achieved with almost equal scores of high, partial/unclear and low RoB.

Discussion

Taken together, these results confirm that there is no consensus on a characteristic histological characterization in CH. Two of the main contributors to this lack of histological consensus are the heterogeneity found among the diagnostic methods used and the RoB of the included articles. Beyond the methodological issues mentioned, another explanation for this could be the clinical scenario that CH entails, where there is no possibility of having a reliable control sample of the contralateral condyle for ethical reasons. Therefore, when there is no histological counterpart, only reliable clinical findings can guide the diagnosis.

Even though 14 articles[3–6,8,11,26,27,29,35–39] observed an augmented thickness of the condylar cartilage, no homogenous histologic features were described among all the articles selected regarding the different layers' descriptions. Apart from that, the time when the sample was obtained could lead to questionable results mostly related to the age of the different patients.

Age and histological characteristics were evaluated in seven articles[4,5,8,11,27,29,40], of which five articles[4,5,8,11,27] observed a positive association between their histological descriptions and the age of their sample. Based on these results, it seems that the histological characteristics observed were related to the age when condylectomy was performed rather than to a specific pathology in the condyle. Ji et al.[39] mentioned that the condyle growth activity varies with age, due to the presence of the secondary cartilage layer, which remains as a cell-proliferating zone until the half of the second decade of life[42]. Additionally, it was reported[4] that the age of the subject and the clinical diagnosis are relevant in the histopathological analysis of the disease, in which older individuals present fewer cartilage islands than younger patients. Indeed, normal histological patterns tracking the human condyle evolution through age have been extensively described in the literature. Condylar articular tissue goes through a first group of changes at late adolescence (15 years old) which are virtually complete by the age of 30 years, characterized by appearance of fibrocartilage accompanied by the cessation of endochondral ossification and the formation of a compact subchondral bone plate[43]. Later on, a second group of transformations appear by the age of 50–60 years old, characterized by progressive decrease in cell density and the conversion of loose fibrous connective tissue into dense connective tissue and fibrocartilage[36,43]. Interestingly, Gray et al.[11] found elements of overlying osteoarthritis in their four oldest patients. They speculated that the compression consecutive to the condyle growth may be an explanation for this finding, and that pressure was responsible for the apparition of these degenerative reactive tissues. The possible effects of mechanical loading were also mentioned by Karssemakers et al.[40], who found an increased cortical bone porosity in eight of 17 CH affected condyles. They proposed that the present cortical abnormalities might be secondary to an increased condylar growth and/or abnormal mechanical loading, assuming that this cortical porosity could be a reflection of a higher bone remodelling activity during CH, without discarding the patients' age influence.

The presence of cartilage islands has been considered as evidence of condylar growth at the moment of the condylectomy[8,11,35]. Martin-Granizo et al.[26] found more frequent cartilage islands in those patients with high activity SPECT uptake, even though they could not find them in the whole sample, and Saridin et al.[4] described that their high condylar bone activity samples, on the scintigram, had a low number of cartilage islands. Certainly, it must be considered that not all cartilage islands are active in the process of condylar growth and, consequently, their presence cannot be necessarily associated with the hyperplastic growth of the mandibular condyle[27,38].

In relation to the diagnostic tools described in the selected studies, there was a great heterogeneity among the methods used for diagnosing CH. In fact, there were five articles[4,5,17,27,29] from a total of nine that did not find an association between PS/SPECT and a histologic pattern. Saridin et al.[14] stated that the percentage of differences between both condyles is not a true quantification of bone activity and is subject to potential variations present in the control contralateral condyle. They suggested that more precise bone activity measurements are possible with PET, combined with histologic analysis of condylar specimens, which provides a greater insight into the bone activity of patients with asymmetric condylar growth. In addition, Villanueva-Alcojol et al.[28] suggested that bone SPECT scintigraphy should not be used as the sole determinant for indicating a condylectomy, because it is a highly sensitive test but lacks specificity. Many pathologic conditions related to inflammation, infection, healing processes or even neoplasms could be interpreted as an active CH with consequent progressive growth of the condyle. In the same line of results, Elbaz et al.[29] found that there was a lack of association between the histologic findings and the radionucleotide uptake in the scintigram. Karssemakers et al.[41] found that an increased condylar bone volume in patients with CH does not influence condylar activity on the bone scan. Moreover, SPECT sensitivity and specificity to diagnose active growth in CH was found to range between 32.4% and 67.6%, and 36.1% and 78.3%, respectively, making SPECT scans inadequate for determining condylar growth status in CH patients, resulting in a large percentage of false-positive and false-negative diagnoses of CH and possibly negatively affecting patients' treatment outcome[44]. These results taken together, highlight the lack of reliability of PS/SPECT scan to confirm an active condylar growth during CH and its lack of association with CH histological findings.

In another scenario, the use of PET has been able to improve relative growth assessment assessed by bone scintigraphy, because it allows a quantitative *in vivo* measurement of condylar activity. Saridin et al.[14] assessed bone growth using PET in patients with suspected CH and compared them with normal symmetric subjects. They found that the bone metabolism in the affected side of CH patients presented no significant differences in comparison with the control group. The authors suggested that in some of the CH-suspected patients, the affected condyle continues to grow at a normal rate, together with a cessation of growth in the contralateral condylar region. Because PET has a better resolution than SPECT[45,46], it could be able to provide a reliable physiologic quantification of metabolism processes in the region of interest[45,47,48], thus, it might be a promising tool for identifying active CH. This improved resolution could be explained at least in part, by the different radioisotopes used in SPECT and PET, from which [^{18}F]-fluoride, used in PET, could offer superior biological properties compared with ^{99m}Tc-MDP, used in SPECT,[45] due to its faster clearance from blood and subsequent lower background radiotracer signal.

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Among the selected articles in this review, only one included SPECT-CT in their methodology[26]. They proposed that SPECT-CT could provide the ability to perform both SPECT and CT tests simultaneously, offering greater anatomical definition. However, Liu et al.[49] found that SPECT-CT with precise region of interest drawings was not superior to SPECT in the assessment of CH, which could mainly relate to differences in region of interest drawing techniques. They stated that these findings could be explained by the fact that the mandibular condyle is a morphologically smaller structure, regarding the SPECT spatial resolution; thus, the radioactivity detected in the condyle could be mostly defined by the point spread function of the imaging method rather than by the actual shape of the condyle. Theerakulpisut et al.[50] found no evidence that indicated superiority of SPECT-CT over simple SPECT for the evaluation of active CH. They stated that using SPECT alone would represent a benefit in terms of reduction of patient radiation exposure.

Considering the specific clinical features that CH entails, two main methodological problems were seen in the included studies. First, no detailed description of the clinical process for diagnosis was encountered. Because there is no gold standard method for diagnosing CH[3], the decision process to indicate condylectomy may give false-positive/-negative histological results. Second, there was no clear differentiation in the age of the patients during the sample groups conformation. It is expected that young individuals have histological features different from adult ones[10,43]. Beyond all the diverse histologic descriptions found in this systematic review, there was a frequently reported association between the age of the patient and the histological features of their condyles. Hence, the augmented thickness in the condylar cartilage reported in these articles could be the representation of the expected histological pattern of a condyle that belongs to younger patients rather than a specific pathology. Nevertheless, not all the articles evaluated this association. Also, those that assessed it[4,5,8,11,27,29] did not differentiate young from adult patients (>20 years old) in their methodologies.

In order to perform an adequate evidence-based decision to diagnose and consecutively treat CH, RoB assessment is fundamental to avoid the misinterpretation of results. To our knowledge, this is the first systematic review with a formal RoB assessment of CH cross-sectional studies and case series. From the 17 articles selected for the final revision, only eight articles[5,6,11,17,36,38,40,41] achieved satisfactory levels in RoB assessment using the NOS tool adapted for cross-sectional studies, and IHEQA checklist for case series.

The NOS scale is a quality-assessment tool for the assessment of nonrandomized/observational studies, which assigns an achievement-based quality score for the risk of bias. The tool's modification for cross-sectional studies, based in the comparability of the exposed and control groups, partly excluding the original follow-up component of the tool was applied in the present work. Four of the cross-sectional studies[3,8,36,39] fulfilled over 50% of the items (56–78%), which could indicate that the methodological rigour is acceptable, and could be improved simply by a more detailed report by the authors. Even though case series studies occupy a low position in the hierarchy of evidence, in some cases such as CH, it is the only available evidence to guide healthcare decisions; therefore, the IHEQA checklist was applied in this study. Several criteria examine how the study was executed, whereas other criteria focus on the quality of the reporting. Based on our results, the case series included showed 50% of positive responses, which means that half of the total number of items evaluating case series studies were unachieved. This could be attributed to the heterogeneous way that the requested item was reported by the authors, or the variable applicability of the items chosen within this checklist, for example some of them have a prospective component, absent in some case series.

Finally, we can conclude based on this revision that: (1) almost all the articles (14)[3–6,8,11,17,26,27,29,35–39] described an augmented thickness of the cartilage layer associated with cartilage islands within the subchondral bone in condyles from patients affected by CH; (2) histological findings seem to be mostly related to the age of the sample rather than a characteristic description of CH; though only five articles (from seven)[4,5,8,11,27] found this; (3) no clear association was found between SPECT/scintigram uptake and a specific histological finding; (4) the RoB of the included studies shows in general an intermediate level of methodological rigor; these results encourage the use of specific reporting guidelines rather than modifying the methodological approach to solve the specific authors' objectives, and (5) there is a necessity for the development of specific tools for evaluating and reporting studies where histology is needed for diagnosis confirmation. Further studies should be carried out that examine the onset and development of CH and enable precise diagnostic methods to assess the continuous asymmetric growth of the mandible. Because CH entails specific clinical features, a coordinated clinical evaluation along with validated imaging tools must be accompanied by a precise and homogenous histologic evaluation for its reporting.

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Address:
Sebastián Espinosa
Hospital Sótero del Río
Av. Concha y Toro 3956
Santiago
Chile
E-mails: sespinosas@uc.cl,