Original Article

Optical Microscopy for Histological Architecture of Skin Prepuce at 1st Six Years of Childhood

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Abstract

Introduction: The prepuce or foreskin represents the skin that covers the glans of the penis. The current study sought to show the histological architecture of preputial skin during the first six years of human aging. Histological characterization is important in identifying the rate of distribution of phimosis and balanitis. **Methods:** Specimens were collected from volunteer boys, and circumcisions were done at the traditional clinic during the period between April to June 2023. All circumcisions were done under local anesthesia. Specimens were microscopically diagnosed. **Results:** The microscopical examination of group G1(six months of age), showed an outer layer composed of epidermis epithelium (basal row, squamous cells, and granular cells) that are coated by strands of keratins. The second group G2 (12- 24 months of age), showed an increase in several epidermal layers which increased with age, represents as basal layer resting on the basement membrane. Third group G3 (24- 36 months of age), the dermis contained a condense of collagen bundles, beneath the epidermis papillae. The fourth group G4 (36- 48 months of age), showed hyperplasia of epidermal epithelial cells with dark basophilic stain outer surface of these layers covered by multiple strands of keratin. The fifth group G5 (48-60 months of age), showed well-differentiated dermal nerve fibers in the hypodermal region. The sixth group G6 (60- 72 months of age) demonstrates epidermis was formed by multiple rows of epidermis, present in a hyperplastic phase with dark chromatin stain, with thick strands of keratin that appear desquamated strands. **Conclusion:** The outer layer of the prepuce is made up of epidermal epithelium with well-differentiated epidermal papillae. The dermis is extensively vascularized and innervated, containing large collagen bundles. Future studies are required to further enhance histological differentiation and the skin layers of the prepuce or foreskin.

Keywords: Preputial Skin, Epidermal Layers, Pericytes, Nerve Fibers.

Introduction

The skin represents the largest organ of the body, covering the body, the proportion of skin is about 15% of body weight.[1-3] The outer layer of prepuce skin (epidermis) was revealing a typical characteristic of thin skin.[4] Foreskin appeared as a simple fold of skin made from a stratified keratinized layer (outer) and inner mucosal layer, lining the prepuce. It works as a protective layer the underneath tissues of the penis (glans of the penis and urethral meatus). A sheath of muscle known as the dartos muscle is present beneath the skin.[5,6] The epidermal layer of prepuce, was composed of a squamous stratified keratinized layer and an inner mucosal layer, lining the preputial sac, so prepuce skin was a part of preputial development.[7,8] The development of the prepuce started dorsally during the 12th week of gestation with the ventral completion of the prepuce at about 16 weeks of gestation.[9] The prepuce and eyelids revealed a reduced stratum and the absence corneum layer.[10] During the childhood developmental period, developed skin prepuce showed thicker epidermal and dermal layers.[11] The prepuce is responsible for protecting

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Quick Response Code:

Website: www.jnsbm.org

DOI: https://doi.org/10.4103/jnsbm.JNSBM_16_1_14

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Submitted: 22nd January, 2025 **Received:** 02nd March, 2025
Accepted: 06th March, 2025 **Published:** 11th March, 2025

How to Cite This Article: Obayes A K, Hamad S M, Salih A I M, Ebraheem A H. Optical Microscopy for Histological Architecture of Skin Prepuce at 1st Six Years of Childhood. J Nat Sc Biol Med 2025;16:127-133

the glans and urethral meatus, due to decreasing external irritation or contamination.[12] The dermis plays a major role in the differentiation of the epidermal cell stratum.[13] So, the prepuce exhibited an essential function to protect the immature glans from chemical or mechanical injuries.[13] A few studies were detailed prepuce skin development in boys' school aged.[14] The present study aims to follow the development of preputial skin during the first six of years age (childhood).

Material and Method

Study designed to following up the prepuce skin development during childhood period, where divided into five groups

Group 1 (G1): 6 – 12 month,
Group 2 (G2): 12- 24 month,
Group 3 (G3): 24 - 36 month,
Group 4 (G4): 36 – 48 month,
Group 5 (G5): 48 – 60 month
Group 6 (G6): 60 – 72 month

Ethical approval: The study was registered and approved by the College of Education for Women, University of Kirkuk (Approval letter Number 1501 on 29.04.2024).

Sample collections: Samples were collected from volunteer boys in traditional clinics during the period of study between April to June 2023. The circumcision was done as a part of their cultural non-medical reasons. All circumcisions were done under local anesthesia.

Histological study: Histological preparation was done in the histology lab. At College of Veterinary College, University of Tikrit (Iraq). The removal prepuce skin was fixed in 10% buffered formalin solution for 24 hours, followed by embedding in paraffin wax 60°C blocking, sectioning was taken and finally stained with Hematoxylin and eosin to prepare for microscopical examination.[15]

Microscopical examination: After staining with hematoxylin and eosin, the skin samples were examined under a light microscope and the examined area was differentiated into the epidermis, dermis, mucosal layer, and lamina propria; the developmental changes were accordingly characterized.

Results

Group 1 (G1): The results of the histological examination of this group (six months of age) show, that the epidermis was a multiple layer of stratified squamous epithelium (basal row, squamous cells, and granular cells) covered by strands of keratins. The dermis was composed of connective tissue, which was infiltrated by WBCs and macrophages. The preputial dermis contained a dense collagen bundle, associated with WBCs and fibrocytes, and sweat glands regular as longitudinal coarse with few blood capillaries around them (Figure 1).

Group 2 (G2): The results of this group (12- 24 months of age) revealed, an increase in several epidermal layers arranged as basal rows of epithelial cells resting on the basement membrane, the spinous layer had spherical nuclei, surrounded by vacuolar zone and the keratin cells layer which was dark stained cells row arranged and covers by dissociated keratin strands, the dermis was containing an upper zone below the basement, formed by delicate connective tissue with many WBCs, macrophages, and fibroblasts. The hypodermal artery is engorged with blood, with well-differentiated smooth muscular fibers of tunics media, and hypodense real vrealis engorged with RBCs, surrounded with infiltrated WBCs and fibroblasts (Figure 2).

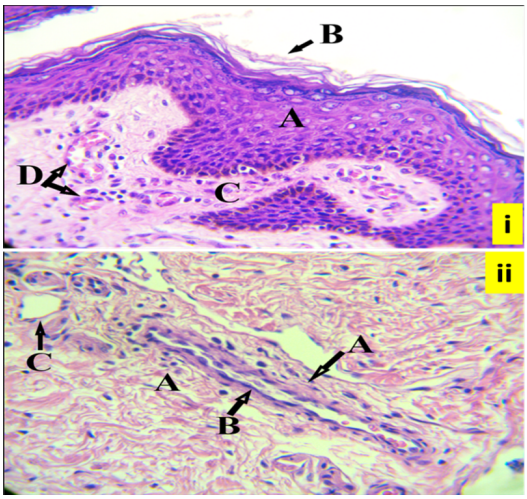

Figure 1: A Representative Image of the Histological Sections of Prepuce Skin of the Group 1 (6 months of age) (i) Epidermis Formed by Stratified Squamous Ep. (A), Keratin (B), Dermis with WBCs (C) and Blood Capillaries (D). (ii) Collagen Bundles with the Presence of WBCs (A), Sweat Gland (B), and Blood Capillaries (C). (H&E. 40X).

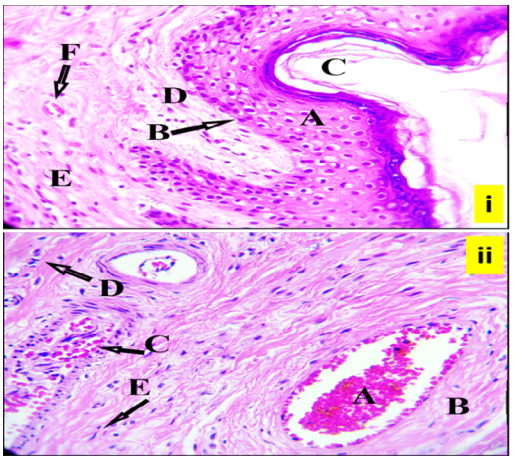

Figure 2: A Representative Image of the Histological Sections of Prepuce Skin of Group 2 (12- 24 months of age), (i) Epidermis with Stratified Squamous Epidermis (A). Basal Layer (B). Keratin Strands (C). Loose Connective Tissue at the Upper Zone of Dermis WBCs (D). Deep Zone of the Dermis with Multiple WBCs (E) and Blood Capillary (F) (Ii) Hypodermal Artery Engorged with Blood (A), Smooth Muscular Fibers of Tunics Media (B), Hypodermal Vein with RBCs (C). WBCs (D) and Fibroblasts (E). (H&E. 40X).

Group 3 (G3): The results of the dermis of this group (24- 36 months of age), containing a condense of collagen bundles, beneath the epidermis papillae which also extend to the lower part of the dermis, WBCs are situated within woven on connective tissues bundles. The regions of the dermis – hypodermis were occupied by collagen bundles in different directions, accumulating around different sizes of blood Results showed, newly formed hair follicles and sweat glands surrounded by different types of WBCs (Figure 3).

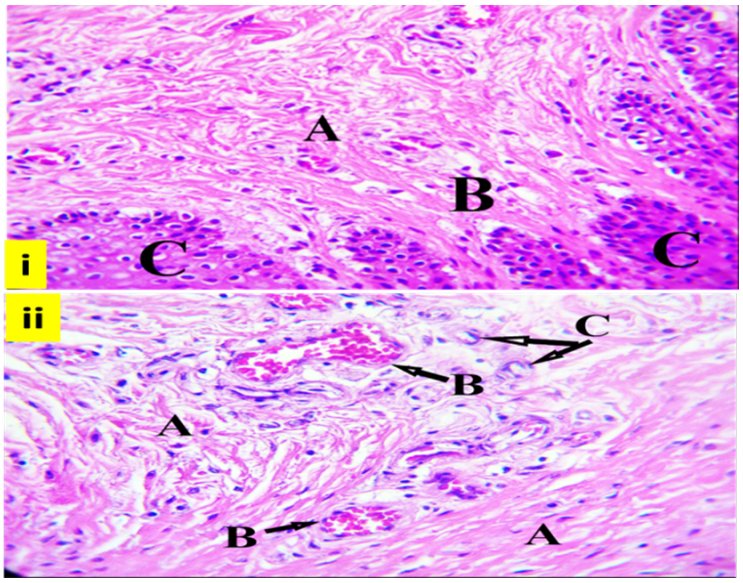

Figure 3: A Representative Image of the Histological Sections of Prepuce Skin of Group 3 (24-36 months of), (i) Dermis with Condensed Collagen Bundles (A), Vacuoles Around WBCs (B), Epidermis Papillae (C) (ii) Dermis – Hypodermis Region Collagen Bundles (A), Blood Vessels with RBCs (B) and Newly Formed Blood Cape Capillaries. (H&E. 40X).

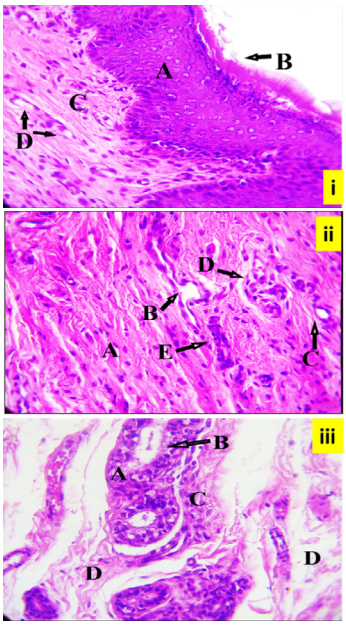

Figure 4: A Representative Image of the Histological Sections of Prepuce Skin of Group 4 (36-48 months of age), (i) Epidermis Formed by Multiple Rows of Epithelial Cells (A). Keratin Zone (B). Dermis with WBCs (C). Blood Capillaries (D). (Ii) Dermis with Collagen Bundles (A). Newly Formed Hair Follicle (B), Blood Capillaries (C). Focal Aggregation of WBCs (D). Macrophage (E). (iii) Hypodermis, Ducts of Sweat Glands (A, B). WBCs (C). Loose Connective Tissue (D) (H&E. 40X).

Group (G4): The obtained results of this group (36-48 months of age), was showing, increased in dense collagen bundles, fibroblasts and WBCs, other specimens showed blood capillaries with newly formation of hair follicles. The ducts of sweat gland penetrate the hypodermis are surrounded by double rows of epithelial cells surrounded by loose connective tissue with infiltrated with WBCs (Figure 4).

Group 5 (G5): The results of this group (48-60 months of age) revealed, hyperplasia of epidermal epithelial cells which appeared crowded with dark basophilic stain, the outer surface of these layers covered by multiple strands of keratin, and increased in dermis thickness and contain many WBCs appeared as groups beneath the dermal papillae or as a diffused pattern. Well-differentiated epidermal papillae appeared finger projection extended deeply into the dermis, the other hand, and the dermis was formed by collagen fibers associated with the presence of focal aggregation of WBCs, macrophages, and giant cells. The hypodermis at four years of age reveals well-differentiated nerve fibers and collagen bundles of fibers that appear separated bundles collagen, these spaces are filled up by WBCs. Other results in the hypodermal region containing many newly formed blood capillaries, surrounded by pericytes, WBCs, macrophages, and giant cells (Figure 5).

Group 6 (G6): In this group (60-72 months of age), the epidermis was formed by multiple rows of epidermis epithelial cells, and the whole cells were demonstrated crowded and present in hyperplastic phase with dark

chromatin stain, with thick strands of keratin which appears as a desquamated strand, on the other hand, epidermis papillae were interdigitated with dermis papillae, this area was occupied by several WBCs and fibroblasts. Dermis – hypodermis region showed medium blood vessels are engorged by RBCs, with spread out of WBCs throughout the dermis and well-differentiated nerve fibers (Figure 6).

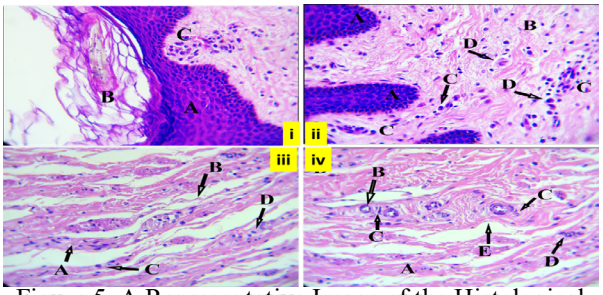

Figure 5: A Representative Image of the Histological Sections of Prepuce Skin of Group 5 (48- 60 months of age), (i)Epidermis with Hyperplasia of the Epidermal Epithelial Cells (A), Multiple Rows of Keratin Strands (B) and Dermal Papilla with WBCs Diffusion (C). (ii) Finger-like Epidermal Papillae (A), Dermis with Collagen Bundles (B), WBCs (C), macrophages, and giant cells (D). (iii) hypodermis, dissociation of collagen bundles (A), nerve Fibers (B), Macrophages (C,) and WBCs (D). (iv) Hypodermis Dissociation Collagen Bundles(A), Newly Formed Blood Capillaries (B), Pericytes (C), WBCs (, D) and Nerve Fibers (E), (H&E. 40X).

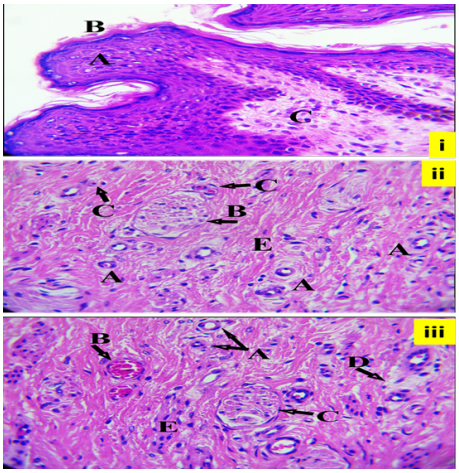

Figure 6: A Representative Image of the Histological Sections of Prepuce Skin of Group 6 (60-72 months of age), (i) Hyperplasia of the Epidermal Epithelium (A), Strands of Keratin (B), Dermal Papillae with WBCs and Fibroblasts (C). (Ii) Collagen Bundles Density of Dermal–hypodermal Region (E), Newly Formed Blood Capillaries (A), Nerve Fibers Bundle (B), Pericytes (C). (H&E. 40X). (iii) Dermis Newly Formed Blood Capillaries (A) Blood Capillaries with RBCs (B), Nerve Bundle (C), Pericytes (D) and WBCs (E). (H&E. 40X).

Discussion

The prepuce or foreskin represents asin that the pings the glans of the penis. Consist of dual coated fold the outer layer which continuous of the skin wraps the glans of the penis and the internal coat was a mucous membrane. A dartos muscle is a muscular sheath situated beneath the skin.[6] Results of the present study, during six months of age, revealed epidermis was composed of multiple layers of stratified squamous epithelium (basal row, squamous cells, and granular cells) covered by strands of keratins, the histological structure of preputial skin of adults is a combination of the following layers: Mucosa (squamous epithelium), lamina propria, dartos muscle, dermis and glabrous outer keratinized stratified squamous epithelium. [16] Cold and Taylor[17], revealed that rough the development of the glans The peruse appeared thick epidermal layer covers the glans which is separated by the influx/invasion of mesenchyme cells that divide the layer of the epidermis into: (1) the upper layer representing the epidermis and the internal coat introduced to the preputial lamina.[17] Several studies deal with preputial skin development which focused on histological components in human embryo. [18] Recently many studies are focused on preputial skin (foreskin) development during schoolboys,[19] but less studies focused on the development of foreskin during the childhood preschool period.

Our obtained results of 24-36 months of age revealed epidermis papillae and dermis with condensed collagen bundles. Hsieh *et al.*[20], showed 90% of prepuces became retractable by the age of three years. Hsieh *et al.*[20] found the dermis at three years containing a condense of collagen bundles, beneath the epidermis papillae which also extended to the lower part of the dermis. On the other hand, results of 36-48 months showed good infiltration and spread out of WBCs near dermal papillae and around new forming blood vessels and covered the wall on new sweat glands. Tsepkolenko *et al.*[21] showed the macrophages and immune cells play a major role in skin remodeling mechanism like pro- fibrotic mediators including regulation of skin collagen fibril manufacture to maintain the three-dimensional model structure. Dinh *et al.*[22] showed increased inflammatory cells such as (Langerhans cells, CD4+ T cells, CD8+ T cells, and macrophages) with a surface area of the foreskin to keep the skin intact environment. Efird *et al.*[23] showed the great function of epidermal macrophages (Langerhans cells) in prepuce that help in body protection against foreign organisms. Castellana *et al.*[24] showed the main function of macrophages underneath skin through the activation of basal row (stem cells) of epithelial and regulate their differentiation activity. The results of 48-60 months of age showed finger-like epidermal papillae, dermis with collagen bundles, WBCs, macrophages, and giant cells. The preputial skin structure of boys aged 3–5 years: Epidermis was composed of layers with uneven distribution of melanin within the basal layer. The Papillae edge and the underneath dermis were formed

by loose fiber bundles, this papillae region was infiltrated by lymphocytic cells, dermis had cellular distribution was moderate and most represented by fibroblast cells.[25] Our results showed the epidermis was formed by stratified squamous epithelium (basal row, squamous cells, and granular cells) which are coated by strands of keratins.[26] The results of 48- 60 months of ages, showed at the hypodermal region, well-constituted nerve fibers. Since the prepuce of uncircumcised males may provide additional sexual sensation, this is due to the terminal nerve ending at the preputial dermis.[27] The innervation at both the prepuce and glans penis subdivide into four neural inputs to the penis: somatosensory, somatomotor, parasympathetic, and sympathetic.[28] The nerve knob balls are referred to as Krause end bulbs. Free nerve endings (FNEs) are the plainest sort of receptors, ideally allocated in the papillary dermis of the epithelium.[29] In present study showed well-differentiated elastic fibers bundles which increased with age.[30]

Fahmy[31] revealed the papillary region contains Meissner corpuscles, The dermal prepuce has elastic fibers more than lamina propria. The imbalance in the distribution of elastic fibers in the lamina propria and dermis may also help to fold around the glans penis. Histological sections of 60-72 months of age showed new blood vessels, nerve bundles, and Pericytes. The prepuce is rich in nerve fibers and lymphatic cells, with extensive blood capillary networks that can be seen in both the upper and lower dermal regions.[3] The blood flow is playing a major role in tissue regeneration.[32] Adisa *et al*.[33] showed the important role of macrophages in angiogenesis (new blood capillaries formation) in different models. Correa-Gallegos *et al*.[34] revealed the role of macrophages mediate blood vessel formation during tissue development, through visualized the Isolectin-stained vasculature in the tissue sections from either the control or clodronate liposomes treated skin for macrophage depletion which final effect on skin regeneration. So, the macrophages are engulfing cells that contribute to homeostasis and control the immune response by ingesting and clearance of apoptotic cells and producing a soluble growth factor.[34] A current study revealed many pericytes constituted around new blood vessels and fibroblasts in between fiber bundles at the dermal region.

Pericytes also exhibit several functions such as muscle-cell activity and induced cytoplasmic actin contractile within smooth muscle. In contrast, single pericytes surround the basal lamina of endothelial cells around small blood vessel walls, the dermis of skin has huge different functions, this is due to the diversity of cells that constitute the dermis, such as fibroblasts, endothelial, neural, dendritic, pericytes and WBCs.[35] Pericytes affect on basal layer cell epithelium through increased cell divisions activate and cell polarity.[36] Paquet-Fifield *et al*.[37] revealed the role of pericytes where present underneath the germinal basal layer of the epidermis, to activate the epithelial divisions, differentiation, and their activity in tissue regeneration and its role in endothelial cell function regulation.

Tan *et al*.[38] showed fibroblast cells accounted for the largest portion of children, and showed the variety of the identification cells in different individuals, throughout their results facilitated the understanding of the heterogeneity of preputial skin cells during development. And revealed the cell-cell communication networks between cells which constitute the prepuce have a great variation in between children and adults.[38] Tuncali *et al*.[4] showed preputial mucosa were in shortage of dense collagenous zones which were demonstrated in alternative areas of dermal skin. Fahmy[31] evaluated human preputial skin including scarce sebaceous and sweat glands.

Conclusions

The current study provides further histological information about foreskin (prepuce) development during the first six years of age of a boy (childhood). The results showed, that the outer layer composed of epidermis epithelium (basal row, squamous cells, and granular cells), well-differentiated in epidermal papillae appeared as finger and dermis was extensive and occupied by great masses of collagen bundles and newly formed blood capillaries and well-differentiated nerve fibers.

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