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The Mucocutaneous Junction at the Lip and a Comparison with other Junction Sites: A Mini-Review

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Abstract

The mucocutaneous junction (MCJ) is a specific site located at body orifices such as the lip and mouth, nasal orifice, eyelid, vulva, prepuce and anus. The present review was conducted to show the similarity and difference among these sites of the MCJ in terms of 1) cytokeratin expression, 2) the distribution of immunoreactive cells, 3) nerves and terminals, and 4) site-specific cell lineage and other features. In near-term fetuses, routine histology clearly demonstrated the putative MCJ due to a transient, thick stratification of the epithelium. This was most evident in the oral mucosa and less evident in the palpebral skin. In the anus and eyelid, the MCJ developed from highly proliferative epithelia of future glands, independent of the growing skin and mucosa of a simple origin from the surface ectoderm. In elderly individuals, the MCJ was expanded in the nose and anus possibly as a result of mechanical stimuli, and was apparently connected to a hemorrhoid venous plexus. At the vulva and prepuce, a morphology intermediate between pseudostratified columnar and stratified squamous epithelia was evident at near-term. Except for the vulva and prepuce, corpuscle-like nerve terminals were sandwiched between the dermal papillae and epidermis, whereas nerves arranged in parallel exhibited free ends beneath the mucosa. Langerhans cells were richly distributed in the skin stratum spinosum, while suppressive T lymphocyte clusters were present in the lamina propria mucosae. Those observations might teach us that the lip does not show a general morphology.

Keywords: Mucocutaneous junction; lower lip; eyelid; external nasal orifice; vulva; prepuce; anus; immunohistochemistry; human fetus; elderly cadaver

Introduction

The mucocutaneous junction (MCJ) is a specific site located at body orifices such as the mouth, nose, eyelid, vulva, prepuce, and anus. Dentists are familiar with a MCJ between the skin epidermis and oral squamous epithelium, but such a pair is rare in the body. Rather than a squamous epithelium, the MCJ is usually adjacent to the columnar or cuboidal epithelium (Table 1). Therefore, usually, a site deep to the MCJ is weak against a mechanical stress and liable to bleeding. The MCJ is much wider and longer than the dentists' expectation because the lip has an exceptionally narrow and short MCJ (Table 2, the first line). At the vulva and prepuce, a morphology intermediate between pseudostratified columnar and stratified squamous epithelia was evident and very widely extended at near-term. The MCJ of the lips does not have papillae like the dermis of the skin, so it resembles a mucosa rather than skin. And, the stratified squamous epithelium of the MCJ of the lips is thinner than mucosa (Table 1 the first line). Therefore, even though the MCJ of the lips is narrow, it is a common site for mucosal diseases such as epidermolysis bullosa. In other words, clarifying the specific structure of the MCJ is very important for understanding oral mucosal diseases. The present mini-review would show a clear difference between the lip MCJ and the other sites of MCJs in the human body. Although dentists may not aware of which site is the lip MCJ, the morphological specificity would provide a new insight for the care, we believe.

Table 1: Mucocutaneous junction and the adjacent mucosal epithelium in usual histology

	Mucocutaneous junction	Mucosa
Lip	thin stratified squamous epithelium (ep)	thin or thick stratified squamous ep
Nasal orifice	thin stratified squamous ep with few goblet cells	pseudostratified columnar ep with cilia (usually called respiratory ep)
Eyelid	thick or thin stratified squamous ep	pseudo-stratified cuboidal ep with goblet cells
Urethral orifice	thin stratified squamous ep (Note: the genital skin has no dermal papillae)	pseudostratified columnar ep
Anus	simple cuboidal ep with few goblet cells (usually called anal transitional zone)	tall columnar ep with abundant goblet cells

Table 2: Characterization of five sites of the mucocutaneous junction

	Lip	Nose	Eyelid	Urethra & anus
Skin(S) to mucosa(M)	sudden & short	gradual at S-MCJ; sudden at MCJ-M	gradual and long	gradual and long (urethra), sudden at MCJ-M (anus)
Cytokeratin expression	same as M	same as S	same as S	same as M
Langerhans cells	S< MCJ < M	absent	S>MCJ> M	fewer than S (absent in M)
Nerve terminals	varicose-like; free ends	free ends	free ends	free ends (urethra), few ganglia (anus)
Comification toward the lumen	no closure	closure	no closure	closure (urethra) no closure (anus)
Cell lineage	surface ectoderm	surface ectoderm	meibomian duct origin possibly	anal sinus origin
Specific structures	recurrent nerve course	striated muscles	eyelash; striated muscles	dilated veins; smooth muscles

Goblet cells at the adjacent M	usually absent	present	present	present	

Lip: reference number [4], [11-13], [28], [29]; Nose: [15], [16], [34] ; Eyelid [2], [3], [14], [33] ; Urethra & anus: [5-7], [10], [17-27], [31], [32], [35-37]

Classically, the MCJ epithelium was known to show desquamation with a lack of both desmosomal contact and a lining of microplicae that anchor the polyanionic glycocalyx [1]. The classical criterion is believed to suggest a histological border as typically seen between the squamous and columnar surfaces (see above the paragraph) because the manner of cell-cell contact determines the histology. Later, using human eyelid specimens, Knop et al. [2] and Tektaş et al. [3] newly defined the MCJ as having a discontinuous epithelium comprising of para-keratinized cells (not fully but partly filled with bulky bundles of keratin). Thus, the recent concept of the MCL is essentially supported by electron microscopy observations. However, the recent definition is difficult to apply to the lip and mouth because an electron microscopic study appears too hard to find the very short and narrow MCJ. The eyelid MCJ corresponds to an almost entire area of the approximation surface in the classical view, but it corresponds to a posterior one-third in the recent view. Such differences may arise from electron microscopy observations that focus on one or a few MCJ cells. To connect between the ultramicroscopic and clinical macroscopic observations, the present results are based on low-magnified microscopic observations including the entire MCJ to reveal 1) the morphology and length of the MCJ, which varies from site to site, and 2) the specific structure of the MCJ compared to skin and mucosa.

Specimens

This study was conducted in accordance with the provisions of the Declaration of Helsinki 1995 (as revised in 2013). We dissected three cadavers (one men and two women; aged 75–86 years) that had been donated to Tokyo Dental College, Tokyo, Japan, for research and education on human anatomy with the approval of the Tokyo Dental College committee for research use (No. 922-2). The five late-stage fetuses (CRL; crown-rump length 150-310mm) were part of the collection kept at the Department of Anatomy, Akita University, Akita, Japan. They had been donated by the families concerned to the Department in 1975–1985 and preserved in 10% w/w neutral formalin solution for more than 30 years. Data for these specimens included the date of donation and the number of gestational weeks, but did not include the name of the family, obstetrician or hospital, or the reason for abortion. The use of these specimens for research was approved by the Akita University Ethics Committee (No. 1428) and the second author (G.M.) is one of members of the research project. The research ethics committee of Tokyo Dental University also approved the use of the materials (No.932-2).

Viewpoints for Comparison of MCJ Morphologies

Cytokeratin polypeptides (CKs), one of cytoskeletal components, show an epithelial type-specific expression. The human skin epidermis strongly expresses CK1 and CK10 [4]. CK7 is a specific marker of the urogenital tract epithelium especially in early fetal development [5, 6], although the urogenital sinus-derived structure later becomes positive for CK14 and CK17 [7]. CK5 and CK6 (usually abbreviated as “CK5/6” because of the specificity of commercially-obtained antibodies) are used as markers of foregut-derived structures [8, 9]. Therefore, CK immunohistochemistry is a commonly accepted approach for studies of the MCJ [2, 3]. However, on sections from human cadaveric specimens, CK immunohistochemistry often yields poor results (inconsistent activity or loss) possibly due to delayed fixation or long-term preservation. Instead, Table 2 (the second line) postulates a simple viewpoint for understanding CK reactivity: which of the adjacent skin or mucosa expresses the CK subtype same as the MCJ (Figure 1h and 3c-e).

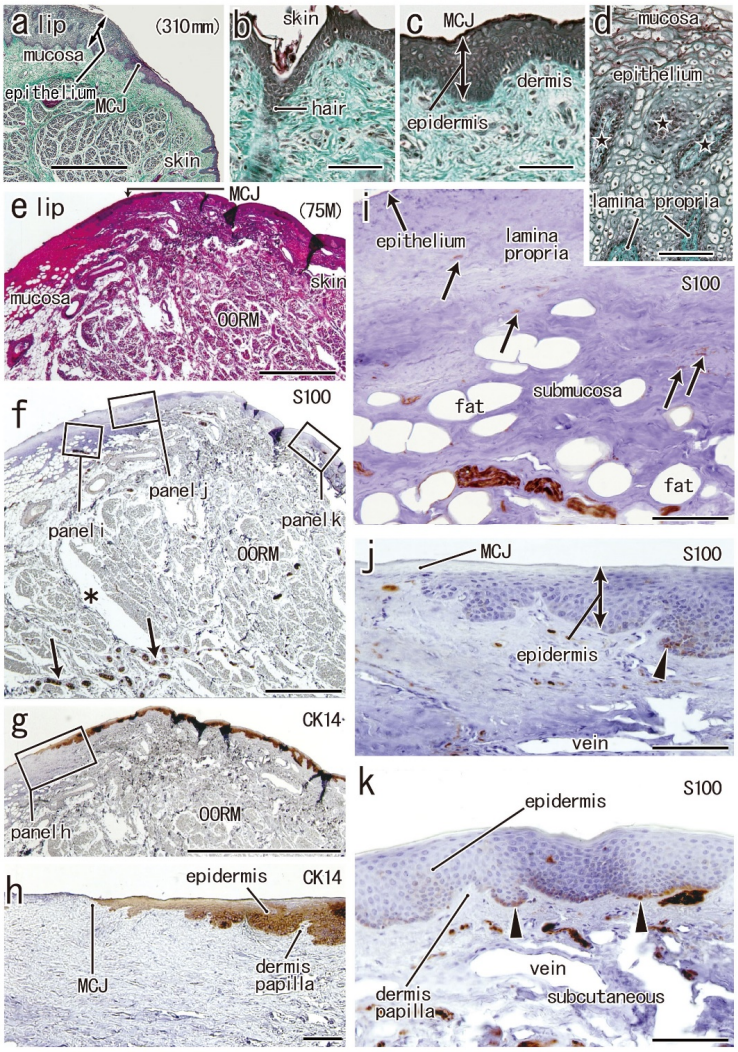

Figure 1: Mucocutaneous junction of the lower lip of a near-term fetus and an elderly man

All panels are sagital section. 310-mm fetus (panels a-d), 75-year-old man (panels e-k). Masson trichrome staining (panels a-d), HE staining (panel e); immunohistochemistry for S100 protein (panels f and i-k); immunohistochemistry for cytokeratin-14 (panels g and h). Higher-magnification views of squares in panel f (or a square in panel g) are/is shown in panels i-k (or panel h). Panels e-g show adjacent sections. Arrows in panel f a perforating nerve to the skin. Stars panel d indicate superficial protrusions of the lamina propria. Arrowheads in panels j and k indicate corpuscle-like nerve terminals. Asterisks in panel d indicates a tissue damage during the histological procedure. OORM, orbicularis oris muscle. Scale bars, 1 mm in panels a and e-g; 0.1 mm in panels b-d and h-k.

Langerhans cells (a type of dendritic cell), CD8-positive suppressor T-lymphocytes and macrophages are generally distributed in and/or beneath the epidermis and mucosal epithelium (Figure 2). However, it seems that few data are available regarding any changes in their distribution and density at the MCJ. Omine et al. [10] performed a limited study of differences in the density of these cells between the skin and mucosa at the eyelid, mouth, prepuce and anus (Figure 2; Table 2, the third line).

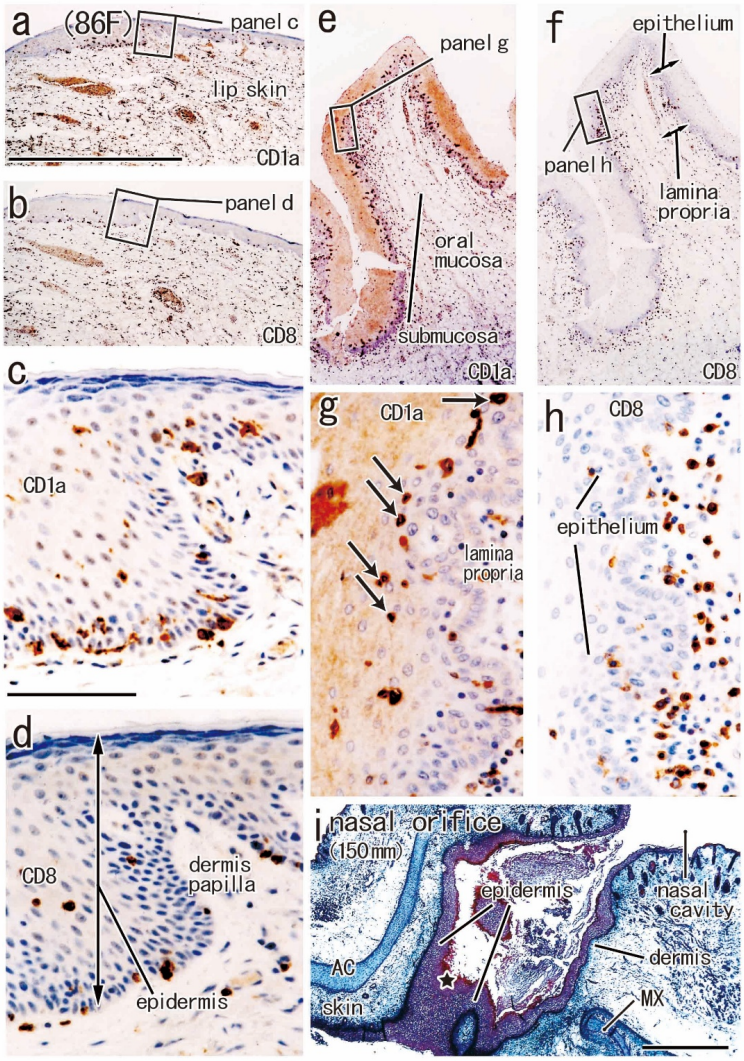

Figure 2: Immunoreactive cells in the oral mucosa and lower lip

An 86-year-old woman. Panels a-d display the lower lip skin, while panels e-h show the oral mucosa near the lower lip. Panels c and d (or panels g and h) are higher-magnification views of the squares in panels a and b (or panels e and f), respectively. Immunohistochemistry of CD1a (panels a, c, e and g) and CD8 (panels b, d, f and h). Panel I, a sagittal section (elastica Masson staining) of the nasal orifice of a 150-mm fetus, exhibits a closure of lumen with cornification (star). AC, alar cartilage; MX, maxilla. Panels a, b, e and f or panels c, d, g and h were prepared at the same magnification (scale bars: 1 mm in panels a and i; 0.1 mm in panel c).

The distribution of free nerve terminals, especially those of pain nerves, and specific corpuscles, has been described at limited sites, including the oral mucosa [11-13] (Figure 1i-k), eyelid [14] (Figure 3ab), nasal respiratory epithelium [15, 16], glans penis [17-19] and anus [20] (Table 2, the fourth line). In the anus, the intestine-specific myenteric plexus disappeared slightly orad to the MCJ. However, parts of intestinal ganglion cells extend lower or superficially and they were sparsely distributed in the intersphincteric zone beneath the MCJ [21-25]. Notably, submucosal free nerve ends are few or even absent beneath the MCJ in con-

trast to the adjacent skin and mucosa. Hörsch et al. [26, 27] demonstrated chromogranin-positive elongated neuroendocrine cells distributing densely at the anal MCJ (Figure 3h).

Few studies have demonstrated differences between the skin and mucosa in the course (depth or lamination) and density of nerves, except for the glans penis [18], the lower lip [13] and the upper eyelid [14]. The upper eyelid contained two types parallel nerves at term: 1) 2 or 3 nerve twigs along the anteroposterior axis (arrowheads in Figure 3b) and 2) abundant nerve twigs along the mediolateral axis (arrows in Figure 3b).

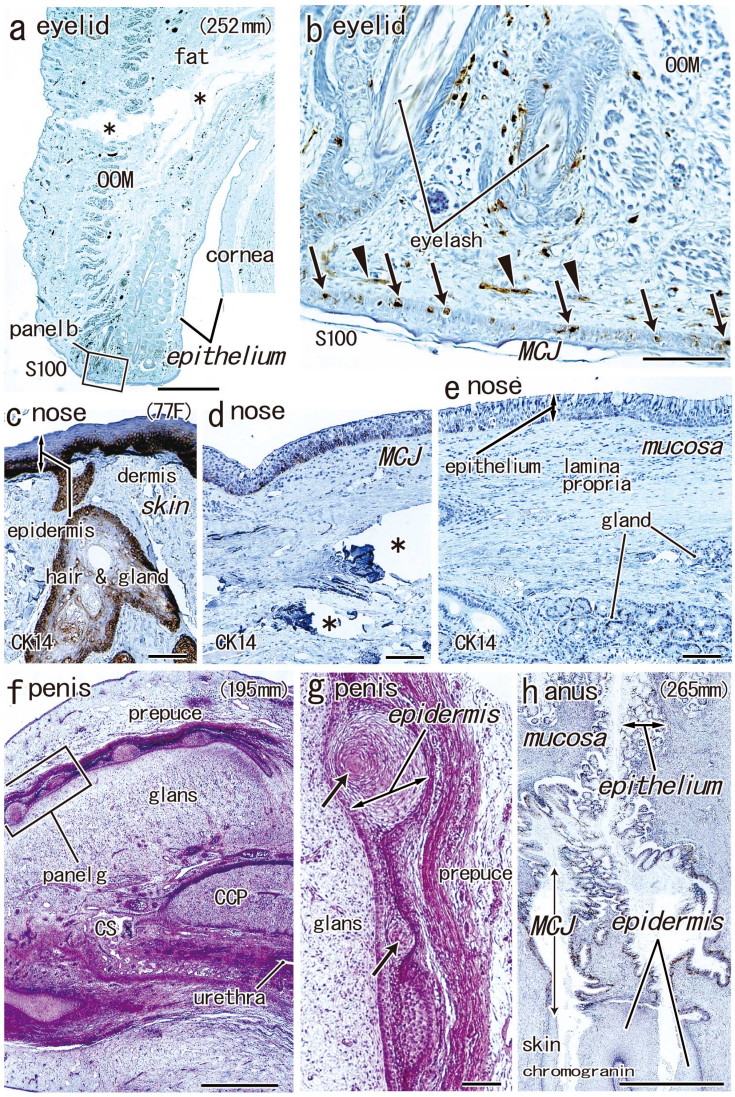

Figure 3: Mucocutaneous junction in the eyelid, nose, penis and anus

Panels a and b (Immunohistochemistry for S100 protein), the upper eyelid of a 252-mm fetus. Panels c-d (Immunohistochemistry for CK14), the nasal orifice of a 77-year-old woman. Panels f and g (HE staining), the glans penis of a 195-mm fetus. Panel h (Immunohistochemistry for chromogranin A), the anal canal of a 265-mm fetus. Panel b (or panel g) is a higher-magnification view of a square in panel a (or panel f). Arrows and arrowheads in panel b indicates the mediolateral and anteroposterior nerve fibers, respectively. Arrows in panel g indicate the hypertrophic epidermis of the glans. Asterisks in panel d indicate tis-

sue damages during the histological procedure. CCP, corpus cavernosum penis; CS, cavernous sinus of subcutaneous veins; OOM, orbicularis oculi muscle. Scale bars, 1 mm in panels a, f and h, 0.1 mm in panels b, c-e and g.

Lip and Mouth

The lips showed the typical changes in MCJ morphology immediately outside or anterior to the approximation surface (free surfaces attached to each other between the upper and lower lips). Thus, the approximation surface corresponded to the mucosa. The change was marked at near-term because, in the mucosa with hypertrophic surface cells, the stratification was 6-7 times taller or thicker than that of the skin (Figure 1a-d).

According to Cho et al. [13], the lip skin epidermis in elderly individuals expressed cytokeratin-14 (CK14) at any depth, while CK14 positivity was limited to the most superficial lamina of the stratified epithelium of the mucosa and MCJ (Figure 1gh). Thus, the lip skin exhibited sudden loss of strong CK14 positivity at the MCJ. CK5/6 and CK19 were negative in three parts of the lip in elderly individuals. Langerhans cells were richly distributed in the stratum spinosum, while CD8-positive T lymphocytes were dominant in the lamina propria beneath the mucosal epithelium (Figure 2). In the elderly, the lip mucosa lacked a tall stratified layer, often resembling simple squamous epithelium (Figure 1a vs. Figure 1e).

Near the free margin of the lower lip, a thick perforating branch of the mental nerve turned superficially (anteriorly) to pass through the upper end of the orbicularis muscle layer to supply the lip skin, whereas another thick branch took a reverse J-shaped course (or the recurrent course) along the stratified squamous epithelium of the approximation surface and reached the MCJ. In the subcutaneous tissue, nerve twigs were concentrated along and around veins and dermal papillae. At the MCJ, terminal nerve twigs running in parallel to the mucosal surface were replaced by capsule-like nerve terminals attached to or surrounding internal protrusions of the skin stratum spinosum between the dermal papillae. This change in nerve terminals was much more evident in elderly individuals than in fetuses (Figure 1i-k). In addition, the oral mucosa contains encapsulated nerve terminals [28] and a Merkel cell-neurite complex [29].

Overall, in the fetal lips, the mucosa was characterized by 1) very thick stratification of the cornified layer and 2) a short and sudden change at the MCJ where thick cornification was lacking. As nerve twigs are likely to be underdeveloped even in late-stage fetuses, a drastic change in nerve terminals at the MCJ would likely occur after birth or when suckling is initiated.

Site-Specific Morphologies of the MCJ

Although it is seen at a short period of fetuses (1-2 weeks), the so-called cornification (Table 2, the fifth line) or hypertrophic keratinized cells consistently close the nasal orifice (Figure 2i), the male urethral orifice [18] (Figure 3fg) and, the external acoustic meatus [30]. The oral mucosa near the lip carries a very thick epithelium (Figure 1ad), but it never closes an opening of the mouth. The cornification site at and around glans penis corresponded to the very wide MCJ at the urethral orifice in adults, but the cornification site at the nose (i.e., vestibulum) is covered by the skin in adults.

The MCJ has specific cell lineages at the anus and eyelid. The anal MCJ (usually called “anal transitional zone”) is originated from the fetal anal sinus epithelium. The anal sinus plays a great role to enlarge the initial, ectodermal anal canal and, in adults, the sinus finally differentiates into anal glands opening to the anal MCJ [31, 32]. Likewise, the eyelid MCJ is most likely to originate from the meibomian duct epithelium. The glands make a large mass in the upper and lower lids and, at late term of fetuses, a rapid proliferation of the lid MCJ closes the duct opening to induce highly dilation of the ducts [33].

The eyelid approximation surface or the MCJ contains eyelashes. In contrast, the palpebral skin (its epidermis and dermis) is possibly the second thinnest in the body (the thinnest, the lip). The anal skin surrounding the lumen has no hairs in fetuses.

Likewise, the female vulva and male prepuce, that largely correspond to the MCJ, have no hairs even in adults. The MCJ is usually adjacent to the mucosal epithelium with goblet cells, but the elderly oral mucosa contains few goblet cells. The MCJ tends to receive a mechanical stress: thus, the nasal MCJ seems to extend deeply or superiorly and the anal MCJ becomes contained dilated veins depending on age.

Finally, muscle cells are usually close to the MCL: 1) striated muscle fibers at the upper eyelid (Riolan's muscle = a marginal enlargement of palpebral parts of the orbicularis oculi muscle), the lip (orbicularis oris muscle), the nasal orifice [34] (nasalis muscle) and 2) smooth muscle fibers at the anus as well as the female vulva and male prepuce [35, 36]. The submucosal anal muscle beneath the MCJ, corresponding to the muscularis mucosae of intestines, shows a great individual variation in thickness and area [21]: it is quite different from the longitudinal anal muscle (smooth muscles) that corresponds to the longitudinal muscle layer of intestines and connecting with the levator ani muscle slings [37].

Conclusion and Clinical Relevance

Because of the sudden change and because of the squamous-to-squamous surfaces, dentists may not make a sense of the lip MCJ. In the elderly, the wide and gradual change at the other MCJs requires a site-specific care such as an ointment containing estrogen, antibiotics and/or lipid. As tried or performed for an intensive care of the oral mucosa and gingiva [38-40], the lip MCJ seems to be a critical target of routine observation and care.

Study Limitation

Because of material limitation due to the age of donation we were unable to observation young adult morphology. Thus the real postnatal development is still unknown.

Declarations

Conflict of Interest

No conflicts of interest declared.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki. The use of the study specimens was approved by the Ethics Committee of Tokyo Dental College (No. 922-2, 932-2).

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