MORPHOLOGY OF THE LATERAL PTERYGOID MUSCLE ASSOCIATED TO THE MANDIBULAR CONDYLE IN THE HUMAN PRENATAL STAGE

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ABSTRACT

The lateral pterygoid muscle (LPM) inserts at the condyle and the articular disc and plays a central role in mandibular movement via the Temporomandibular Articular Complex. The aim of this study was to examine the association between the morphology of LPM muscular fascicles and the degree of mineralization of the mandibular condyle in the prenatal stage employing structural, ultrastructural and microanalytical evaluation. Sixteen human fetuses at 11-37 weeks of gestation, with no apparent pathology and resulting from spontaneous abortions, were included in the study. Samples from lateral pterygoid muscle and the mandibular condyle were processed for light microscopy and electron microscopy and microanalysis. Desmin immunolabeling (dilution 1: 25 Dako) and alpha sarcomeric actin immunolabeling (dilution 1:50 Dako) employing the avidin-biotin system were used in paraffin embedded samples. Contralateral samples were examine by transmission electron microscopy. Four condyles (at 17-21 weeks of gestation) were used to measure the relative content of calcium and phosphorous employing the X-ray diffraction microanalytical technique.

At 11-16 weeks of gestation, the LPM was composed of secondary myotubes associated to satellite cells and nerve fibers. At 18 weeks, the muscle exhibited multiple compact fascicles and the condyle showed a thin, external, subperiostal mineralized layer with few central bone spicules. At 20 weeks, at the site of insertion of the LPM, the bone trabeculae of the condyle contained an electrondense matrix with abundant mineralization nuclei. At 17-21 weeks of gestation no significant variations in the contents of phosphorous and calcium were observed. At 24 weeks, transmission electron calcium and microscopy studies revealed a marked increase in the functional units of the muscle fascicles. Also, at this age muscle fibers exhibited differences in the expression of desmin and alpha sarcomeric actin. At 37 weeks the muscle became multipennate in appearance, exhibiting a more complex organization than younger fetuses. Alpha sarcomeric actin labeling became light with age.

This results suggest that between 16 and 22 weeks of gestation the differentiation and maturation process of the muscle fibers precedes and prevails over the development and mineralization process from mandibular condyle. The rudimentary performance of the prenatal LPM would be one of the factors that regulate the process of ossification at the level of the mandibular condyle. The rate of ossification would increase starting from 22 of gestation week.

Key words: *lateral pterygoid, morphology, prenatal stage.*

MORFOLOGIA DEL MUSCULO PTERIGOIDEO LATERAL ASOCIADO AL CONDILO MANDIBULAR EN LA ETAPA PRENATAL HUMANA

RESUMEN

El músculo pterigoideo lateral (MPL) establece una relación directa con el cóndilo y el disco articular, desempeñando un rol importante en el movimiento mandibular a través del Complejo Articular Témporomandibular (CATM). El objetivo de este trabajo fue determinar la correspondencia entre las características morfológicas de los haces musculares del MPL y el grado de mineralización del cóndilo mandibular en la etapa prenatal, mediante un análisis estructural, ultraestructural y microanalítico. Se utilizaron 16 fetos humanos de 11 a 37 semanas de gestación procedentes de abortos espontáneos y sin patologías aparentes. Se obtuvieron muestras del músculo pterigoideo lateral y cóndilo mandibular para ser examinados mediante microscopía óptica, electrónica y técnicas de microanálisis. Muestras incluidas en parafina se emplearon en los estudios de inmunomarcación con desmina (dilución 1: 25 Dako) y alfa actina sarcómerica (dilución 1:50 Dako) visualizados con sistema avidina-biotina. El lado contralateral de cada una se utilizó para microscopía electrónica de transmisión. En cuatro cóndilos de 17 y 21 semanas del desarrollo se analizó el contenido relativo de calcio y fósforo con la técnica microanalítica por difracción de rayos X.

Entre las 11 y 16 semanas el MPL estuvo constituído por miotubos secundarios asociados a células satélites y fascículos

nerviosos. A las 18 semanas, el músculo mostró numerosos haces compactos y el cóndilo presentó una delgada capa externa subperióstica mineralizada con escasas espículas óseas centrales. A las 20 semanas, en la zona de inserción del MPL las trabéculas óseas del cóndilo contenían una matriz electrodensa con abundante núcleos de mineralización. Entre las 17 y 21 semanas no se registraron variaciones significativas en el contenido de calcio y fósforo. Las fibras musculares a las 24 semanas, mostraron un notable aumento de las unidades funcionales al MET y diferencias en su expresión a desmina y alfa actina sarcomérica. La organización del músculo a las 37 semanas fue más compleja con aspecto multipeniforme y con la edad se redujo la intensidad en la inmunomarcación con alfa actina sarcomérica.

Estos resultados sugieren que entre las 16 y 22 semanas el proceso de diferenciación y maduración de las fibras musculares precede y prevalece sobre el desarrollo y mineralización del cóndilo mandibular. La funcionalidad aún rudimentaria del MPL prenatal, sería uno de los factores reguladores del proceso de osificación a nivel del cóndilo mandibular, cuyo ritmo incrementaría a partir de las 22 semanas de gestación.

Palabras clave: *músculo pterigoideo lateral, cambios morfológicos, etapa prenatal humana.*

INTRODUCTION

The lateral pterygoid muscle (LPM) plays a central role in mandibular movement. It is the only muscle that inserts directly at the condyle and the articular disc (1,2).

This muscle has been studied from different viewpoints, i.e. anatomy, histology and electromyography, due to its clinical relevance in temporomandibular disorders (3,4).

In the adult, the LPM is composed of 2 fascicles of fibers. The superior fascicle inserts at the front-medial edge of the capsule and the disc and the inferior fascicle inserts at the front-inner fossa of the condyle neck (5). It has been reported that these fascicles have different functional properties, probably due to differences in the distribution of the fibers of the mandibular and buccal nerves (6,7). The superior fascicle of the LPM carry out the disc forwards and inwards, whereas the inferior fascicle moves the condyle forwards and downwards, protracting the mandible according to their movement, anteriorand/or lateral respectively. When both pterygoid muscles are contracted simultaneously, the opening of the jaw takes place aided by the infra- and suprahyoid muscles (3,6,8).

However, various studies suggest less defined roles for these fascicles. The superior fascicle exhibits great functional heterogeneity due to the existence of muscle cells that differ in contractile activity and metabolism. These cells can be equally active during opening, protrusion and contralateral movements. In patients with dysfunction of the Temporomandibular Articular Complex the superior fascicle exhibits abnormal activity, i.e. it is active both during opening and closing mandibular (9,10). The presence of a third, intermediate fascicle termed the medial pterygoid has been reported. The medial pterygoid acts in conjunction with the masseter muscle to elevate the mandible during mandibular closing (8,11).

The complex structure from LPM is in relationship to its function and so that this capacity is manifested from previous stages to the birth, the muscle must have beenreached a certain degree of morphological maturity during prenatal life (12).

Several studies have described the internal organization of the LPM in fetuses of different mammalian species (13,14). However, few studies have analyzed the human prenatal stage (15,16,17,18,19).

The development of the myogenic elements of the LPM fascicles has been described as heterogeneous and asynchronous (20). The superior fascicle is smaller than the inferior and its muscle cells differentiate earlier (21).

Our previous studies on the structural changes in human temporomandibular articulation revealed qualitative signs of calcification in the condyle at the site of insertion from LPM at 16 weeks of gestation (18,22). These findings are in agreement with Sato et al. (23) who described the importance of the differentiation process from masticatory muscles in the mandible, the condylar cortical and components from temporal bone in the calcification process. These authors also suggested that the masticatory muscles insert at the mandible are responsible for the maturation of the articular structures.

Within this context, we observed that at 24 weeks of gestation the articular bone components were similar to those of the newborn (18,22). A certain degree of maturation of the structures of the Temporomandibular Articular Complex is necessary to guarantee coordinated movements of suction and swallowing in the newborn.

The aim of the present study was to determine the potential correlation between the morphology of the

muscle fascicles and the degree of mineralization of the mandibular condyle in human prenatal life employing structural, ultrastructural and microanalytical analyses.

MATERIALS AND METHODS

The study group comprised 16 human fetuses at 11-37 weeks of gestation, determined according to the cephalo-caudal length tabulated by Patten (24) for different stages of human development. The age distribution of the fetuses is shown in Table 1.

Specimens without apparent pathology were obtained from spontaneous abortions and were kindly provided by the Hospital Universitario Maternidad Nacional de Córdoba, Argentina. The samples from lateral pterygoid muscle (right and left) and condyle were obtained according to the dissection technique of Carranza et al. (17). The samples from the right side were fixed in 10% formalin, pH 7, embedded in paraffin and processed by routine techniques for light microscopy evaluation. Samples were processed for immunolabeling with desmin (dilution 1: 20, monoclonal, Sigma) and alpha sarcomeric actin (dilution 1: 50, monoclonal, Dako), employing the avidin-biotin system and using 3,3'-diaminobenzidine (DAB) as chromogen. Negative controls were used simultaneously omitting the specific antibody. Contralateral samples were processed for transmission electron microscopy observation by fixation in 2.5% glutaraldehyde in phosphate buffer, post-fixation in osmium and embedding in epon. Ultrathin sections were stained with uranyl acetate and lead citrate and observed under a Jeol-Jem (Japan) transmission electron microscope.

The mandibular condyle was submitted to qualitative analysis according to von Kossa for the detection and analysis of the distribution of calcium and to a microanalytical assay to determine the relative contents of calcium and phosphorous. Four condyles of human fetuses at 17-21 weeks of gestation were cryofixed in liquid nitrogen and then cryodissected at –80°C for 24 hours in an Emitech K 775 unit (Emitech, Watford, U.K). The samples were carbon coated for observation under a scanning electron microscope Philips XL30 (Philips, Eindhoven, Holanda) and x-ray dispersive energy analysis (EDAX DX-4, Eindhoven, Holanda).

Evaluation was performed under the following conditions: voltage = 15 kV; spot size = 500 nm; surface angle = 35º; perception angle = 61.34º; counts per second = 1200 cps; time of count accumulation = 50 s. Ten readings were performed per sample. The spectra were taken at magnifications of up to x 40,000. Ca and P salt standards were processed similarly for quantitative analysis. Concentration was measured employing the ratio peak/background. The content of calcium and phosphorous was calculated as weight fraction in millimoles per kilogram of dry weight (mM/kg dry weight). The mean values for each condyle were obtained from 10 measurements per sample. The statistical analysis of the data was performed by Mann-Whitney's non-parametric U test. The level of statistical significance was at $p< 0.05$.

TABLE I. Sample distribution according to gestational age.

Age in weeks	11	15	16	17	18	19	21	22	37
Number of samples	2	2	1	1	3	1	3	2	1

RESULTS

At 11 weeks of gestation, the LPM exhibited muscle fascicles adhered to the condylar surface. These muscle fascicles were composed of zigzagging myofibrils associated to small nerve fascicles. Electron microscopy observation of the LPM revealed the presence of myotubes with euchromatic nuclei and prominent nucleoli. The nuclei often spanned the full thickness of the muscle cell (Fig. 1A). Fine myofibrils showed Z-discs which define sarcomeres. Satellite cells exhibited dense chromatin granules and were located in the vicinity of the myofibers (Fig. 1B).

At 15 to 16 weeks of gestation, the condyle (in the process of endochondral ossification) exhibited a thin, external, subperiostal mineralized layer with few central bone spicules. These exhibited fine, brown, homogeneously distributed granules that corresponded to the deposits of calcium salts evidenced by von Kossa's technique. (Fig. 1C).

At this gestation time, the muscle fibers that inserted at the anterior edge of the condyle were parallel to each other, undulating and loosely packed. Undifferentiated cells with ovoid nuclei were observed on the inner edge of the condylar periostal membrane (Fig. 1D). Lining cells with large nuclei and secretory osteoblasts surrounded by an osteoid

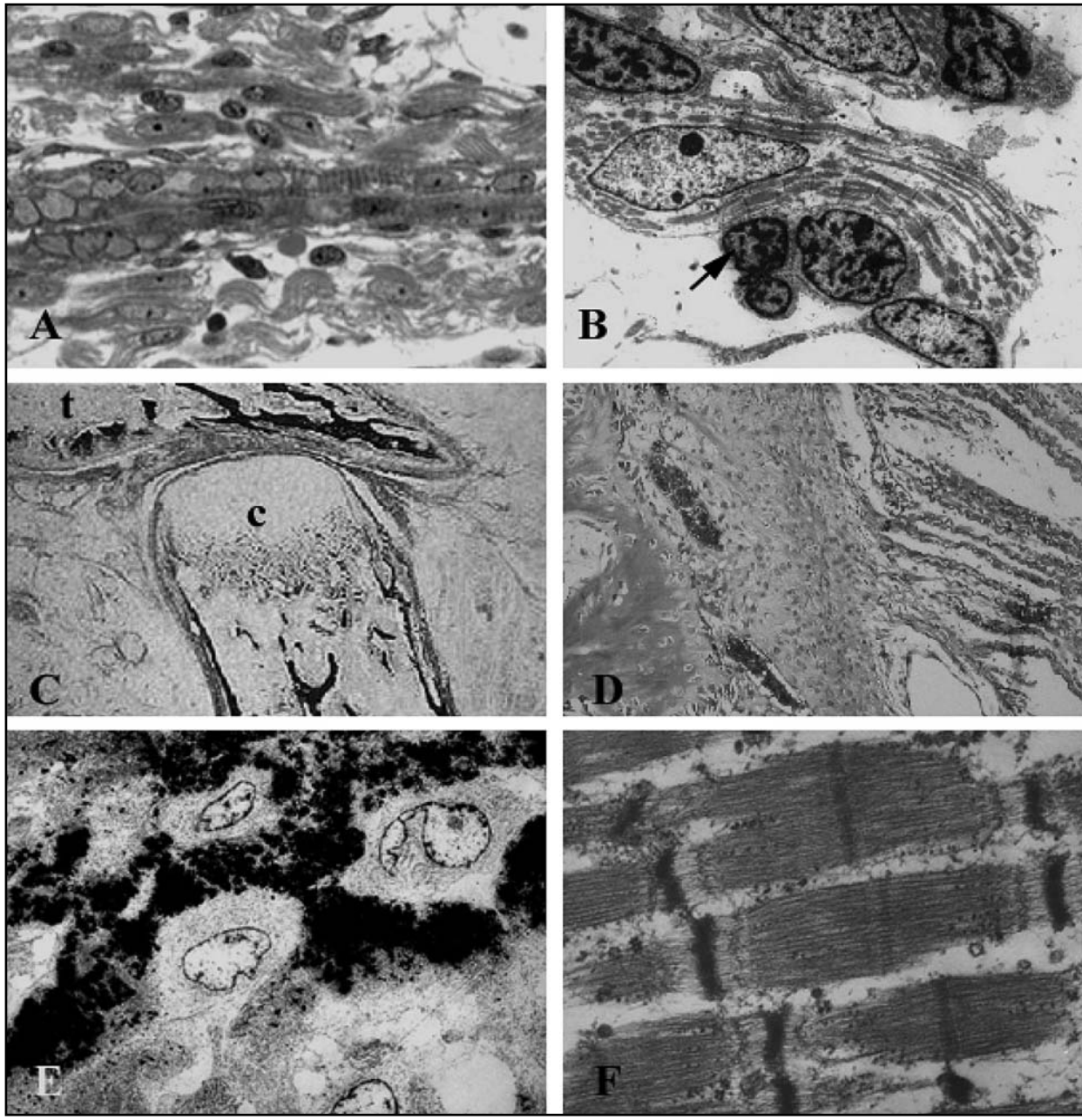

Fig. 1: *Myotubes of the LPM of fetuses at 11 weeks of gestation.* ***A****: Nuclei with prominent nucleoli occupy all the perimeter of the myotubes. Semithin section, toluidin blue stain, original magnification: 450X* ***B:*** *Muscle cells with fine myofibrils in the cytoplasm and euchromatic nuclei with prominent nucleoli associated to satellite cells (arrow) with smaller nuclei containing dense chromatin granules. Original magnification: 2500X.* ***C:*** *Panoramic view of the temporomandibular articulation of the human fetus at 16 weeks of gestation. Calcified bone trabeculae are stained black by the deposit of silver salts, c: condyle; t: scale of the temporal bone. Von Kossa's technique, original magnification: 40X.* ***D:*** *Insertion of the myofibrils of the LPM at the periostium of the condyle cortical at the level of the neck. Sixteen weeks of gestation; original magnification: 100X.* ***E:*** *Condyle osteoblasts surrounded by electrondense, partially mineralized areas of osteoid matrix. Eighteen weeks of gestation; original magnification: 1200X.* ***F:*** *Myofibrils with sarcomeres at a more advanced stage of development. Twenty-one weeks of gestation; original magnification: 8000X.*

matrix with an electrondense mineralization front were found in the vicinity of the trabeculae.

At 17-18 weeks the pterygoid muscle was composed of several compact fascicles surrounded by lax connective tissue. The superior fascicle of the lateral pterygoid muscle was observed innarrow relationship with the anterior band from disk and the inferior fascicle with the anterior border fromcondyle in development.

TABLE II. Mean values ± SD of the content of calcium and phosphorous expressed as weight fraction (mM/kg dry weight) in the mandibular condyle of human fetuses at 17 and 21 weeks of gestation.

	Calcium Mean ± SD	Phosphorous Mean ± SD
17 weeks	30.95 ±6.32	18.14 ±5.55
21 weeks	32.36 ± 4.00	16.45 ±2.89
P =	0.7095	0.1202

The thicker condylar cortical exhibited secretory osteoblasts with large euchromatic nuclei surrounded by a partially mineralized osteoid matrix (Fig. 1E).

At 20 weeks of gestation, the bone trabeculae (from erosion area) of the condyle were composed of lamellae where the osteocytes were surrounded by an electrondense matrix with abundant mineralization nuclei. At 17-21 weeks of gestation the microanalytical assay did not show significant variations in the calcium and phosphorous content (Table 2) and the mandibular condyle did not show changes in its anatomical dimensions.

Electron microscopy observation of the LPM at 21 weeks of gestation revealed the presence of numerous larger functional units in the myofibrils (Fig. 1F). In addition, the cytoskeleton stained less intensely for alpha sarcomeric actin, contrasting with the intense immunolabeling for desmin was observed (Fig.2 A and B).

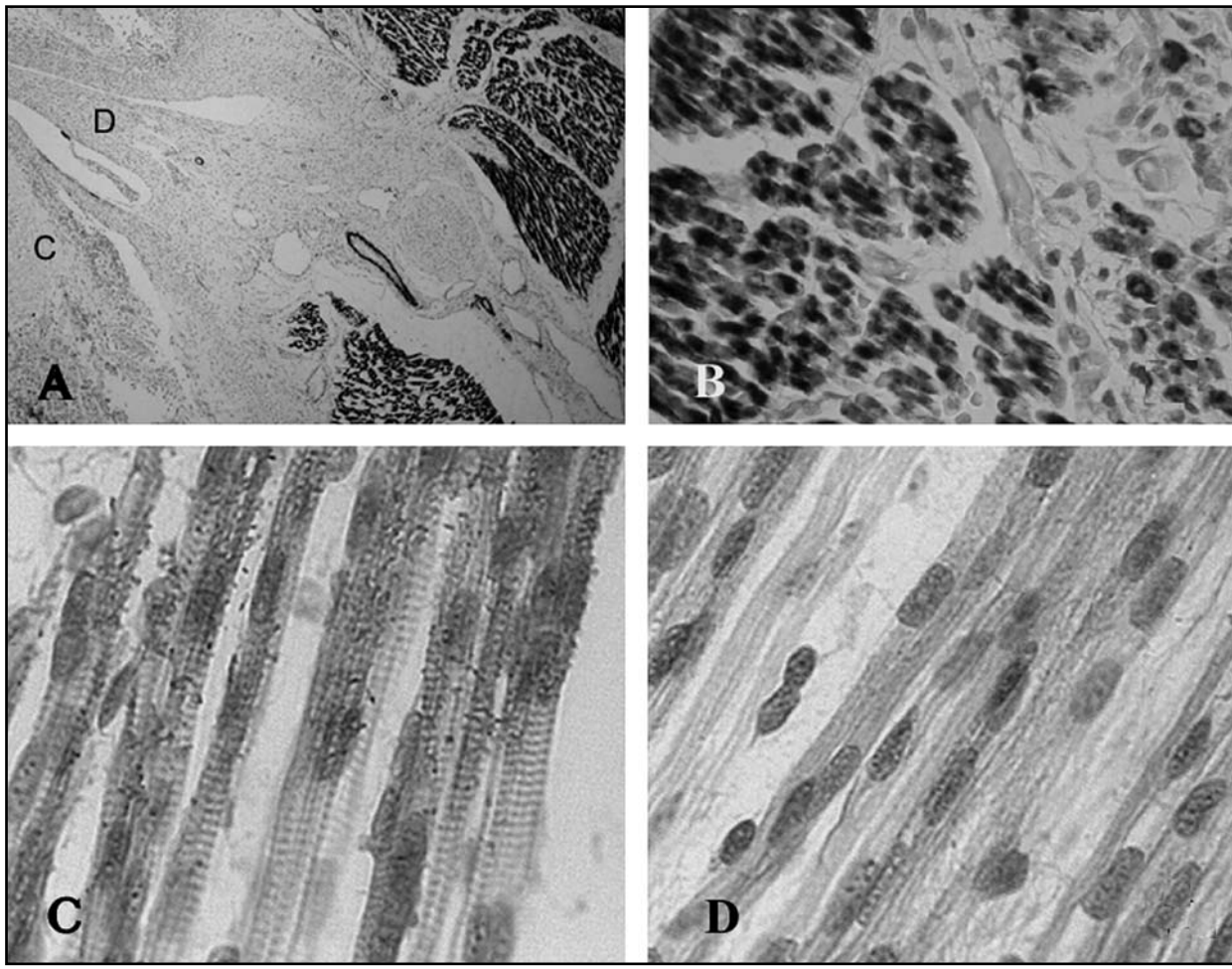

Fig. 2: *Immunolabeling of the LPM at 21 weeks of gestation.* ***A:*** *Fascicles associated to the condyle (C) and disc (D) with positive alpha sarcomeric actin immunolabeling. Original magnification: 40X* ***B****: Myofibrils with positive desmin immunolabeling. Original magnification: 100X* ***C and D:*** *Comparative analysis of myofibrils of the LPM with positive alpha sarcomeric actin immunolabeling. Original magnification,100X* ***C:*** *Immunolabeling is more intense in fetuses at 17 weeks of gestation.* ***D*** *Immunolabeling is fainter in fetuses at 21 weeks of gestation.*

Expression of alpha sarcomeric actin was heterogeneous in the longitudinal fibers of the LPM in the samples taken from the younger fetuses. A single fiber exhibited negative areas of cytoplasm that alternated with intensely positive areas. Labeling intensity decreased progressively as gestational age (Fig. 2 C and D).

At 24 weeks of gestation, the LPM was composed of typical skeletal multinucleated fibers whereas at 37 weeks these muscle fibers were larger and exhibited smaller peripheral nuclei than early stage. The LPM fascicles were more compact, multipennate in appearance and with a larger proportion of blood vessels and nerves than in younger fetuses.

DISCUSSION AND CONCLUSIONS

The importance of the process of differentiation of the masticatory muscles in the calcification from mandible, condylar cortical and components of the temporal bone has been described by Sato et al. (23). These authors suggested that the masticatory muscles inserted at the mandible are responsible for the maturation of the articular structures. These muscles are responsible for the mandibular movements associated to suction and swallowing in the newborn and play an important role in craneofacial growth. The complex and heterogeneous morphology of most of these muscles reflect to functional adaptability (16, 25, 26). The intensity, vector and/or direction of the forces exerted by masticatory muscles have been described as factors that contribute to the mineralization of the mandibular cortical. The intensity and direction of the forces generated by these muscles lead to mandibular protrusion, retrusion and lateral movement within a certain energy range to modify bone cell activity (27).

In the present study the fibers of the LPM were associated to nerve fascicles from 11 weeks of gestation, in contrast to the studies of other authors who reported this association at 20 weeks of gestation (20, 21). With gestational age, the fibers of the LPM exhibited an increase in the number of nuclei and a reduction in the nucleus-cytoplasm ratio, suggesting an increase in cell thickness, probably due to the fusion of satellite cells (14).

The satellite cells associated to myoblasts are a source of new myonuclei that contribute to the growth or hypertrophy of the muscle cell (28, 30).

It has been shown in experimental animals that the number and size of the fibers determine the muscle mass responsible for mandible movement. A high number of muscle fibers is correlated with more rapid and efficient growth. These features are established since birth (29).

This study revealed qualitative differences in LPM muscle mass size. In addition, we evidenced a more complex organization of the smaller fascicles that are surrounded and bound by connective tissue.

At the more advanced stages of gestation, the osteoid matrix of the cortical, the thin trabeculae and the spicules of the condyle exhibited a larger proportion of mineralized areas compared to the earlier stages of gestation. However, there were no statistically significant differences in calcium and phosphorous content between specimens of 17 and 21 weeks. There were no noteworthy changes in dimensions or structure either. These findings suggest that no significant condylar growth or development occurred during this period.

However, over approximately the same period, the muscle fibers exhibited marked differences in terms of cytoskeleton organization, number and development of sarcomeres. These findings are in keeping with reports by other authors (23, 27).

Myofibrils exhibited alpha sarcomeric actin immunoreactive areas alternating with negative areas, suggesting a non-uniform organization of the cytoskeleton throughout each muscle cell at the same gestational age. In addition, alpha sarcomeric actin was expressed less intensely in the more mature myofibers, suggesting a process of progressive differentiation in the fascicles of the lateral pterygoid muscle.

Within this context, previous studies reported that the cross section of the fibers increases markedly during the last trimester of gestation, exhibiting a positive, significant correlation between diameter, number of nuclei and density of capillaries in the muscle fascicle (31). Piatkowski and Wosniak (21), reported a significant increase in the length of the fibers and the muscle in general between 11 and 20 weeks of gestation, the inferior fascicle being longer than the superior.

The specimens examined herein exhibited a marked increase in the thickness of the muscle fascicles, probably due to an increase in the size or number of the muscle cells. In this context, it has been described that the growth of skeletal muscles depends on the number of fibers that are formed during gestation and that the number of

fibers is inversely proportional to the thickness of the fiber at the end of the period of high growth rate (14).

In the present study we observed that the compact areas of mineralization in the condyle correspond to the insertion sites of the inferior LPM. The tension forces exerted by the fibers would play an important role in the development and growth of the condyle after 21 weeks of gestation. According to Christensen et al. (29) the expression of Myo D would control the differentiation process of the fibers to different types (Type I and II).

Other factors such as osteoprotegerin (OPG) and the expression of RANK-L would also play a role in modulating the activity of osteoblastic and osteoclastic cells during the process of condyle differentiation (33).

From 24 to 37 weeks of gestation, the fibers of the LPM and the condylar process exhibited the classical morphology of the newborn, analyzed by our laboratory in previous studies (17, 18).

The results of the present study suggest that between 16 and 22 weeks of gestation the process of differentiation and maturation of the muscle fibers precedes and prevails over the development and mineralization of the mandibular condyle. These findings would explain the slight radiopacity of the condylar cortical described in previous radiographic studies (32). Possibly, the rudimentary function of the prenatal LPM would be one of the factors that regulate osteoblastic activity and the calcification process of the mandibular condyle, as suggested by Maki et al. (27). These processes would increase their rate as from 22 weeks of gestation.

The events described after birth resemble prenatal development, suggesting that the morphogenetic and growth processes are continuous throughout gestation and post-natal life (34). The present data are a starting point to evaluate the morphological and functional relations between the masticatory muscles during post-natal life.

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