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Review

The dynamic anatomy and patterning of skin

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Abstract: The skin is often viewed as a static barrier that protects the body from the outside world. Emphasis on studying the skin's architecture and biomechanics in the context of restoring skin movement and function is often ignored. It is fundamentally important that if skin is to be modelled or developed, we do not only focus on the biology of skin but also aim to understand its mechanical properties and structure in living dynamic tissue. In this review, we describe the architecture of skin and patterning seen in skin as viewed from a surgical perspective and highlight aspects of the microanatomy that have never fully been realized and provide evidence or concepts that support the importance of studying living skin's dynamic behaviour. We highlight how the structure of the skin has evolved to allow the body dynamic form and function, and how injury, disease or ageing results in a dramatic changes to the microarchitecture and changes physical characteristics of skin. Therefore, appreciating the dynamic microanatomy of skin from the deep fascia through to the skin surface is vitally important from a dermatological and surgical perspective. This focus provides an alternative perspective and approach to addressing skin pathologies and skin ageing.

Key words: ageing – architecture – dynamic anatomy – patterning – skin

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Introduction

Our views of skin structure tend to be static and two-dimensional and focus largely on biological functions (1). Often overlooked is the dynamism of skin, which involves multidirectional stretch and compression, allowing for low friction gliding movement (2). Only when skin is diseased, scarred or aged do we appreciate how important this feature is to daily activity. Skin also provides a 'live feed' of information of the body's systemic physiology through physical signs, such as flush, sweating and pallor, and can inform us of disease states, such as hypothyroidism, jaundice or Cushing's disease to name but a few (3).

This review focuses on the dynamic structure and pattern of skin as seen in the living and reviews the biology and concepts that relates to its form and function. It is hoped that this information will inform *in silico* development or tissue design and engineering (4) and more accurate algorithms for automated assessment (5).

The continuum of skin

The skin acts as an envelope to the body and is closely integrated to the underlying fascial endoskeleton through retinacular ligaments (6,7), blood vessels (8), nerves (9) and lymphatics (10). Skin can be defined from the hypodermal fat and fascial endoskeleton by 'dissection or surgical planes' which are created artificially through loose connective tissue regions that are key to the gliding of skin over muscle contraction. The fascial endoskeleton or retinacular system (11) is important in determining the limits of skin movement. Specific tethering points from this retinacular system define the appearance of skin; for example, well-defined retaining ligaments have been studied around the head that define specific skin compartments of the face (12), and skin retinacula are thicker in glabrous areas such as the sole of the foot (13,14) and hand (15) so that the skin does not shear easily in these specialized regions. The key concept is that the connections between fascia and skin act as a continuum for finite movement.

When the retinacular system degenerates in ageing, obesity and disease, we see a change in form (16). Surgical undermining of these retaining structures can lead to loss of form as seen in symmastia (17) or loss of the inframammary fold (18). On the other hand, undermining these ligaments can be used to restore form with facial rejuvenation surgery (19). This anchoring system is therefore also fundamental to the appearance of skin.

Human skin is composed of three distinct layers: epidermis, dermis and hypodermis, with varying degrees of specialization within each layer (Fig. 1). The epidermis and dermis are well characterized, but very little attention has been given to the hypodermis and retinacula.

Proteomic studies of microdissected skin have found that there are between 155 and 174 different proteins in skin with the main constituents consisting of collagens (I, II, III, VI, XII and XIV), extracellular matrix proteins (elastin, lumican, mimecan, prolargin, periostin, decorin), keratins ([type I cytoskeletal 9, 10, 13, 14, 15 and 16] and [type II cytoskeletal 1, 2, 5 and 75]) and cellular proteins (vimentin, desmoplakin, actin, myosin, tubulin, laminin, histones, annexins and 14-3-3 protein) (20). How the structural mechanics of the skin relates to the assembly these matrix components remains largely unknown.

The epidermis

The epidermis is the most superficial and biologically active of these layers as the basal layer of the epithelium (*stratum basale*) is constantly renewing. Despite the high turnover, a stable landscape of fractal geometric shapes is seen on the skin surface. These shapes deform on movement, responding to the translation of forces through the underlying dermal fibrillar network and form topographical lines. Over 40 different names have been ascribed the different skin lines and folds (21) (Fig. 1a).

Epithelial cells densely pack the epidermis to a depth of between 75 and 150 μm (up to 600 μm thick on palms/soles).

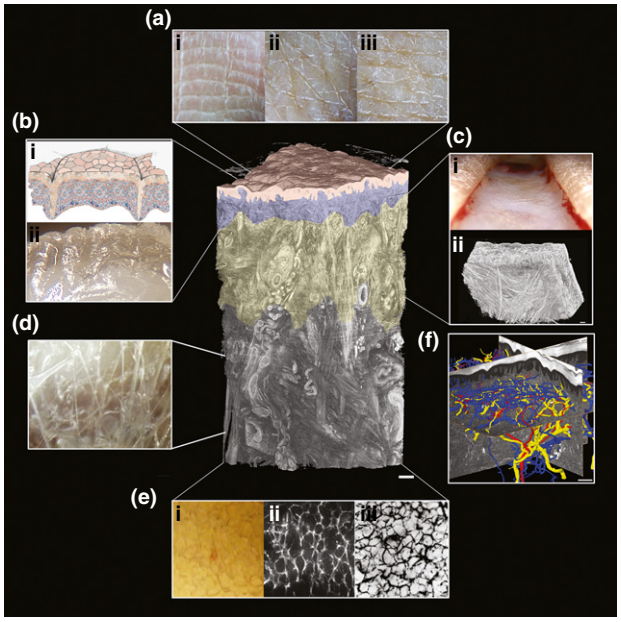

Figure 1. The architecture of skin (centre image is a 3D render of human skin using episcopic imaging). Epidermis (pink); papillary dermis (blue); reticular dermis (yellow); Hypodermis (white). Scale bar represents 200 μm. (a) Surface topography of skin at different body sites. Note different subunit shapes of skin. Fixed regions show more ridged pattern for enhanced surface area grip (i) volar surface of finger. Body sites with high mobility show large triangular subunits, such as (ii) dorsum of hand and (iii) abdomen. (b) (i) Schematic of the epidermis illustrating the cluster of hexagonally shaped corneocytes formation from the replication of the basal epithelium. (ii) Cross section through human epidermis. Lucid ceramide rich layer of epidermis visible above and dermis seen as white due to high collagen content. (c) (i) Skin cut down to the reticular dermis level. (ii) Episcopic imaging of dermis showing collagen fibre orientations that interweave. Scale bar represents 200 μm. (d) The loose extendible and flexible collagenous microvacuolar network. (e) Images of the hypodermal fat as seen through different imaging modalities. (i) Hypodermal fat as viewed by operative endoscopy in living tissue showing yellow-coloured fat globules (ii) Hypodermal fat as viewed with two-photon excited fluorescence showing fibroelastic fibres. Reprinted with permission from Wiley and Son (Heuke et al. 2013). (iii) Hypodermal fat as viewed with Indian ink injection of the lymphatics. Reprinted with permission Macmillan Publishers Ltd, *J Invest Derm* (10). (f) 3D rendering of the skin vascularity using episcopic imaging. Note no forming of a dermal plexus but branching configuration of arterial tree (Red). Venous drainage of skin on the other hand forms venous plexuses (Blue) with many interconnections. The nerve endings also follow these branching systems closely (Yellow).

The superficial epidermis undergoes a process of cornification which is one of the adaptive processes to providing the body with a barrier to the elements (22) common to many species except fish (23). The pattern of the epidermal ridges in humans forms at around the 10th week of pregnancy from undulations in the basal layer of the epidermis (24). Formation of ridge and whorl pattern is thought to occur by growth stress from expansion being resisted by compressive stress (25). Merkel cell alignment with ridges during development also has a theoretical role in determining pattern by signal transduction (26). The formation of pattern in the epidermis may be explained by the nature of self-replication of the basal keratinocytes which is limited by contact inhibition between cells (27).

The epidermal structure changes from anuclear cells of the stratum corneum superficially to distinct hexagonal shaped cells in the stratum basale (28). Adherence between neighbouring keratinocytes is maintained by tight junction complexes (e.g. Claudins, Zo-1, Occludins) which form an important intracellular barrier (29). The hexagonal confirmation has been mathematically shown to be the most efficient two-dimensional building block in nature (30) as seen in other anatomical sites such as liver lobules and retina. The interfollicular epidermis form further hexagonal clusters of around 30 cells with intervening furrows that act as a fulcrum for movement (Fig. 1bi) (31). It remains unclear whether these furrows are purely produced through mechanical forces or arise through predetermined pattern expression. The corneocytes have dimensions of 30–40 μm in diameter and a thickness of 0.1–1.0 μm embedded in a multifaceted matrix of multilamellar organized lipids (32). Their presence gives the epidermal layer their suppleness to flex and move with the body it is covering. The high lipid content, from ceramides, cholesterols and fatty acids generated by the stratum granulosum, accounts for the firmness and partial lucidity of the epidermis (33) (Fig. 1bii). These sit on a complex assembly of collagen IV, laminin, nidogen, perlecan, heparin sulphate proteoglycans and junctional molecules known as the basement membrane (34). This is an important part of the dermoepidermal junction (35) that defines and also adheres the epidermis and dermis together, providing a strong mechanical barrier against pathogens.

The dermis

The dermis is usually <2 mm thick, but maybe up to 4 mm thick (e.g. adult back) and provides most of the mechanical strength to the skin. Shear forces and breaking strength of dermis are 5–15 MPa on the face and up to 27 MPa from skin on the back (36). Forces resisted in the hypodermis are only 1–5 MPa (37). The orientation in which skin is stretched affects its tensile strength, hence applying traction parallel to Langer's lines have the strongest ultimate tensile strength (36, 38) but least extendability (39) which begins to fail once skin is stretched beyond 1.5 times its length. This needs to be carefully considered during surgery.

The dermis has two regionally distinct areas: the superficial papillary dermis and the deeper reticular dermis. Lineage tracing studies have shown that the papillary dermis and reticular dermis are formed from distinct fibroblast lineages that may explain their differences in fibril architecture (40).

The papillary dermis interacts closely with the rete ridge projections from the epidermis as well as surrounding individual hair follicles. The patterning of hair follicles and associated adnexal structures and eccrine glands either arise from local signalling from with cellular precommitment or long range signalling and pattern derived through diffusion reaction (41, 42). These undulations of the dermoepidermal junction along with anchoring fibrils inside and around the basement membrane provide a greater surface area for attachment and are important to resist shear forces (43, 44). Small diameter collagen fibres (mean 38 000 nm) interspersed with elastic fibres are found in the papillary dermis (45). The reticular dermis is made up of predominantly large diameter collagen fibres (mean 80 000 nm), which is less densely packed and organized into large interwoven fibre bundles of branching elastic fibres which form a superstructure around the collagen fibres (45, 46) (Fig. 1c). These fibres consist of oxytalan (fine branch such as fibrillin-rich microfibrils), elaunin (arciform microfibrils with an elastin core) and elastic fibres (thick, fibrillin-rich microfibrils with elastin rich core) making up an elastic microfibrillar network (47, 48). The distinct organized calendula pattern of the elastic tissues, specifically fibrillin 1, is directly

proportion to the youthful appearance of skin (49) and can be used as a bioassay to assess revitalization of skin (50).

The predominant collagens found are type I (80–90%) and type III (10–20%) (51), although collagen IV (52) and other collagens (20) have also been identified. The collagen fibre configuration of the dermis forms visible vertical tethers or 'retinaculum cutis' which gives rise to the troughs seen on the epidermal surface.

The hypodermis

The hypodermis mainly consists of loose connective tissue which depending on site forms gliding layers or large pockets of adipose tissue that insulates and protects the skin (Fig. 1d). The tissue is particularly rich in proteoglycan and glycosaminoglycans, which attracts fluid into the tissue giving it mucous-like properties (53). The types of cells found in the hypodermis are fibroblasts, adipose cells and macrophages which have a particular role in adipocyte homoeostasis in obesity (54), possibly associated with tissue remodelling (55) and may stimulate thermogenesis of fat during cold exposure and exercise (56, 57). Adipocytes are organized into lobules with the fibrous septa and rich blood and lymphatic supply in between (Fig. 1e). The hypodermis has an important role in adipose homoeostasis and is particularly rich in G protein-coupled receptors, which regulate lipolysis, adiponectin and leptin secretion (58). Rose et al. (1978) examined the hypodermis in porcine and human skin and showed that the structure involves a predominately vertically orientated lattice network of fibrous tissue arranged into geometric shapes. The deepest extent of the hypodermis is largely devoid of fat and where the chaotic pattern of fibres is best appreciated. It can be seen to coalesce and separate to form new vacuoles with compression, expansion, shearing and stretch. The polyhedral shape of these vacuoles has been demonstrated to be the most efficient 3D structure to maintain space and fibre confirmation (59). The polyhedral spaces formed by the gelatinous fibres allow for large excursions to occur by scaling down movement to each individual microvacuole dispersing the force into small alterations in sliding tissue movement. This patterning is seen extensively in nature and is governed by basic mathematical rules (60).

The 'microvacuolar' tissue that makes up the hypodermis (53) acts as an active reservoir for interstitial fluid that can dynamically alter the structural stiffness of the tissue (61, 62). The hyaluronan, glycosaminoglycan and proteoglycan composition of the matrix acts as a sponge for interstitial fluid when the capillary osmotic pressures are exceeded, for example during inflammation. The tissue swelling is limited by the fibrous components of this tissue which has been shown to have an active role in either increasing or decreasing the interstitial compartment pressure through cytoskeletal tension that the cells exert on the collagen fibrils (61). The integrity of the microvacuolar tissue is therefore very important to fluid distribution homoeostasis in the body. Conceptually, it has been argued that microvacuolar units make up the building blocks of biological form (63).

Neurovascular and lymphatic patterning

Regulation of fluid flow in skin requires carefully controlled vasomotor activity; therefore, it is no coincidence that during development, there is synergistic expression of transmembrane protein NRP1 which signals both neuronal (via SEMA3A) and vascular (via VEGF164) progenitor cell migration (64). The overlapping vascular and neuronal patterning to the skin is dictated by mathematical branching rules such as the diffusion-limited aggregation model (Fig. 1f) (65). Many somatosensory and autonomic neurons exist in the skin and may be associated with Merkel cells (Aβ fibres), hair follicles (Aβ fibres), the epidermis (C fibres) and the dermis (Aδ fibres) to provide sensory feedback (66, 67). The sensory spatial acuity is greater in glabrous skin than hair-bearing skin, and the acuity increases in a gradient away from the body (9). The exception to this is the face that has a high spatial acuity and is rich in both myelinated and unmyelinated nerve fibres (68).

Patterning that exists to distinct regions of the body is largely perfused by defined arterial domains known as 'angiosomes' (69) or perforating vessels known as 'perforasomes' (70), which are frequently associated with nerves but do not necessarily overlap with dermatomes.

Recent studies have shown in the dermis that perforating vessels form tree-like ramifications (71) although others have argued there is significant flow through a horizontal subpapillary and dermal–hypodermal junction plexus of arteries (72). The terminal branches of the arterial tree give rise to capillary loops that form small dermal arterial units. In the thumb pad, these dermal arteries start at 150–242 μm in diameter and divide into 5–11 generations of branching where they eventually enter the epidermal papilla at a diameter of 8–15 μm (73). Large islands of skin can be perfused on a single perforating vessel (70), which indicates that the skin has significant horizontal flow.

Each unit of skin supplied by these terminal capillary loops is between 0.77 and 1.88 mm^2 (74). Depending on the vascular requirements of the area of tissue, interconnecting 'choke' anastomoses can open up to allowing blood perfusion from neighbouring territories (75). Draining of the skin does appear to arise from a fine dermal plexus of venous polygons at the subpapillary level with branches approximately 70 μm in diameter (76); hence, the territories for artery and vein are quite distinct. The superficial lymphatic plexus are less easily visualized and situated below the subpapillary venous plexus (10). The deeper lymphatic plexus is found in the lower dermis and hypodermis and forms a pattern that outlines the fat globules (Fig. 1e) allowing for efficient interstitial fluid turnover.

These neurovascular networks are cushioned by the microvacuolar system, which allows them to be incredibly mobile, extendible and compressible to accommodate the movement of skin (Fig. 2a, b, f).

Factors that affect the dynamism of skin

The skin structure is designed to minimize stress across the tissue as it is deformed through movement or external forces. Gibson described how differing densities of collagen in the papillary dermis, reticular dermis and hypodermis ensure that the skin can extend in any direction when a force is applied. It also contracts in a plane at right angles with a progressive reduction in volume in the stretched specimen (2). The assembly of the collagen network is carefully intertwined so that pull in any direction is possible. However, there is a favoured 'grain' or anisotropy, which more stretch can be applied before a mechanical plateau and endpoint is reached (Fig. 2c). This is an important characteristic to understand when trying to close skin wounds. Skin can adapt to these forces by mechanical relaxation of the collagen fibres and biological remodelling of the fibrous structure resulting in

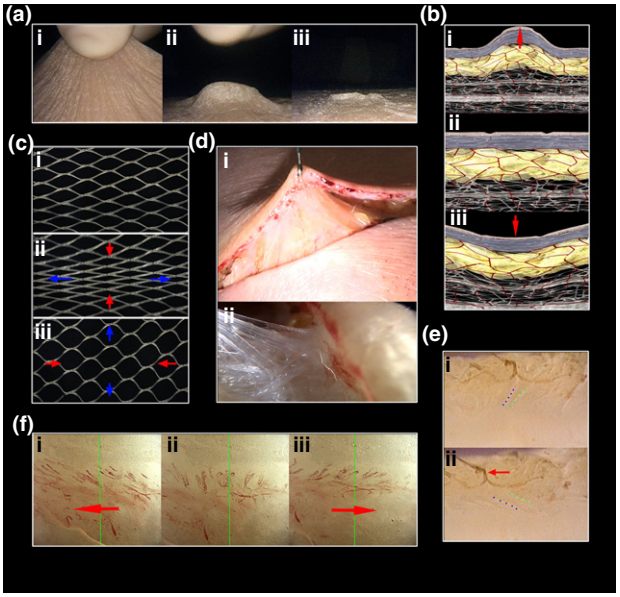

Figure 2. The dynamism of skin showing deformation (a) by stretch and recoils (i-iii). (b) Computerized modelling of (i) stretched, (ii) static, and (iii) compression of virtual skin. (c) A simple two-dimensional interwoven network that demonstrates the anisotropic relationship of the collagen fibres. (i) Static network; (ii) pulled network in direction of grain (blue arrows), and red arrows show greater lateral recruitment; (iii) pulled network in opposite direction to grain (blue arrows), and red arrows show a lesser degree of lateral recruitment. (d) (i) Composite nature of living skin after cutting. (ii) Loose connecting microvacuolar tissue. (e) Fibrillar: (i) Fibrous tethers of retinaculum cutis as seen by endoscopic magnification with independent fibres highlighted in blue and green. (ii) Notice when direction of skin (indicated by red arrow) is moved, the fibres change orientation. (f) Movement of the blood vessels on directional movement of the dermis and hypodermis. (i) shear to left, (ii) neutral position, (iii) shear to right.

mechanical and biological 'creep', respectively (77). Manipulation of this phenomenology is frequently used in tissue expansion for breast and burns reconstruction (78).

The movement of skin relates to the large amounts of amorphous matrix, fibrillar collagen, sulphated proteoglycans, glycoproteins, glycosaminoglycans and hyaluronic acid (Fig. 2d). This binds up to 3000 times their own volume of water due to their negative charge influencing dermal and hypodermal volume and compressibility (79). The difference in fibrillar composition from superficial to deep becoming less dense is what allows a huge range of excursion of the deep tissues translating to very little movement on the surface (Fig. 2e, f). The interstitial fluid provides hydrostatic turgor to the fibrous components of the skin that are important in maintaining tissue volume and pliability.

Site differences

The characteristics of skin differ vastly in topology, pH, temperature, moisture and microbiology at different body sites (1). On an area such as the face, thickness can vary from 0.1 mm on the upper eyelid to 1 mm to on the nasal upper lip (80). Studies have shown that certain parts of the body vary greatly in terms of laxity and extensibility. For example, the groin skin is very lax, whereas the deltoid, chest and abdominal skin is less lax despite having similar collagen concentrations, indicating that the dermal and hypodermal structure influences the overall elastic modulus at these sites (81). In addition, skin has different mechanical properties at different body sites due to skin ligament distribution. In the head, neck, upper trunk and limbs, many skin ligaments anchor the skin to the areas that have underlying muscle movement, whereas sites such as the abdomen and buttocks have very irregular skin ligament patterns which may facilitate changes in volume in these areas to store adipose tissue (7). Skin on the palms and soles is specialized to increase surface area and enhance grip (82). The surface lines on skin facilitate fluid microscopic drainage and drying of the skin surface which in turn increases the dynamic friction coefficient of skin enhancing grip; hence, a small degree of moisture greatly enhances the capillary adhesion of skin (83).

Race differences

There are a variety of differences in skin structure depending on race despite the obvious differences in pigmentation associated with melanin types and distribution (84). There are differences in stratum corneum thickness and adherence. The *stratum corneum* in African skin is found to be thicker but lower in lipid and water content than Caucasian epidermis, and Asian skin found to be the thinnest and the highest in lipid and water content (85). A recent immunohistochemical study characterized photo-protected epidermal and dermal features for a mixed ethnic population and found that Caucasian and Asian skin had less fibrillar collagen but more elastin than African skin, and African skin was thicker with significantly greater fibrillin-rich microfibrils in the dermis (86). Asian and Caucasian facial skin has fewer pores and smoother pore architecture than seen in Hispanic or African skin (87) which is associated with a more youthful look (88). African skin also has a higher number of mast cells which has been postulated to provide the inflammatory driver for the higher incidence of hypertrophic and keloid scars seen in these populations (89,90). The differences in the mechanical behaviour of ethnic skin remain largely under studied, which has huge implications to generalizing effects of skin treatments to all races.

Sex differences

Gender differences in skin can partly be attributed to hormonal differences between sexes which regulate facial and body hair distribution, sebum production, sweating and skin pH (91). Structurally skin is thicker in men than women (92), and loss of oestrogen in menopause causes the skin to thin even further which can be reversed by oestrogen therapy (93). MRI studies show that men have more fibrous tethers making smaller lobular compartments of fat, whereas women have larger lobules with less fibrous septations (94). When women have thickening of the fibrous septations through vascular or lymphatic fibrous change, or fat saturates the fibrous compartments, cellulite dimpling occurs (95). These changes all lead to differences in skin movement.

Age differences

One of the most studied areas of skin architecture relates to aged skin. Clinical hallmarks of aged skin include xerosis, melanocytic hyperplasia, telangiectasia and diminished elasticity (96). With age, the number of topographical cutaneous channels decreases resulting in greater plateau regions causing the visible lines to fold and get deeper (97). Dermal torqueometry and *in vivo* ultrasound imaging show there is rigidification of the stratum corneum with loss of echogenicity and weakening in the upper dermis that leads to wrinkles (98). Other causes of wrinkle formation include loss of retinaculum cutis and thinning of dermis (99), thickening of the stratum corneum and thinning of the stratum spongiosum

(100), thinning of the epidermis and loss of collagens IV and VII at dermoepidermal junction at the base of the wrinkle (101). This suggests that changes in any one of the tissue properties of the fibrous lamellar components of the skin can result in the surface buckling. The Young's modulus of skin also gradually decreases with age. It measures 12.3 kPa in your mid 20's reducing to 5.4 kPa in your 70's. (97). This reduction is secondary to the loss of elastin, degradation of collagen and changes in tissue interstitial fluid with age. Collagen becomes sparser and less soluble in intrinsically aged skin but more thickened and soluble in sun-damaged skin with elastin deposited in the papillary dermis (102) making the skin more mechanically fragile (103). Studies have found a generalized loss in skin volume from 30% at 50 years to 52% at 80 years (104), so relatively, it seems that elastic fibre density increases (105).

In healthy undamaged skin, the distribution of elastic fibres is uniform throughout the dermis, whereas clumping of elastic fibres in the papillary dermis is a hallmark sign of photoaged skin (46). It is speculated that components of the elastic fibre network such as the fibrillin-rich microfibrils may play a role in absorbing the damaging effects of ultraviolet radiation (106).

Despite the wealth of studies in aged skin is remarkable that little is known about how ageing affects the mechanical integrity of the retaining structures which visibly degenerate over time.

Pathology differences

The normal composition and architecture of skin is fundamental in allowing us to appreciate the pathological manifestations in skin.

Acanthosis and increase in intra-epidermal nerve fibres is a hallmark sign of atopic dermatitis (107). Subtle abnormalities in certain important proteins in skin can lead to dramatic structural changes, seen in conditions such as Stevens–Johnson syndrome and epidermolysis bullosa resulting from loss of dermoepidermal junction integrity (108,109). Scarring results in the thickening of the epidermis and disorganized architecture between the papillary and reticular dermis and can extend into deeper tissues leading to tethering of the hypodermis (Fig. 3). The extend of this depends on the quality of the scarring process (epidermal thickness 30.9 μm in mature scar, 38.5 μm in hypertrophic scar and 48.9 μm in keloid scar compared with 25 μm in normal skin) (45).

With gross obesity, it can be anticipated that there will be an altered epidermal barrier function, lymphatic stasis and altered sebaceous gland activity. Histological changes include degraded acellular matrix, spots of inflammation, abnormal collagen architecture, loss of elastin and areas of scar tissue which eventually leads to fibrotic, inelastic and indurated skin, and is prone to ulceration (111).

The loose matrix of the hypodermis allows for the diffusion of inflammatory and cascading cytokines to permeate with relative ease. Certain conditions such as burns and severe sepsis may result in the 'waterlogging' of the tissue compartment very rapidly in the acute phase of injury leading to 'third space' fluid loss. Rapid spreading cellulitis can occur during severe bacterial diseases, especially those that produce glycoside hydrolases, streptodornases and hyaluronidase, which may progress to necrotising fasciitis if thrombosis of small vessels occurs along the gliding planes (112,113). After the resolution of inflammation/injury, scarring and fibrosis in the microvacuolar tissue can result in taut, inelastic, swollen and easily traumatized tissue. Injury also results in a distinct change in the microangiographic patterning of the capillaries in skin which may explain the prolonged period of erythema seen in burn wounds and immature scar (114). Other fibrotic conditions such as desmoplasia, scleroderma and radiotherapy changes can all have dramatic changes to skin mobility throughout various depths in the skin architecture but are rarely studied because the tools to assess skin dynamism are lacking.

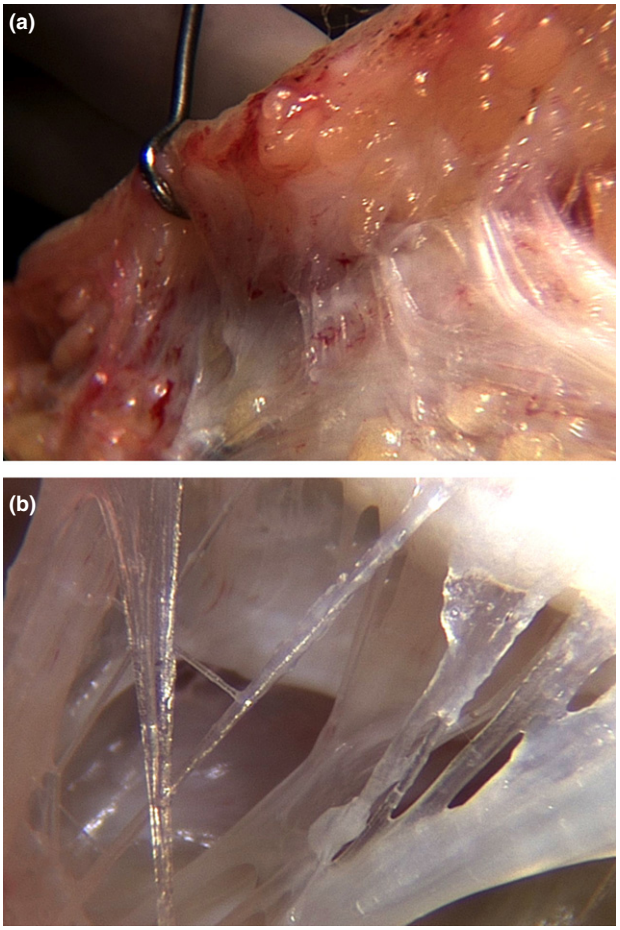

Figure 3. (a) Scarring of the hypodermis that leads to a tethered scar on the arm. Note the dense white collagen fibres causing the skin to be firmly adherent to the deep fascia. (b) Closer view of the scarring adhesions between the layers of the skin. Note the greater fibrous and less gelatinous appearance.

Many other conditions also lead to architectural changes that change the mechanical properties and appearances of skin, where accumulation of mucopolysaccharides leads to swelling and inelasticity in mucinosis and myxoedema, or degeneration of key components such as fibrillin 5 can lead to elastolysis in conditions such as Cutis laxa (115).

Conclusions

Knowledge of the microarchitectural patterning seen in skin is vital to understanding how to aesthetically close wounds but also is an important blueprint to understanding how to develop skin replacements with the same mechanical properties so that they

appear 'life like'. The manipulation of skin goes beyond purely understanding the 'grain' of skin; hence, to achieve precise restoration and replacement needs to consider the continuum of skin below the surface aesthetics.

The appreciation of the architectural continuum of skin provides us with many concepts that help us better understand how ageing, disease and injury affect the skin health and cosmesis. By studying the physical and temporal dynamism of skin, we can further appreciate, simulate or engineer more realistic skin.

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Author Contributions

RW prepared and wrote the manuscript. SG provided data and imaging. WW provided imaging and edited the manuscript. JCG provided the original concept and idea. JW prepared, conceptualized, wrote and revised the manuscript.

Conflict of interests

The authors have declared no conflicting interests.

Supporting Information

Additional supporting data may be found in the supplementary information of this article.

Movie S1. Video introduction to the dynamic anatomy and patterning of skin.

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