



HAL
open science

Newborn and elderly skin: two fragile skins at higher risk of pressure injury

Anne-france Bengy, Jérôme Lamartine, Dominique Sigauco-roussel, Bérengère Fromy

► To cite this version:

Anne-france Bengy, Jérôme Lamartine, Dominique Sigauco-roussel, Bérengère Fromy. Newborn and elderly skin: two fragile skins at higher risk of pressure injury. *Biological Reviews*, In press, 10.1111/brv.12827 . hal-03621154

HAL Id: hal-03621154

<https://hal.science/hal-03621154>

Submitted on 31 Mar 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1
2
3 **1 Newborn and elderly skin: two fragile skins at higher risk of**
4
5
6 **2 pressure injury**
7
8
9
10
11
12
13
14
15
16
17
18

19
20
21 **4 Anne-France de Bengy^{1,*}, Jérôme Lamartine², Dominique Sigaud-Roussel² and**
22
23
24 **5 Bérengère Fromy^{2,*}**
25
26
27
28
29
30

31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

7 *¹AF BioCell, 59 Avenue du Point du Jour, 69005 Lyon, France*

8 *²Univ. Lyon, Université Claude Bernard Lyon 1, CNRS, LBTI UMR5305, 7 Passage du*
9 *Vercors, F- 69367 Lyon Cedex 7, France*

10
11
12 *Authors for correspondence: A.F. de Bengy (E-mail: annefrance.debengy@afbiocell.com;
13 Tel.: +33664352957) and B. Fromy (E-mail: berengere.fromy@ibcp.fr).
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

15 **ABSTRACT**

16 Skin is a key organ maintaining internal homeostasis by performing many functions such as
17 water loss prevention, body temperature regulation and protection from noxious substance
18 absorption, microorganism intrusion and physical trauma. Skin ageing has been well studied
19 and it is well known that physiological changes in the elderly result in higher skin fragility
20 favouring the onset of skin diseases. For example, prolonged and/or high-intensity pressure
21 may suppress local blood flow more easily, disturbing cell metabolism and inducing pressure
22 injury (PI) formation. Pressure injuries (PIs) represent a significant problem worldwide and
23 their prevalence remains too high. A higher PI prevalence is correlated with an elderly
24 population. Newborn skin evolution has been less studied, but some data also report a higher

1
2
3 25 PI prevalence in this population compared to older children, and several authors also consider
4
5 26 this skin as physiologically fragile. In this review, we compare the characteristics of newborn
6
7 27 and elderly skin in order to determine common features that may explain their fragility,
8
9 28 especially regarding PI risk. We show that, despite differences in appearance, they share
10
11 29 many common features leading to higher fragility to shear and pressure forces, not only at the
12
13 30 structural level but also at the cellular and molecular level and in terms of physiology. Both
14
15 31 newborn and elderly skin have: (1) a thinner epidermis; (2) a thinner dermis containing a less-
16
17 32 resistant collagen network, a higher collagen III:collagen I ratio and less elastin; (3) a flatter
18
19 33 dermal–epidermal junction (DEJ) with lower anchoring systems; and (4) a thinner
20
21 34 hypodermis, resulting in lower mechanical resistance to skin damage when pressure or shear
22
23 35 forces are applied. At the molecular level, reduced expression of transforming growth factor β
24
25 36 (TGF β) and its receptor TGF β receptor II (T β RII) is involved in the decreased production
26
27 37 and/or increased degradation of various dermal extracellular matrix (ECM) components.
28
29 38 Epidermal fragility also involves a higher skin pH which decreases the activity of key
30
31 39 enzymes inducing ceramide deficiency and reduced barrier protection. This seems to be
32
33 40 correlated with higher PI prevalence in some situations. Some data also suggest that stratum
34
35 41 corneum (SC) dryness, which may disturb cell metabolism, also increases the risk of PI
36
37 42 formation. Besides this structural fragility, several skin functions are also less efficient. Low
38
39 43 applied pressures induce skin vessel vasodilation *via* a mechanism called pressure-induced
40
41 44 vasodilation (PIV). Individuals lacking a normal PIV response show an early decrease in
42
43 45 cutaneous blood flow in response to the application of very low pressures, reflecting vascular
44
45 46 fragility of the skin that increases the risk of ulceration. Due to changes in endothelial
46
47 47 function, skin PIV ability decreases during skin ageing, putting it at higher risk of PI
48
49 48 formation. In newborns, some data lead us to hypothesize that the nitric oxide (NO) pathway
50
51 49 is not fully functional at birth, which may partly explain the higher risk of PI formation in
52
53
54
55
56
57
58
59
60

1
2
3 50 newborns. In the elderly, a lower PIV ability results from impaired functionality of skin
4
5 51 innervation, in particular that of C-fibres which are involved in both touch and pain sensation
6
7 52 and the PIV mechanism. In newborns, skin sensitivity differs from adults due to nerve system
8
9 53 immaturity, but the role of this in PIV remains to be determined.
10
11

12 54

13
14 55 *Key words:* pressure injury, pressure ulcer, newborn skin, elderly skin, skin ageing, fragile
15
16 56 skin, skin integrity.
17
18

19 57

20
21 58 CONTENTS22
23 59 I. Introduction24
25 60 II. Common structural features of newborn and elderly skin26
27 61 (1) Infant and elderly skin: thickness and fragility28
29 62 (2) Infant and elderly skin: a respectively immature and altered dermal–epidermal
30
31 63 junction (DEJ)32
33 64 (a) Features of the DEJ in infant and elderly skin34
35 65 (b) A specific molecular network in the DEJ of infant and elderly skin36
37 66 (3) Dermal cells and extracellular matrix (ECM)38
39 67 (a) Dermis thickness40
41 68 (b) Fibroblast and ECM evolution42
43 69 (i) Fibroblast evolution over time44
45 70 (ii) A more fragile collagen network46
47 71 (iii) Lower skin elasticity48
49 72 (c) A key role of transforming growth factor beta (TGF β) signalling50
51 73 (4) Infant and elderly skin vasculature52
53 74 (5) Infant and elderly skin hypodermis
54
55
56
57
58
59
60

1
2
3 75 III. Functional features of newborn and elderly skin favouring PI formation
4

5 76 (1) A higher pH impairing SC barrier function
6

7 77 (2) Skin hydration and external humidity
8

9
10 78 (3) Lower endothelial functionality might explain a lower resistance to pressure in
11
12 79 newborn and elderly skin
13

14 80 (a) Functionality of the NO pathway
15

16 81 (b) Higher expression of thrombospondin-1 (TSP1)
17
18

19 82 (4) Newborn and elderly skin innervation
20

21 83 (a) Sensory nerve function in elderly skin
22

23 84 (b) Sensory nerve function in newborn skin
24
25

26 85 IV. Conclusions
27

28 86 V. References
29
30
31
32

33 88 **I. INTRODUCTION**
34

35 89 Skin is a dynamic and complex organ forming the interface between the body and the external
36
37 90 environment. Its main function is to maintain internal homeostasis by preventing water loss or
38
39 91 regulating body temperature and to provide protection from noxious substance absorption,
40
41 92 microorganism intrusion and physical trauma. It also mediates the sense of touch and plays a
42
43 93 role in hormone production and social communication (Rittié & Fisher, 2015).
44
45

46 94 Many extrinsic factors can disrupt skin homeostasis, including the application of prolonged
47
48 95 and/or high-intensity pressure which may induce pressure ulcers (PUs), recently redefined and
49
50 96 renamed pressure injuries (PIs) by the National Pressure Injury Advisory Panel (NPIAP)
51
52 97 (Edsberg *et al.*, 2016; Gefen *et al.*, 2020).
53
54

55
56 98 Despite increased attention and a focus on prevention, PI prevalence remains very high, in
57
58 99 particular in intensive care units (ICUs), representing a significant problem worldwide. A
59
60

1
2
3 100 recent study involving 13,254 adult patients in 1,117 ICUs from 90 countries revealed a total
4
5 101 prevalence of 26.6%, ranging from 13.8 to 28.9% depending on the continent, with an ICU-
6
7 102 acquired prevalence of 16.2%, ranging from 9.1% to 22.8% (Labeau *et al.*, 2021). To our
8
9 103 knowledge, no such comprehensive study has been conducted in the paediatric population and
10
11 104 data for this age group remain scarce. However, a systematic review, including 21 studies
12
13 105 concerning subjects aged <21 years old, recently reported a hospital-acquired prevalence
14
15 106 ranging from 0.47% to 31.2% with a pooled prevalence and cumulative incidence respectively
16
17 107 estimated at 7% and 14.9% (Triantafyllou *et al.*, 2021). Although these data cannot be
18
19 108 compared because ICU patients are at greater risk of developing PIs than other hospital
20
21 109 patients, they show that PIs can affect people of all ages.
22
23
24
25
26 110 PIs are often correlated with advanced age and many studies concerning adult populations
27
28 111 identified age as a factor increasing PI prevalence (Amlung, Miller & Bosley, 2001; Manzano
29
30 112 *et al.*, 2010; Cox, 2011; O'Brien *et al.*, 2014; Nassaji, Askari & Ghorbani, 2014; Tayyib,
31
32 113 Coler & Lewis, 2016; Labeau *et al.*, 2021). Fewer data are available for the paediatric
33
34 114 population (Bernabe, 2012; Luton *et al.*, 2017; Triantafyllou *et al.*, 2021) and they show
35
36 115 highly variable results depending on the study (Jackson *et al.*, 2019; Triantafyllou *et al.*,
37
38 116 2021), although some data suggest that PI prevalence is age dependent with the observed
39
40 117 prevalence higher for the youngest children. For example, Fujii *et al.* (2010) reported a
41
42 118 prevalence of 16% for children under 1 month old, also called newborns or neonates
43
44 119 according to the National Library of Medicine, *versus* 2.5% for all ages in Japanese hospitals.
45
46
47 120 Schlüter, Halfens & Schols (2012) found in paediatric ICUs (PICUs) a prevalence of 43% for
48
49 121 children under 1 year old, also called infants, *versus* 31% for children of more than 12 years
50
51 122 and Triantafyllou *et al.* (2021) reported an estimated pooled prevalence of 27% among
52
53 123 neonates, 19.2% among infants and 12.3% for children older than 1 year. In neonatal ICUs
54
55 124 (NICUs), incidence and severity are inversely proportional to birth weight and gestational age
56
57
58
59
60

1
2
3 125 (Fischer *et al.*, 2010). However, many factors (lack of mobility, nutritional status, length of
4
5 126 hospitalization, care practices, medical devices used, etc.) may vary among populations or
6
7 127 among hospitals that could modulate PI incidence (August *et al.*, 2014; NPUAP, EPUAP &
8
9 128 PPIAP, 2014; Edsberg *et al.*, 2016; EPUAP, NPIAP & PPIAP, 2019; Gefen *et al.*, 2020),
10
11 129 meaning that comparisons must be made with caution. Overall, the data do suggest that
12
13 130 elderly people among the adult population and newborns among the paediatric population are
14
15 131 more at risk of PI formation.

16
17
18
19 132 PIs are thought to be formed when blood and lymphatic vessels collapse under external
20
21 133 pressure (Graff, Bryant & Beinlich, 2000; Grey, Harding & Enoch, 2006; Coleman *et al.*,
22
23 134 2014). This reduces cell nutrition, oxygenation and waste elimination, leading to a gradual
24
25 135 progression of damage. Moreover, during the unloading reperfusion phase, the release of
26
27 136 harmful oxygen free radicals may exacerbate such damage (Coleman *et al.*, 2014; EPUAP,
28
29 137 NPIAP & PPIAP, 2019). More recent studies have revealed that high and sudden pressure
30
31 138 leading to sudden cell and tissue deformation can also contribute directly to rapid
32
33 139 deterioration, both in skin (or mucosa) and underlying tissues (Coleman *et al.*, 2014; Oomens
34
35 140 *et al.*, 2015; EPUAP, NPIAP & PPIAP, 2019). These different injury mechanisms can interact
36
37 141 to induce various impacts. Cell deformation, inflammation and/or ischemia and reperfusion
38
39 142 damage can form a vicious circle as described by Gefen (2018) and Gefen & Soppi (2020).
40
41 143 This leads to PI formation beginning either at the skin or mucosa level or in deeper tissues
42
43 144 (Loerakker *et al.*, 2011; Oomens *et al.*, 2015; EPUAP, NPIAP & PPIAP, 2019).
44
45 145 From the most recent EPUAP/NPIAP/PPPIAP guideline (EPUAP, NPIAP & PPIAP, 2019),
46
47 146 PI is defined as “a localized damage to the skin and/or underlying tissue” that appears “as a
48
49 147 result of intense and/or prolonged pressure or pressure in combination with shear” and that
50
51 148 PIs “usually occur over a bony prominence but may also be related to a medical device or
52
53 149 other object.” (EPUAP, NPIAP & PPPIAP, 2019, p. 16; Kottner *et al.*, 2019). Thus, PI
54
55
56
57
58
59
60

1
2
3 150 formation and severity depend both on the mechanical load characteristics (pressure or
4
5 151 pressure and shear duration, intensity, etc.) and the tolerance/resistance of the soft tissue
6
7
8 152 (Coleman *et al.*, 2014).

9
10 153 A lack of mobility and activity, often observed in preterm neonates or very old people and
11
12 154 correlated with poor sensory perception in some cases, increases pressure duration and hence
13
14 155 the risk of PI formation. The use of some medical devices, often used in ICUs and exerting
15
16 156 locally high and/or prolonged pressures, is also well known to increase the risk of PI
17
18 157 formation (NPUAP, EPUAP & PPIAP, 2014; Edsberg *et al.*, 2016; EPUAP, NPIAP &
19
20 158 PPIAP, 2019; Gefen *et al.*, 2020).

21
22
23 159 PI formation also depends on tissue tolerance modulated by many extrinsic and intrinsic
24
25 160 factors such as skin moisture, nutrition, perfusion and cell oxygenation (Braden & Bergstrom
26
27 161 1987; Coleman *et al.*, 2014; Schlüter, Schols & Halfens, 2014; EPUAP, NPIAP & PPIAP,
28
29 162 2019), microclimate, temperature, or comorbidities (Coleman *et al.*, 2014; EPUAP, NPIAP &
30
31 163 PPIAP, 2019). These factors exert an effect on the structure and/or the properties of the skin
32
33 164 and underlying tissues, thus modulating their ability to resist pressure and repair damage
34
35 165 (Braden & Bergstrom, 1987; Coleman *et al.*, 2014). Obviously, intrinsic factors such as age or
36
37 166 genetic background also define tissue mechanical properties and physiology, influencing the
38
39 167 risk of PI formation (Coleman *et al.*, 2014; EPUAP, NPIAP & PPIAP, 2019). Given the
40
41 168 higher prevalence of PIs in both elderly and newborn skin, we can speculate whether there are
42
43 169 common skin characteristics that could explain a lower resistance to pressure in these two
44
45 170 skin types. This review compares the structure of the different parts of newborn and elderly
46
47 171 skin, taking into account their evolution over time, and some biological mechanisms directly
48
49 172 or indirectly involved in skin resistance to pressure and shear. As PIs are mainly formed in
50
51 173 areas not exposed to the sun (Labeau *et al.*, 2021), we only considered intrinsic ageing. We
52
53
54
55
56
57
58
59
60

1
2
3 174 also focused on the skin and PIs that begin at the skin level, not on deep tissue injuries
4
5 175 initiated below skin level.
6

7
8 176

9 10 177 **II. COMMON STRUCTURAL FEATURES OF NEWBORN AND ELDERLY SKIN**

11
12 178 The protective function of the skin is based on the existence of three layers: epidermis, dermis
13
14 179 and hypodermis. Table 1 provides a comparison of skin structure and barrier functionality in
15
16 180 the skin of newborns, young adults and the elderly.
17

18
19 181

20 21 182 **(1) Infant and elderly skin: thickness and fragility**

22
23 183 The exterior of the epidermis mainly consists of keratinocytes which proliferate in the deepest
24
25 184 layer (basal layer) and differentiate progressively while migrating upwards through the
26
27 185 stratum spinosum, the stratum granulosum and the stratum corneum (SC) (Fig. 1). The SC
28
29 186 consists of metabolically inactive and protein-enriched keratinocytes, called corneocytes,
30
31 187 tightly linked by corneodesmosomes and embedded in a lipid-rich extracellular matrix (Elias,
32
33 188 Goerke & Friend, 1977; Proksch, Brandner & Jensen, 2008). Despite its thinness (7–35 μm)
34
35 189 (Telofski *et al.*, 2012), the SC constitutes the main physical barrier of the skin, preventing
36
37 190 water loss and noxious substance or microorganism entry (Proksch *et al.*, 2008; Elias *et al.*,
38
39 191 2010; Blume-Peytavi *et al.*, 2016). Melanocytes, which produce melanin which protects skin
40
41 192 against ultraviolet (UV) radiation, and dendritic cells, which participate actively in the
42
43 193 immune response, are also present. The epidermis does not contain blood vessels and
44
45 194 therefore depends on the dermis for its nutrition.
46
47
48

49
50 195 The skin barrier appears *in utero*. From weeks 22–24, a stratified and keratinized epithelium
51
52 196 is formed (Coolen *et al.*, 2010) and a thick and well-developed epidermis emerges at 34
53
54 197 weeks of gestation with a functional SC and dermal–epidermal junction (DEJ) undulations
55
56 198 (Evans & Rutter, 1986; Telofski *et al.*, 2012; Visscher *et al.*, 2015). SC development seems to
57
58
59
60

1
2
3 199 reach complete maturity between 30 and 37 weeks of pregnancy (Fluhr *et al.*, 2010; Telofski
4
5 200 *et al.*, 2012). It allows little or no drug percutaneous absorption in full-term infants (Harpin &
6
7 201 Rutter, 1983) and prevents full-term neonate dehydration at birth as demonstrated by trans-
8
9 202 epidermal water loss (TEWL) analysis. Indeed, increased or decreased TEWL is respectively
10
11 203 associated with skin barrier dysfunction or an intact skin barrier. Although many factors can
12
13 204 modulate TEWL, a systematic review concluded that full-term newborn TEWL is either
14
15 205 similar to or lower than in adults, depending on skin area (Ludriksone *et al.*, 2014). For this
16
17 206 reason, some authors consider infant skin as fully mature at birth.
18
19 207 Nevertheless, several studies revealed a continuous maturation of the skin after birth. Pulsed
20
21 208 ultrasound was used to show a linear increase in skin thickness up to the age of 20 years (Tan
22
23 209 *et al.*, 1982) and a progressive increase of epidermis thickness after birth (Evans & Rutter,
24
25 210 1986). A comparison of infant skin (3–24 months of age) with that of their mother (25–43
26
27 211 years of age) found the thickness of the infant epidermis and SC to be 20% and 30% thinner,
28
29 212 respectively, than in adults (Stamatas *et al.*, 2010). This finding is consistent with the slight
30
31 213 increase in the number of SC layers reported for back and cheek skin between birth and
32
33 214 adulthood (Ya Xian, Suetaki & Tagami, 1999). A recent *in vivo* study used high-frequency
34
35 215 ultrasound imaging to identify a lower epidermal thickness (mean of 0.081 mm for extended
36
37 216 forearm; 0.083 mm for thigh) in <24 h-old newborns (Przybysz *et al.*, 2021) than in adults
38
39 217 (0.132 mm for inner forearm; 0.147 mm for outer forearm; 0.125 mm for cheek; 0.143 mm
40
41 218 for chin) (Mlosek *et al.*, 2011, 2013). These values were obtained by the same researchers
42
43 219 with the same methods and for similar Caucasian populations, while another study recorded a
44
45 220 thickness of 0.108 mm or 0.090 mm for an adult forearm depending on the arm position (90°
46
47 221 flexion or 180° extension, respectively) using optical coherence tomography (Maiti *et al.*,
48
49 222 2016). Such data indeed suggest that newborn epidermis is thinner than adult epidermis.
50
51
52
53
54
55
56
57
58
59
60

1
2
3 223 At the cellular level and considering the cell surface area, infant corneocytes were found to be
4
5 224 20% and granular cells 10% smaller than those of adults indicating a more rapid cell turnover
6
7 225 (Stamatas *et al.*, 2010) which is highlighted *in vivo* by greater desquamation (Hoeger &
8
9 226 Enzman, 2002). According to Michel *et al.* (1996, 1997) this may be correlated with a higher
10
11 227 stem cell number. Taking into account current knowledge concerning stem cell evolution
12
13 228 during skin ageing (Giangreco *et al.*, 2008, 2010; Charruyer *et al.*, 2009; Keyes *et al.*, 2013),
14
15 229 we can also hypothesize a higher proliferative ability of those stem cells which may explain
16
17 230 the well-known more rapid amplification of human newborn primary keratinocytes observed
18
19 231 in 2D cultures. Infant corneocytes have also been shown to be thicker (in height) than those of
20
21 232 adults and detailed three-dimensional morphometry using atomic force microscopy
22
23 233 highlighted that although adult corneocytes are flatter than in infants, the total volume
24
25 234 remains statistically similar between the two groups (Kashibuchi *et al.*, 2002). Another study
26
27 235 performed in Japan using confocal laser scanning microscopy reported a decrease in SC
28
29 236 thickness over the 3 months after birth and an increase of epidermis thickness during the first
30
31 237 month after birth. This study identified no difference between adult skin and infants older
32
33 238 than 3 months (Miyachi *et al.*, 2016).
34
35 239 Despite newborn epidermis being thinner than in young adults, a recent systematic study
36
37 240 using histological data highlighted the paucity of data, significant differences between
38
39 241 sampling sites, and technical problems that limit data reliability (de Souza *et al.*, 2019). As
40
41 242 contradictions among results may be linked to inaccurate measurements, skin anatomical
42
43 243 region or ethnic origin, further investigations using precise measurement tools, large sample
44
45 244 sizes and including various skin anatomical regions and subjects of recorded ethnic origins
46
47 245 are needed. This would allow us to describe and understand skin modifications better, the
48
49 246 underlying mechanisms that take place after birth, and would enable a more accurate
50
51 247 assessment of newborn skin fragility.
52
53
54
55
56
57
58
59
60

1
2
3 248 For preterm babies, skin immaturity is highlighted by a transparent, reddish and gelatinous
4
5 249 appearance (Razmus, Lewis & Wilson, 2008). The epidermis is significantly thinner (Razmus
6
7 250 *et al.*, 2008; Przybysz *et al.*, 2021) than in young adults. The SC and the underlying epidermal
8
9 251 layers change during pregnancy: there is virtually no SC at 23–24 weeks gestational age
10
11 252 (GA), 2–3 layers at 30 weeks (Razmus *et al.*, 2008) and 16 layers in young adults (Fairley &
12
13 253 Rasmussen, 1983; Holbrook, 2000). Evans & Rutter (1986) reported a mean \pm SD of 2.9 ± 0.5
14
15 254 cell layers from the epidermal basal layer to the granular layer in preterm neonates compared
16
17 255 with 4.3 ± 0.7 cell layers in full-term neonates. It takes 2–8 weeks for preterm neonates to
18
19 256 develop a functional epidermis similar to that of full-term infants, depending on their degree
20
21 257 of prematurity (Fox, 2011). Recent studies have correlated epidermis thickness to both
22
23 258 gestational age and body mass (Przybysz *et al.*, 2021) and have even proposed epidermis
24
25 259 thickness as a marker of gestational age to assess prematurity (Vital *et al.*, 2018). This poor
26
27 260 epidermal barrier makes preterm infants susceptible to increased water loss, higher
28
29 261 permeability to exogenous materials and a higher risk of skin damage and infection during the
30
31 262 first weeks following birth (Harpin & Rutter, 1983; Evans & Rutter, 1986; Neidig, Kleier &
32
33 263 Oppliger, 1989; Cartlidge, 2000; Lund & Osborne, 2004; Fox, 2011; Blume-Peytavi *et al.*,
34
35 264 2012).
36
37
38
39
40
41
42 265 During human skin ageing, thinning of the skin is observed, with a linear decrease in skin
43
44 266 thickness *in vivo* with age (Tan *et al.*, 1982). Clinically, chronologically aged skin appears
45
46 267 thin, dry, and finely wrinkled (Rittié & Fisher, 2015). *Ex vivo* studies have confirmed this
47
48 268 thinning: Xu *et al.* (2017) reviewed 16 studies of epidermal thickness by mean age and found
49
50 269 an average of $75.03 \mu\text{m}$ for ages 0–60 compared to $45.56 \mu\text{m}$ for ages 60 and older. This
51
52 270 thinning is due to a decrease in epidermal turnover which has been correlated by some authors
53
54 271 to reduced cell proliferation and stem cell number (Kligman, 1979; Michel *et al.*, 1997;
55
56 272 Stamatas *et al.*, 2006). However, this remains controversial as other studies have reported a
57
58
59
60

1
2
3 273 decreased proliferative capacity but a constant stem cell number in mouse skin until the end
4
5 274 of life (Giangreco *et al.*, 2008; Charruyer *et al.*, 2009; Keyes *et al.*, 2013). According to
6
7 275 Giangreco *et al.* (2010), the cell density in the epidermal basal layer also decreases during
8
9 276 human skin ageing. Moreover, expression levels of two stem cell markers of human
10
11 277 interfollicular epidermis – $\beta 1$ integrin and melanoma chondroitin sulfate proteoglycan
12
13 278 (MCSP) – are lower in people >60 years old (Giangreco *et al.*, 2010). This implies either a
14
15 279 decrease in stem cell number or a reduction in the activation or proliferation potential of stem
16
17 280 cells, but further studies are needed. The SC remains functional (Kligman, 1979; Lavker,
18
19 281 Zheng & Dong, 1989; Lavker, 1995; Newton *et al.*, 2017), allowing maintenance of a TEWL
20
21 282 similar to or lower than that of young adults (Akdeniz *et al.*, 2018a). Its thickness has been
22
23 283 reported to be similar or slightly higher than in young adults, depending on body area and
24
25 284 study (Waller & Maibach, 2005; Rawlings, 2017) (Fig. 1, Table 1).
26
27
28
29
30
31
32

33 286 **(2) Infant and elderly skin: a respectively immature and altered dermal–epidermal** 34 35 287 **junction (DEJ)**

36
37 288 The DEJ is a specific zone forming more or less marked undulations and where the epidermis
38
39 289 is tightly associated to the dermis due to the hemidesmosomes of basal keratinocytes, the
40
41 290 anchoring filaments linking the hemidesmosomes to the basement membrane, and the
42
43 291 anchoring fibrils connecting the basement membrane to the underlying dermis (Ellison &
44
45 292 Garrod, 1984; Villone *et al.*, 2008). This structure plays an important part in skin cohesion,
46
47 293 resistance and homeostasis. The DEJ also prevents direct contact between the dermis and
48
49 294 epidermis or epidermal migration into the dermis and therefore controls the numerous
50
51 295 exchanges between the dermis and epidermis (including nutrients and signalling molecules)
52
53 296 (Amano, 2016). Moreover, the DEJ maintains the proliferative state of the basal layer and
54
55 297 determines the polarity of the epidermis (Amano, 2016).
56
57
58
59
60

298

(a) Features of the DEJ in infant and elderly skin

A weakly undulating DEJ with flat rete ridges and few fibrils in the epidermal basal layer characterizes the skin of the newborn (Evans & Rutter, 1986; Razmus *et al.*, 2008). It was also reported that dermal papillae were not present in neonatal skin but appeared gradually over the first 3 months following birth (Miyachi *et al.*, 2016). DEJ undulations, cell attachments and epidermal cellularity increase gradually in neonates and young infants during skin maturation (Evans & Rutter, 1986; Cartlidge, 2000; Miyachi *et al.*, 2016). Consequently, newborn skin is more susceptible to traction and shear forces. The DEJ is flat before 34 weeks GA in preterm neonates (Cartlidge, 2000) and there are fewer anchoring structures with wide spaces between connecting points (Holbrook, 1982), leading to increased fragility of the skin (Fig. 1, Table 1).

DEJ flattening with shorter rete ridges and dermal papillae rarefaction and reduction is also a well-known characteristic of intrinsic skin ageing (Lavker *et al.*, 1987, 1989; Moragas, Castells & Sans, 1993; Desai, 1997; Giangreco *et al.*, 2010; Farage *et al.*, 2013; Newton *et al.*, 2017). It is associated with a reduction of anchoring molecules such as $\beta 1$ integrins, transmembrane proteins of basal keratinocytes involved in their anchoring to the DEJ, and a decrease in basal cell proliferation ability (Giangreco *et al.*, 2010). These modifications are thought to reduce skin resistance to shearing forces (Lavker *et al.*, 1987, 1989; Desai, 1997; Farage *et al.*, 2013; Hatje *et al.*, 2015), the area of the exchange surface for epidermis nutrition (Farage *et al.*, 2013) and the proliferative capacity of epidermal cells (Lavker *et al.*, 1987; Giangreco *et al.*, 2010). This results in higher skin fragility with an increased risk of skin rupture (Farage *et al.*, 2013). There is also likely to be a decrease in waste elimination which might alter the epidermal cellular environment, but this remains to be investigated (Fig. 1, Table 1).

1
2
3 323 The flatter DEJ observed in both newborn and elderly skin is significantly associated with
4
5 324 higher susceptibility to traction and shear forces. In addition, it may limit cell nutrition and
6
7 325 waste elimination, favouring cell alterations under pressure or shear force conditions.
8
9
10 326 Consequently, a higher risk of PI formation may be hypothesized although the underlying
11
12 327 mechanisms require investigation.
13

14 328

15
16
17 329 *(b) A specific molecular network in the DEJ of infant and elderly skin*

18
19 330 At the molecular level, the DEJ contains a well-organized network of various proteins
20
21 331 including laminin 332 (also called laminin V), types IV and VII collagens, heparan sulfate
22
23 332 proteoglycan (perlecan) and nidogens. Laminin 332, a ligand of basal keratinocyte integrins,
24
25
26 333 is essential for epidermal attachment in mice and humans (Rousselle *et al.*, 1991, 1997;
27
28 334 Nakano *et al.*, 2002; Rousselle & Beck, 2013; Tayem *et al.*, 2021). It has been reported to
29
30 335 enhance hemidesmosome formation and reinforce the DEJ in skin-equivalent models
31
32
33 336 (Amano, Nishiyama & Burgeson, 1999), but also to regulate the differentiation of mouse and
34
35 337 human interfollicular epidermal stem cells which themselves produce laminin 332 (Yamada *et*
36
37 338 *al.*, 2018; Tayem *et al.*, 2021), to inhibit sensory mechanotransduction and thereby decrease
38
39 339 pain sensitivity in mice, and to control sensory axon branching behaviour (Chiang *et al.*,
40
41
42 340 2011)
43

44
45 341 During human skin ageing, the expression level of a laminin 332 subunit (Lamb3) has been
46
47 342 shown to decrease (Yamada *et al.*, 2018), as well as the number of interfollicular epidermal
48
49 343 stem cells and/or their activation potential which is thought to be one of the main causes of
50
51 344 epidermal dysfunction such as delayed cell turnover (Giangreco *et al.*, 2010; Akamatsu *et al.*,
52
53 345 2016; Yamada *et al.*, 2018). As laminin 332 has been shown to regulate the proper
54
55
56 346 differentiation of human interfollicular epidermis stem cells (Yamada *et al.*, 2018), this
57
58
59
60

1
2
3 347 decrease in laminin 332 expression probably leads to slower epidermal renewal, contributing
4
5 348 to the thinner and more fragile skin observed in the elderly.

7 349 Perlecan is well known to have many functions such as regulating the molecular assembly of
8
9
10 350 the extracellular matrix (ECM), stabilizing the ECM molecular network and binding and
11
12 351 transporting growth factors to cells (Lord *et al.*, 2018). Perlecan has also been reported to
13
14 352 promote epidermal renewal *in vitro* (Dos Santos *et al.*, 2016). As levels of perlecan decrease
15
16 353 in the elderly, a role in epidermal thinning during skin ageing has been suggested.

19 354 Very few data focusing on the DEJ of infant skin DEJ at the molecular level are available. To
20
21 355 our knowledge, there are no data concerning perlecan. One study reported similar expression
22
23 356 of laminin 332 and decreased expression of laminins 511 (= laminin 10) and 521 (= laminin
24
25 357 11) in adult skin compared to infant skin (Pouliot, Saunders & Kaur, 2002). As laminins 511
26
27 358 and 521 seem to facilitate keratinocyte adhesion and to stimulate their proliferation, this might
28
29 359 explain the high proliferative ability of infant skin. We hypothesize that skin maturation
30
31 360 during infancy involves deep modifications of the DEJ molecular network, but further studies
32
33 361 will be needed to understand the underlying mechanisms better.
34
35
36
37
38
39

40 363 **(3) Dermal cells and extracellular matrix (ECM)**

41
42 364 Thicker than the epidermis, the dermis mainly contains fibroblasts embedded in ECM
43
44 365 composed of collagen, elastin and glycosaminoglycans respectively involved in resistance,
45
46 366 elasticity and hydration of the skin. The dermal layer also includes skin appendages (hair
47
48 367 follicles, sebaceous glands, sweat glands and nails), capillary beds that feed the skin, and
49
50 368 various nerve endings responsible for skin sensitivity.
51
52
53
54
55

56 370 *(a) Dermis thickness*

57
58
59
60

1
2
3 371 In humans, dermis thickness depends greatly on body area, genetic factors (Vital *et al.*, 2018)
4
5 372 and age. After a slight decrease during the first 7 days following birth (Reed, Johnson & Nie,
6
7 373 2021) it has been found to increase over time (Tan *et al.*, 1982). The thickness of outer
8
9 374 forearm dermis was found to be close to 0.722 mm for a newborn (<24 h old), regardless of
10
11 375 sex (Przybysz *et al.*, 2021) *versus* 1.187 mm in adults (Mlosek *et al.*, 2011). For adults, higher
12
13 376 values were reported for males than in females (Van Mülder *et al.*, 2017). Intrinsic ageing
14
15 377 also induces a thinner dermis in contrast to photoageing (Shuster, Black & McVitie, 1975;
16
17 378 Giangreco *et al.*, 2010) (Fig. 1, Table 1).
18
19
20
21
22
23

24 380 (b) Fibroblast and ECM evolution

25
26 381 As fibroblasts produce various ECM components including collagen and elastin, but also
27
28 382 enzymes able to degrade those components, ECM composition is highly dependent on
29
30 383 fibroblast state and metabolism.
31
32
33
34

35 385 (i) Fibroblast evolution over time

36
37 386 Fibroblasts are the most characteristic cells of the dermis. Less mature than adult fibroblasts,
38
39 387 human newborn fibroblasts (<16 days) can maintain keratinocyte immaturity and avoid scar
40
41 388 formation (Živicová *et al.*, 2017). In newborn mice, as for keratinocytes, a higher proliferation
42
43 389 level of fibroblasts has been observed compared to adult skin (Pablos *et al.*, 1997). In elderly
44
45 390 humans, fibroblast motility decreases *in vitro* (Pienta & Coffey, 1990), as well as fibroblast
46
47 391 number *in vivo* (Sgonc & Gruber, 2013) and a correlation with increased cellular senescence
48
49 392 is observed *in vitro* and *in vivo* (Dimri *et al.*, 1995).
50
51
52
53

54 393 Overall, fibroblast immaturity in newborns and fibroblast senescence in the elderly leads to
55
56 394 reduced ECM production at both ages, resulting in higher skin fragility (Table 1).
57
58
59
60

1
2
3 396 (ii) *A more fragile collagen network*
4

5 397 The dermal collagen network allows skin resistance to rupture. ECM contains various
6
7 398 collagen types of which the main ones are collagen I (85–90% in human adult skin) and
8
9 399 collagen III (8–11% in human adult skin) (Smith, Holbrook & Madri, 1986).
10
11 400 Collagen fibre volume has been shown to increase progressively from less than 1 year to 30
12
13 401 years in human papillary dermis as well as in reticular dermis of the trunk and limbs
14
15 402 (Vitellaro-Zuccarello *et al.*, 1994). Collagen fibrils were even smaller in preterm neonates
16
17 403 (Holbrook, 1982). Moreover, the collagen bundles of the upper reticular dermis, normally
18
19 404 thicker than in papillary dermis, are less thick in newborns and infants. This leads to a more
20
21 405 gradual transition between the papillary and reticular dermis (Vitellaro-Zuccarello *et al.*,
22
23 406 1994; Holbrook, 1982; Stamatias *et al.*, 2010; Przybysz *et al.*, 2021). Collagen 1 synthesis was
24
25 407 found to increase in a gender-specific manner despite no observable differences between
26
27 408 males and females at birth. Women aged 15–93 years were reported to have a thinner dermis
28
29 409 with a lower collagen density compared to men of the same age (Shuster *et al.*, 1975). A study
30
31 410 on mice found an increase in collagen 1 synthesis until 30 days of age with higher values in
32
33 411 males older than 16 days correlated with testosterone production (Arai *et al.*, 2017).
34
35 412 In young adult skin, collagen is abundant, tightly packed and well organized, whereas it
36
37 413 progressively becomes less dense, fragmented and coarsely distributed in aged skin (Shuster
38
39 414 *et al.*, 1975; Shin *et al.*, 2019). With skin ageing, collagen I is progressively degraded and
40
41 415 over time accumulates around fibroblasts. The surface area of fibroblasts, and their contact
42
43 416 points with the surrounding matrix decrease with age in humans (Varani *et al.*, 2001).
44
45 417 Consequently, the strength of the matrix and the mechanical forces within resident fibroblasts
46
47 418 both decrease. This stimulates reactive oxygen species (ROS) production, synthesis of
48
49 419 metalloproteinases (MMPs) and decreased collagen levels (Rittié & Fisher, 2015; Fisher *et*
50
51 420 *al.*, 2016), which might explain the higher sensitivity of elderly skin to shear forces (Table 1).
52
53
54
55
56
57
58
59
60

1
2
3 421 The changes in collagen synthesis and degradation with age lead to an evolution of the ratio
4
5 422 between collagen I and collagen III over time. This ratio is much lower in foetal skin than in
6
7 423 adult humans (Epstein, 1974; Cheng *et al.*, 2011), as well as in guinea pigs (Shuttleworth &
8
9 424 Forest, 1975), and decreases from age 65 years onwards (Lovell *et al.*, 1987). A lower ratio in
10
11 425 skin has been correlated with a lower ratio in the abdominal wall fascia of hernia patients
12
13 426 (Peeters *et al.*, 2014), leading us to hypothesize that this ratio may also be involved in
14
15 427 newborn and elderly skin fragility, but further investigations are required to confirm this
16
17
18
19 428 (Table 1).

20
21
22 429

23
24 430 *(iii) Lower skin elasticity*

25
26 431 Skin elasticity arises from elastin. Elastin is composed of fibrillin microfibrils (Sakai, Keene
27
28 432 & Engvall, 1986) together with an amorphous component (Rosenbloom, Abrams &
29
30 433 Mechams, 1993) synthesized by fibroblasts and vascular smooth muscle cells. Skin elastin
31
32 434 synthesis occurs at high rates during late gestation and in early life before decreasing
33
34 435 progressively with age. In newborns, elastin mainly appears as thin bundles of microfibrils,
35
36 436 which gradually enlarge and evolve, to appear mostly as amorphous elastin surrounded by a
37
38 437 few fibrils in adolescents. Thus, the volume density of the elastin network increases from
39
40 438 birth, reaching approximately 2–4% of the tissue volume at sexual maturity, with variations
41
42 439 depending on dermis area and subject (Swee, Parks & Pierce, 1995; Pasquali-Ronchetti &
43
44 440 Baccarani-Contrì, 1997). Thereafter, elastin synthesis is drastically reduced (Swee *et al.*,
45
46 441 1995; Shin *et al.*, 2019). This has been correlated with decreased levels of lysyl oxidase
47
48 442 (LOX) and lysyl oxidase-like (LOXL), which are both responsible for elastin crosslinking
49
50 443 (Cenizo *et al.*, 2006). As elastin has a very high physiological stability with an estimated half-
51
52 444 life of 74 years in humans (Shapiro *et al.*, 1991), modifications are mainly due to elastin
53
54 445 degradation which mostly occurs in the elderly and are correlated with a higher level of
55
56
57
58
59
60

1
2
3 446 elastase activity (Shin *et al.*, 2019). This leads to a decrease in elastin level during intrinsic
4
5 447 ageing (Braverman & Fonferko, 1982; Lavker *et al.*, 1989; Shin *et al.*, 2019) which has also
6
7 448 been correlated with a decrease in fibulin-5 deposition (Kadoya *et al.*, 2005).

8
9
10 449 Given its synthesis mainly at the beginning of life and increased degradation at the end of life,
11
12 450 skin elasticity is lower in both newborn and aged skin. As a result, the ability of the skin to
13
14 451 return to its original shape after a deformation is lower in both cases and we hypothesize that
15
16 452 this makes it more difficult or slower for skin cells and tissues to return to a normal
17
18 453 physiological state with appropriate nutrition after a traumatic deformation. Further
19
20 454 investigations would therefore be of great interest to evaluate better the involvement of lower
21
22 455 elasticity in newborn and elderly skin fragility (Table 1).
23
24
25

26 456

27
28 457 *(c) A key role of transforming growth factor beta (TGF β) signalling*

29
30 458 Transforming growth factor β (TGF β)/ Suppressor of mothers against decapentaplegic (Smad)
31
32 459 signalling plays a key role in ECM formation. Long known to stimulate collagen synthesis
33
34 460 (Gessin *et al.*, 1993), it also enhances the expression of multiple collagens, fibronectin,
35
36 461 decorin and versican and controls the expression of matrix metalloproteinases (MMPs) and
37
38 462 their inhibitors (TIMPs) which are respectively down-regulated and up-regulated by TGF-
39
40 463 β /Smad signalling (Quan & Fisher, 2015) (Fig. 2).
41
42
43

44 464 During skin ageing, ROS generation decreases TGF β receptor II (T β RII) production and
45
46 465 impairs TGF β signalling thus increasing MMP activity and leading to collagen fragmentation,
47
48 466 a coarser distribution and decreased production (Quan & Fisher, 2015; Shin *et al.*, 2019).

49 467 These alterations to TGF β signalling lead to modifications of proteoglycans such as decorin
50
51 468 and versican and to decreases in their levels. Decorin interacts with collagen and is involved
52
53 469 in collagen fibrogenesis, wound repair, angiogenesis while versican is a component of the
54
55 470 elastic fibres and is involved in elastogenesis, ECM remodelling, cell phenotype,
56
57
58
59
60

1
2
3 471 proliferation, adhesion and migration (Ruiz Martinez *et al.*, 2020). Changes to these
4
5 472 proteoglycan functions could lead to higher skin fragility during ageing (Fig. 2).
6
7 473 Activation of the TGF β pathway is higher in human adults compared to newborns (Zhang *et*
8
9 474 *al.*, 2019), as is the expression of T β RII (Živicová *et al.*, 2017) and collagen I production
10
11 475 (Zhang *et al.*, 2019). Thus, we hypothesize that TGF β is involved in the progressive
12
13 476 maturation of the dermis after birth *via* increasing the levels and progressive maturation of
14
15 477 collagen but also probably of ECM proteins such as decorin or versican. This probably
16
17 478 contributes to the higher fragility of newborn skin, although further investigations will be
18
19 479 needed to determine the precise evolution of the dermal matrix after birth, the underlying
20
21 480 mechanisms and the role of TGF β (Fig. 2).
22
23
24
25 481 TGF β is also involved in various processes including epidermis differentiation (Barbollat-
26
27 482 Boutran *et al.*, 2017; Kahata, Dadras & Moustakas, 2018), wound healing (Liarte, Bernabé-
28
29 483 Garcíá & Nicolás, 2020), skin-resident immune cell maintenance and cell fate determination
30
31 484 (Kel *et al.*, 2010; Mohammed *et al.*, 2016; Mani *et al.*, 2019). Thus, the lower levels of TGF β
32
33 485 in newborn and elderly skin may be involved in many ways in the increased fragility of the
34
35 486 skin at these ages.
36
37
38
39
40
41

42 488 **(4) Infant and elderly skin vasculature**

43
44 489 Preserving skin homeostasis requires the maintenance of the cutaneous blood circulation
45
46 490 allowing cell nourishment. Human skin circulation is organized into two plexuses located in
47
48 491 the upper dermis just below the DEJ and at the dermal–subdermal junction. Most vessels are
49
50 492 in the upper plexus which is composed of terminal arterioles, papillary loops and postcapillary
51
52 493 venules. The deeper plexus gives rise to ascending arterioles connecting to the upper plexus
53
54 494 and lateral vessels feeding pilosebaceous units and sweat glands. Mainly in glabrous skin,
55
56
57
58
59
60

1
2
3 495 richly innervated arteriovenous anastomoses (AVAs) allow blood to bypass the high
4
5 496 resistance of the papillary loops (Johnson, Minson & Kellogg, 2014).
6
7 497 The microvasculature in the skin of newborns presents a horizontal plexus with a capillary
8
9 498 network that is not yet organized (Fig. 1, Table 1). At birth, capillary loops are observable
10
11 499 only on the nail beds, palms and soles. They become evident in all anatomical sites at 14–17
12
13 500 weeks of age (Perera, Kurban & Ryan, 1970). A recent study confirmed these observations *in*
14
15 501 *vivo*, also associating capillary loop establishment with that of dermal papillae (Miyachi *et*
16
17 502 *al.*, 2016). Preterm newborns have a lower capillary density which remains lower during
18
19 503 childhood (Bonamy *et al.*, 2007). Interestingly, one study reported an increase in capillary
20
21 504 density after blood transfusion in preterm newborns (Genzel-Boroviczény, Christ & Glas,
22
23 505 2004).

24
25
26 506 Human skin ageing is also associated with a reduced number and size of blood vessels,
27
28 507 especially in the upper dermis, and a reduced number of pericyte-covered blood vessels
29
30 508 (Kligman, 1979; Kelly *et al.*, 1995; Chung *et al.*, 2002; Betsholtz *et al.*, 2005; Helmbold *et*
31
32 509 *al.*, 2006).

33
34
35 510 We hypothesize that a lower organization and blood vessel number can lead to a less-efficient
36
37 511 or less finely regulated response following pressure application and therefore to reduced skin
38
39 512 resistance to pressure and shear forces, but further investigations are needed.
40
41
42
43
44

45 513

46 514 **(5) Infant and elderly skin hypodermis**

47
48 515 Under the dermis, the hypodermis, also called subcutaneous adipose tissue (SAT), is mainly
49
50 516 composed of adipocytes which may allow attenuation of shocks applied to the skin surface. In
51
52 517 mice, SAT has been shown to contribute to thermal insulation, energy storage, thermogenesis
53
54 518 (Kasza *et al.*, 2014), hair follicle regeneration (Festa *et al.*, 2011), wound healing (Plikus *et*
55
56
57
58
59
60

1
2
3 519 *al.*, 2017; Schmidt & Horsley, 2013), skin fibrosis (Marangoni *et al.*, 2015) and protection
4
5 520 against infection (Zhang *et al.*, 2015).
6

7 521 In humans, SAT appears progressively during foetal development. Fat lobules are visible
8
9 522 from 28 weeks GA (Orsso *et al.*, 2020), with an important increase in lipid accumulation
10
11 523 reported from 28 to 40 weeks GA (Berger-Kulemann *et al.*, 2012; Orsso *et al.*, 2020) before a
12
13 524 rapid decrease at birth, followed by a dramatic increase until 3 months of age, with a
14
15 525 subsequent decrease after 6 months (Breij *et al.*, 2017; Orsso *et al.*, 2020). Nevertheless, the
16
17 526 hypodermis thickness of newborns, children and adolescents, is significantly lower than that
18
19 527 of adults: mean abdominal SAT thickness was reported to be 2 and 2.2 mm respectively for
20
21 528 boys and girls 7–28 days old (Ferreira *et al.*, 2014), 4.3 mm and 4.4 mm for babies 3–6
22
23 529 months old (Breij *et al.*, 2017), 2.6 and 2.7 mm for boys and girls 15–18 years old (Rahmani
24
25 530 *et al.*, 2018), 15.2 mm for healthy men 25–26 years old (Grunnet *et al.*, 2019) and 17.8 mm
26
27 531 for healthy women 18–39 years old (Perin *et al.*, 2000). Data for the body locations most at
28
29 532 risk of PI formation are missing, but we hypothesize that similar age-dependent values apply,
30
31 533 with newborns more likely to have the thinnest hypodermis, although further investigations
32
33 534 are needed to confirm this.
34
35
36
37
38
39

40 535 During skin ageing, a redistribution of fat resulting in SAT atrophy has been reported (Palmer
41
42 536 & Kirkland, 2016; Wollina *et al.*, 2017), in particular for men (Levakov *et al.*, 2012), and this
43
44 537 has been associated with a reduced subcutaneous/visceral fat ratio (Rittié & Fisher 2015).
45
46 538 Consequently, SAT function allowing attenuation of shocks is likely to be lowest both in
47
48 539 newborns and in the elderly.
49

50
51 540 SAT is known to undergo significant changes with ageing, including a decrease in functional
52
53 541 adipocyte cell number, an alteration of endocrine signalling with higher insulin resistance,
54
55 542 metabolic dysfunction, inflammation and impaired regenerative capacity (Rittié & Fisher,
56
57 543 2015; Palmer & Kirkland, 2016). Interestingly, despite a thicker SAT, similar changes are
58
59
60

1
2
3 544 observed in obese people (Palmer & Kirkland, 2016) while epidemiological studies suggest
4
5 545 either a protective effect of obesity against PI formation or, on the contrary, a higher risk
6
7 546 despite thicker SAT (Compher *et al.*, 2007; EPUAP, NPIAP & PPPIAP, 2019). As no clear
8
9
10 547 relationship between obesity and PI formation has been established (EPUAP, NPIAP &
11
12 548 PPPIAP, 2019), the involvement of SAT modifications in PI prevalence remains to be
13
14 549 defined. We cannot exclude that SAT characteristics other than thickness are involved in a
15
16
17 550 higher risk of PI formation.

18
19 551 While additional data are needed to clarify the evolution of SAT thickness, organization and
20
21 552 functionality over the lifetime and in various body areas, the available data do suggest that the
22
23 553 ability of the hypodermis to attenuate shocks and reduce the likelihood of skin damage is
24
25
26 554 lower in newborns and the elderly compared to young adults, putting the skin at higher risk of
27
28 555 PI formation (Table 1). Moreover, the risk may be particularly high for preterm infants as
29
30 556 subcutaneous fat is very thin or even absent until 32 weeks GA (Fox, 2011; Orsso *et al.*,
31
32
33 557 2020). In addition, a recent study reported that a subcutaneous oedema was present in all
34
35 558 healthy newborns studied (Przybysz *et al.*, 2021), which presumably impacts responses to
36
37 559 pressure application or shear forces, either by providing a protective cushioning effect or by
38
39 560 favouring skin detachment from subcutaneous tissues and associated damage. These effects
40
41
42 561 remain to be investigated.

43
44
45 562

46 563 **III. FUNCTIONAL FEATURES OF NEWBORN AND ELDERLY SKIN FAVOURING**

47 564 **PI FORMATION**

48 565 **(1) A higher pH impairing SC barrier function**

49
50
51 566 The pH of human adult skin ranges from 4.1 to 5.8 depending on body location and results
52
53
54 567 from many factors, including filaggrin degradation, lamellar body exocytosis, fatty acid
55
56
57 568 content and ionization, Na⁺/H⁺ exchanger activation and melanosome release (Ali &
58
59
60

1
2
3 569 Yosipovitch, 2013; Proksch, 2018). An acidic skin pH is necessary for effective functioning
4
5 570 of enzymes involved in SC formation, SC cell cohesion, healthy skin microbiota homeostasis
6
7 571 and protection against pathogens (Yosipovitch *et al.*, 2000; Fluhr *et al.*, 2001).
8
9
10 572 At birth, skin pH is high, with a mean of 6.34 or 7.08 (Lund *et al.*, 1999; Yosipovitch *et al.*,
11
12 573 2000) and ranging from 6.11 to 7.5 across different body regions (Yosipovitch *et al.*, 2000;
13
14 574 Ludriksone *et al.*, 2014). Skin pH decreases rapidly during the first week and more gradually
15
16 575 during the next 3 weeks, for both premature and full-term newborns (Fox, Nelson &
17
18 576 Wareham 1998; Ludriksone *et al.*, 2014). This higher pH of newborn skin allows increased
19
20 577 activity of serine protease (kallikrein 5 and 7) leading to higher corneodesmosome and lipid-
21
22 578 processing enzyme degradation (Hachem *et al.*, 2005). Moreover, a higher pH reduces the
23
24 579 activity of key enzymes such as β -glucocerebrosidase and acidic sphingomyelinase involved
25
26 580 in the synthesis of ceramides (Ali & Yosipovitch, 2013). This potentially puts newborn skin at
27
28 581 higher risk of chemical or mechanical trauma, invasion of microorganisms and infections
29
30 582 (Fig. 3).
31
32
33
34
35 583 In the diapered area where skin is subject to strong alkalinizing agents (urine, faeces), skin
36
37 584 fragility is increased. In preterm babies less than 28 weeks GA, the vernix caseosa which
38
39 585 normally decreases skin pH is absent, potentially leading to higher skin fragility (Visscher *et*
40
41 586 *al.*, 2011*a,b*). Interestingly, maintaining the vernix caseosa instead of removing it
42
43 587 immediately after birth in full-term deliveries has been shown to be beneficial for acid skin
44
45 588 surface development (Visscher *et al.*, 2005).
46
47
48
49 589 During human skin ageing, an increase in ceramidase activity and a decrease in eccrine sweat
50
51 590 gland (ESG) function result in ceramide deficiency. This is correlated to an increased pH, for
52
53 591 example on the forehead, forearm or temple (Man *et al.*, 2009; Schreml *et al.*, 2012; Ali &
54
55 592 Yosipovitch, 2013; Rittié & Fisher, 2015). This higher pH leads to a higher fragility and
56
57
58
59
60

1
2
3 593 susceptibility to diseases which could be treated by using acidic treatments and appropriate
4
5 594 buffers (Hachem *et al.*, 2010; Proksch, 2018; Kilic *et al.*, 2019).
6
7 595 As for babies, skin fragility in the aged is increased in diapered areas containing urine and
8
9 596 faeces. Well known to increase incontinence-associated dermatitis, a high pH has also been
10
11 597 suggested to increase PI prevalence, as a treatment including pH-balanced cleansers decreased
12
13 598 PI incidence (Park & Kim, 2014; Avşar & Karadağ, 2018). In skin care, it is of great
14
15 599 importance to consider skin pH and to take into account all factors that might modulate it. A
16
17 600 significant effect of the skin pH alone on PI formation remains to be demonstrated.
18
19
20
21
22
23

24 602 **(2) Skin hydration and external humidity**

25
26 603 Skin hydration influences barrier function, percutaneous absorption, reactivity to irritants and
27
28 604 the skin's mechanical properties (Giusti *et al.*, 2001). It may be modulated by external
29
30 605 humidity and temperature as well as body site, diaper occlusion (Giusti *et al.*, 2001) and fluid
31
32 606 intake (Akdeniz *et al.*, 2018b). The term 'skin hydration' can cover different concepts
33
34 607 depending on the author. *In vivo*, this parameter is often assessed either by considering the
35
36 608 clinical symptoms of dryness on the skin surface or at the SC level using non-invasive
37
38 609 methods. But skin hydration may also correspond to the hydration level in the underlying
39
40 610 living skin layers.
41
42
43

44
45 611 Several studies have reported lower SC hydration in 0–5-day-old newborns compared to
46
47 612 young adults on the forehead, back, abdomen (Yosipovitch *et al.*, 2000), forearm and dorsa of
48
49 613 the hand and foot (Saijo & Tagami, 1991) or forearm and thigh (Chittock *et al.*, 2016). SC
50
51 614 hydration increases during the first weeks after birth in or close to the diapered area (Visscher
52
53 615 *et al.*, 2000) as well as on the forearm (Saijo & Tagami, 1991; Hoeger & Enzmann, 2002),
54
55 616 forehead, cheek or gluteal surface (Hoeger & Enzmann, 2002). Infant SC hydration becomes
56
57 617 higher than that of adults at least on the forearm of 1–6 or 3–24-months-old children (Saijo &
58
59
60

1
2
3 618 Tagami, 1991; Giusti *et al.*, 2001), the buttocks of 3–24-months-old children (Giusti *et al.*,
4
5 619 2001), and the upper ventral and lower dorsal arm of 3–12-months-old infants (Nikolovski *et*
6
7 620 *al.*, 2008). No significant differences were observed between male and female newborns
8
9 621 (Hoeger & Enzmann, 2002), infants less than 3 months old (Hoeger & Enzmann, 2002) or 8–
10
11 622 24-months-old children (Giusti *et al.*, 2001). Overall, SC hydration of young newborns seems
12
13
14 623 to be lower than that of adults before increasing during the neonatal period. This has been
15
16 624 correlated to the dry and rough skin surface of young newborns and the progressive
17
18 625 smoothing of the skin surface observed during the first 4 weeks (Hoeger & Enzmann, 2002).
19
20 626 The skin of elderly people tends to become progressively dry and rough, especially in winter
21
22 627 with a low relative humidity (Kligman, 1979; Tagami, 2008). During skin ageing, a decrease
23
24 628 in SC hydration has often been reported, but is not always the case. A decrease on the
25
26 629 forehead and forearm, to a greater extent in women than in men, was reported in a Chinese
27
28 630 population aged >70 years (Man *et al.*, 2009), while a significant decrease was also observed
29
30 631 in German men aged 60–70 years on the forehead, cheek and neck, but not on the forearm or
31
32 632 hand compared with a 20–29-years-old group (Luebberding, Krueger & Kerscher, 2014).
33
34 633 Thus, elderly skin dryness observed on the surface is not necessarily correlated with low SC
35
36 634 hydration. Moreover, there is no correlation with dermis water content as elderly skin dermis
37
38 635 contains more water than young adult skin (Kligman, 1979; Nakagawa, Matsumoto & Sakai,
39
40 636 2010, Téllez-Soto *et al.*, 2021).
41
42 637 Skin hydration depends on lipid production (Kligman, 1979; Picardo *et al.*, 2009), ESG
43
44 638 activity (Emery *et al.*, 1991; Saijo & Tagami, 1991; Shiohara *et al.*, 2018) and the
45
46 639 concentrations of a mix of amino acids, ions, organic acids and sugar that together form
47
48 640 natural moisturizing factor (NMF) (Verdier-Sévrain & Bonté, 2007).
49
50 641 On its surface, skin is covered by a mix of lipids secreted by keratinocytes and sebaceous
51
52 642 glands. Dysfunction of the sebaceous glands may lead to skin dryness (Picardo *et al.*, 2009).
53
54
55
56
57
58
59
60

1
2
3 643 In the elderly a decrease in sebum production has been associated with progressive skin
4
5 644 dryness (at least for women) (Pochi, Strauss & Downing, 1979; Luebberding, Krueger &
6
7 645 Kerscher, 2013; Farage *et al.*, 2013). For newborns, few data are available. Some studies
8
9 646 suggest that sebum production is slightly lower in young newborns, compared to young adults
10
11 647 and progressively decreases during infancy, remaining at a low level until puberty (Agache *et*
12
13 648 *al.*, 1980; Henderson, Taylor & Cunliffe, 2000). Consequently, the likely correlation between
14
15 649 decreased sebum production and skin dryness in the elderly is unlikely to apply to the skin of
16
17 650 young newborns.

18
19
20
21 651 ESGs are known to be involved in body temperature regulation. But they also produce water
22
23 652 and natural moisturizers (lactate and urea) which help to prevent skin dryness (Shiohara *et al.*,
24
25 653 2018). As they are not fully mature at birth, a correlation between gradual ESG maturation
26
27 654 allowing improved activity and progressive hydration of the newborn skin surface has been
28
29 655 suggested, at least for the first weeks after birth for full-term newborns (Foster, Hey & Katz,
30
31 656 1969; Saijo & Tagami, 1991; Emery *et al.*, 1991). For preterm births of less than 36 weeks
32
33 657 GA, no sweating has been detected at birth highlighting ESG immaturity (Harpin & Rutter,
34
35 658 1982; Fluhr *et al.*, 2010; Kutlubay *et al.*, 2017). During skin ageing, a progressive decrease in
36
37 659 ESG function has also been observed, suggesting possible involvement of ESGs in elderly
38
39 660 skin dryness (Rittié & Fisher, 2015).

40
41
42
43
44 661 NMF mainly results from filaggrin proteolysis occurring during the corneocyte maturation
45
46 662 process (Caspers *et al.*, 2001; Bouwstra *et al.*, 2008). For newborns, NMF also depends on the
47
48 663 amount of vernix caseosa present at birth which increases NMF level and maintains skin
49
50 664 surface hydration for a few hours (Visscher *et al.*, 2005). NMF level seems to be correlated
51
52 665 with SC hydration. Chittock *et al.* (2016) measured low NMF levels in <72 h newborns, a
53
54 666 significantly higher level at 4 weeks, and a significant decrease in healthy adults on the
55
56 667 forearm and the thigh. A recent study also reported an increase in NMF levels between young
57
58
59
60

1
2
3 668 (<48 h) and older newborns (>48 h) on the cheek, nose tip and elbow flexure (McAleer *et al.*,
4
5 669 2018). A lower level of NMF was reported in 3–12-months-old infants compared to young
6
7 670 adults in the top 28 μm of the arm skin (Nikolovski *et al.*, 2008), highlighting that additional
8
9 671 data are needed to understand the link between NMF level and SC hydration. For post-term
10
11 672 newborns more than 41 weeks GA, the amount of vernix progressively decreases *in utero*
12
13 673 after term: the NMF increase due to the presence of vernix is therefore lower and the NMF
14
15 674 produced by keratinocytes is partly removed by the amniotic fluid. These effects may explain
16
17 675 the dryer post-term newborn skin (Visscher *et al.*, 2005, 2015). During skin ageing, data
18
19 676 concerning changes in NMF levels remain controversial (Rawlings, 2017) and its involvement
20
21 677 in elderly skin dryness requires additional studies.

22
23
24 678 Overall, some data suggest that both young newborn and elderly skin can be considered as
25
26 679 ‘dry skin’ given their SC hydration. This influences skin barrier function as SC hydration
27
28 680 level regulates the activity of hydrolytic enzymes involved in SC maturation and corneocyte
29
30 681 desquamation (Telofski *et al.*, 2012). Nevertheless, this relative dryness depends on body
31
32 682 location and is not true for older newborns and infants. Moreover, SC hydration depends on
33
34 683 many factors such as NMF level, lipid production and ESG activity which do not evolve in
35
36 684 the same way over time. The relationships between all these factors are complex and remain
37
38 685 unclear. A better understanding of this phenomenon and a possible correlation with skin
39
40 686 fragility will need further investigations (Table 1).

41
42 687 Maintaining a higher humidity in the external environment, for example in diapered areas or
43
44 688 with inappropriate dressings, cannot help to maintain skin hydration. On the contrary, it leads
45
46 689 to a decrease in skin barrier competence highlighted by an increased TEWL (Fluhr *et al.*,
47
48 690 2010; Giusti *et al.*, 2001). Excess moisture and maceration is well known to enhance skin
49
50 691 rupture during PI formation (Mervis & Phillips, 2019) and special care to avoid this situation
51
52 692 is needed.
53
54
55
56
57
58
59
60

1
2
3 693
4
5 694 **(3) Lower endothelial functionality might explain a lower resistance to pressure in**
6
7
8 695 **newborn and elderly skin**

9
10 696 Blood flow through the loops of the skin plexus is controlled in humans by highly innervated
11
12 697 arterioles which comprise an internal layer of longitudinally arranged endothelial cells
13
14 698 surrounded by vascular smooth cells in a helicoidal arrangement (Johnson *et al.*, 2014).
15
16 699 Endothelial cells produce various signalling molecules such as nitric oxide (NO) and
17
18
19 700 prostaglandin PGE2 which induce smooth muscle cell relaxation and blood vessel
20
21 701 vasodilation thus reducing vessel resistance and increasing blood flow (Warren, 1994;
22
23 702 Coffman, 1994; Medow, Glover & Stewart, 2008). This phenomenon occurs for example after
24
25 703 local thermal stimulation or UVB exposure (Warren, 1994; Sokolnicki *et al.*, 2009; Jan *et al.*,
26
27 704 2009; Fromy *et al.*, 2010). It can increase nutritional exchanges with surrounding cells,
28
29 705 immune cell arrival and assists body temperature regulation.

30
31
32
33 706 When healthy human skin is locally subjected to low pressure (<20 kPa), a specific
34
35 707 mechanism called pressure-induced vasodilation (PIV) allows the skin to maintain an
36
37 708 appropriate blood flow and tissue oxygenation (Fromy, Abraham & Saumet, 1998). PIV
38
39 709 results from the interaction of primary afferent nerves with the vascular endothelium of skin
40
41 710 vessels (reviewed in Fouchard *et al.*, 2019). In some disorders in which there is impairment of
42
43 711 skin vasodilation ability due to endothelial dysfunction or peripheral nerve alteration, PIV is
44
45 712 altered leading to a reduced blood flow in response to local low pressure and consequently an
46
47 713 increased incidence of PI (Fromy *et al.*, 2010, 2012; Vouillarmet *et al.*, 2019).

48
49
50
51 714
52
53 715 *(a) Functionality of the NO pathway*

54
55
56 716 Besides vessel network modifications, a reduction in skin vasomotor capacity,
57
58 717 especially with regard to skin vasodilation, has been observed in ageing skin and is strongly
59
60

1
2
3 718 correlated with endothelial dysfunction highlighted by a decrease in NO and prostaglandin
4
5 719 levels and an increase in endothelium-derived hyperpolarizing factor (EDHF) involvement in
6
7 720 humans (Algotsson, Nordberg & Winblad, 1995; Rossi *et al.*, 2002 ; Tao *et al.*, 2004 ;
8
9 721 Holowatz *et al.*, 2005; James *et al.*, 2006; Jan *et al.*, 2009; Fromy *et al.*, 2010), rats (Muller-
10
11 722 Delp *et al.*, 2002) and mice (Gaubert *et al.*, 2007) (Fig. 4).

12
13
14 723 The early postnatal period is associated with remarkable changes in the morphology
15
16 724 and functioning of arterial and capillary endothelium correlated with a progressive increase in
17
18 725 microvascular pressure and network blood flow (Boegehold, 2010) in sheep (Abman *et al.*,
19
20 726 1991), piglets (Zellers & Vanhoutte, 1991), rats (Kobayashi & Sakai, 1994) and mice
21
22 727 (Flavahan *et al.*, 2013; Flavahan & Flavahan, 2014). During this period, various molecules
23
24 728 [e.g. cyclooxygenase products, hydrogen peroxide, carbon monoxide, NO, endothelin 1 (ET-
25
26 729 1)] were shown to regulate vasomotricity, depending on the species and the organ, but also on
27
28 730 neonate age. Shifts from one pathway to another were also found. For example, in mice
29
30 731 immediately after birth, endothelial cells lining central arteries express high levels of ET-1
31
32 732 peptides and rapidly release ET-1 and initiate ET-1-mediated endothelium-dependent
33
34 733 constriction in response to stimulation by endothelial secretagogues. Endothelial cells also
35
36 734 show a markedly reduced ability to initiate endothelial NO-mediated dilation. During the
37
38 735 following days, the ET-1 pathway is progressively inhibited, probably due to increased
39
40 736 responsiveness to the NO pathway which inhibits both ET-1 production and secretion. Owing
41
42 737 to this change, the same endothelial secretagogues which induce vasoconstriction
43
44 738 immediately after birth become able to induce vasodilatation a few days later (Chang,
45
46 739 Flavahan & Flavahan, 2016). The contribution of NO to endothelium-dependent dilation has
47
48 740 been reported to increase in the lung, cerebral cortex and skeletal muscle, but to decrease in
49
50 741 the intestine (Abman *et al.*, 1991; Zellers & Vanhoutte, 1991; Kobayashi & Sakai, 1994;
51
52 742 Boegehold, 2010; Flavahan *et al.*, 2013; Flavahan & Flavahan, 2014).

1
2
3 743 There are few data available concerning human skin, especially for newborns.
4
5 744 Nevertheless, the size of the newborn head (length and circumference) and birth weight have
6
7 745 been shown to be positively associated with skin vessel vasodilation induced by acetylcholine
8
9 746 which is also inversely proportional to maternal hypertension during pregnancy; no
10
11 747 significant correlation was observed for sodium nitroprusside (SNP)-induced vasodilatation,
12
13 748 except with gestational age (Touwslager *et al.*, 2012; Martin, Gazelius & Norman, 2000).
14
15 749 Low birth weight has been correlated to cardiometabolic disease in adult life (Gluckman *et*
16
17 750 *al.*, 2008) as well as a lower capillary density both in newborn and adult skin (Lewandowski
18
19 751 *et al.*, 2015). For human adults, endothelial dysfunction measured in the skin vasculature was
20
21 752 also found to correlate with cardiovascular disease risk (Ijzerman *et al.*, 2003). Altogether,
22
23 753 these data suggest an important role of the NO signalling pathway in the skin vasodilation
24
25 754 control of newborns and therefore the local resistance of skin to pressure, but also in baby
26
27 755 growth, blood pressure and cardiovascular health.

28
29
30
31
32
33 756 Many studies on various mammals have reported a succession of pathways regulating
34
35 757 vasodilation in the early postnatal period. This may explain a lower induced vasodilation and
36
37 758 we suggest that the NO pathway is not fully functional at birth in human skin (Fig. 4). This
38
39 759 might result in a greater sensitivity of skin to pressure and a higher risk of PI, especially in
40
41 760 preterm neonates. Further studies would be of great interest, especially in terms of PI
42
43 761 prevention and treatment.

44
45
46 762 Further studies should investigate (1) the exact pathways involved in newborn skin
47
48 763 vasodilation, (2) endothelial cell maturation of newborn skin, (3) interindividual variability
49
50 764 and associated factors, (4) the impact of GA as we can expect lower maturity in premature
51
52 765 neonates, and (5) how to prevent and/or treat newborn PIs.

53
54
55
56 766

57
58 767 **(b) Higher expression of thrombospondin-1 (TSP1)**
59
60

1
2
3 768 The matricellular protein thrombospondin-1 (TSP1) and its receptor CD47, which are
4
5 769 expressed in normal skin, limit the ability of NO to relax blood vessels by exerting
6
7 770 vasopressor activity as shown in mice (Isenberg *et al.*, 2009). Consequently, blood vessel
8
9 771 vasodilation depends on the balance between NO and TSP1.
10
11 772 In wild-type murine skin, TSP1 and CD47 were reported to increase with ageing and this was
12
13 773 suggested to decrease cutaneous NO signalling and therefore skin blood flow. Interestingly,
14
15 774 targeting CD47 was shown to enhance skin blood flow (Rogers, Roberts & Isenberg, 2013).
16
17 775 UV exposure was also shown to increase TSP1 expression in human skin dermis and dermal
18
19 776 fibroblasts (Seo *et al.*, 2010).
20
21 777 One study suggests that human endothelial cells produce a matrix, of which a major
22
23 778 component is TSP1, in newborn skin whereas this molecule is almost absent in the matrix
24
25 779 produced by adult endothelial cells (Kramer *et al.*, 1985). This suggests higher TSP1
26
27 780 production in newborn skin.
28
29 781 We hypothesize that a higher proportion of TSP1 and CD47 in human newborn and elderly
30
31 782 skin reduces the effect of NO and vessel vasodilation ability (Fig. 4). If further investigations
32
33 783 confirm this hypothesis, we could consider treating PIs by targeting those molecules, thus
34
35 784 improving wound healing and blood flow.
36
37
38
39
40
41
42
43
44

786 (4) Newborn and elderly skin innervation

46 787 The ability of skin to respond to light pressure with the PIV mechanism depends not only on
47
48 788 endothelial function but also on sensory fibre functionality (Tew *et al.*, 2011). This
49
50 789 mechanism begins with the activation of acid-sensing ion channel 3 (ASIC3), a neuronal
51
52 790 mechanoreceptor largely expressed in sensory neurons (Fromy *et al.*, 2012), which induces
53
54 791 the release of various vasodilatory neuropeptides inducing nitric oxide synthase (NOS) and
55
56 792 cyclooxygenase (COX) stimulation (reviewed in Fouchard *et al.*, 2019).
57
58
59
60

1
2
3 793 Skin innervation includes (1) sensory nerves allowing detection of temperature, touch and
4
5 794 pain whose axonal ends terminate in the dorsal horn of the spinal cord (DHSC) and (2)
6
7 795 efferent nerves coming from the DHSC and modulating for example AVAs and arteriole
8
9 796 vasodilation or vasoconstriction by releasing various molecules such as norepinephrine,
10
11 797 acetylcholine, neuropeptide Y, atrial natriuretic peptide, calcitonin gene-related peptide
12
13 798 (CGRP), vasoactive intestinal polypeptide (VIP), peptide histidine methionine (PHL) and
14
15 799 pituitary adenylyl cyclase activating peptide (PACAP) into the skin (Johnson *et al.*, 2014;
16
17
18 800 Fouchard *et al.*, 2019). The release of these molecules depends on both stimulation by the
19
20
21 801 sensory nerves and activity of spinal cord interneurons which are able to inhibit efferent nerve
22
23
24 802 stimulation.

25
26 803 Cutaneous sensory nerves include highly myelinated A α fibres, moderately myelinated A β
27
28 804 fibres, thinly myelinated A Δ fibres and unmyelinated C fibres. C fibres represent 45% of the
29
30 805 fibres and are present in both the dermis and epidermis (Johnson *et al.*, 2014). The fibre
31
32 806 endings are either free (for sensing temperature, touch and pain) or are linked to specific
33
34 807 receptors such as the Merkel cell neurite complex and Meissner's, Pacini's or Rufini's
35
36 808 corpuscles (various touch sensations). As cutaneous sensory nerves are linked to the spinal
37
38 809 cord, skin sensitivity not only depends on the sensitive fibre endings, but also on the sensory
39
40 810 neuron's ability to conduct the signal and connectivity to other neurons at the spinal cord
41
42
43 811 level.

44 45 46 47 812 48 49 813 *(a) Sensory nerve function in elderly skin*

50
51 814 Human skin ageing is associated with decreased sensory perception correlated to a reduced
52
53 815 number of Meissner's corpuscles, Merkel cell neurite complexes (Garcia-Piqueras *et al.*,
54
55 816 2019) and nerve fibre endings in the dermis and epidermis, including mechano-sensitive C-
56
57 817 fibres (Panoutsopoulou *et al.*, 2009; Fromy *et al.*, 2010; Namer, 2010; Tew *et al.*, 2011;
58
59
60

1
2
3 818 Bowden & McNulty, 2013). A recent study also found a correlation between sensory
4
5 819 perception degradation and skin structural changes such as dermis thinning and DEJ flattening
6
7 820 (Jobanputra *et al.*, 2020). Correlated reductions in nerve myelination and nerve conduction
8
9 821 speed were also reported in mice (Canta *et al.*, 2016) (Table 1). As a result, tactile, thermal
10
11 822 and mechanical perception decrease, thermal-induced vasodilation is slowed down (Tew *et*
12
13 823 *al.*, 2011) and PIV is progressively impaired (Fromy *et al.*, 2010) putting elderly skin at
14
15 824 higher risk of skin damage and PIs (Fig. 4).
16
17
18
19 825

20
21 826 *(b) Sensory nerve function in newborn skin*

22
23
24 827 At birth, skin sensitivity exists in humans and the newborn nerve apparatus has been reported
25
26 828 to be similar to that of adults with one superficial and one deep plexus containing nerve fibres
27
28 829 parallel to the skin surface, densely interconnected and ending more or less deeply in the
29
30 830 dermis (Feito *et al.*, 2018).

31
32
33 831 Nevertheless, the skin sensory system remains immature at some levels. Human Pacini's and
34
35 832 Meissner's corpuscles undergo structural modifications until 4 and 8 months of life,
36
37 833 respectively (Feito *et al.*, 2018). In mice, the proportion of mechanically and heat-sensitive C
38
39 834 fibres was shown to increase in the first two weeks after birth compared to mechanically
40
41 835 sensitive heat-insensitive C fibres (Jankowski *et al.*, 2014). In rats, a lower withdrawal
42
43 836 threshold to mechanical stimulation was observed in 2-week-old rats compared to older ones
44
45 837 (Ririe & Eisenach, 2006). Nerve conduction and myelination extent were reported in mice
46
47 838 and humans to increase until adulthood, especially during infancy for humans (Canta *et al.*,
48
49 839 2016; Jenny, Lütshg & Broser, 2020). Neural growth factor (NGF) is needed for the proper
50
51 840 maturation of A Δ nociceptors (Ritter *et al.*, 1991; Ritter, Lewin & Mendell, 1993) as well as
52
53 841 C-fibres (Lewin & Mendell, 1994). Postnatal rearrangement and refinement of synaptic
54
55 842 connections occurs in the dorsal horn (Fitzgerald & McKelvey, 2016) and it seems that C-
56
57
58
59
60

1
2
3 843 fibre activity is also needed to stimulate the maturation of some interneurons releasing glycine
4
5 844 which inhibit efferent nerves. In mice, it has been shown that during the first 2 weeks after
6
7 845 birth, this phenomenon explains the striking sensitivity of newborns to tactile and noxious
8
9 846 mechanical stimulation of the skin and their lower sensory thresholds and greater amplitude
10
11 847 and duration reflexes (Koch *et al.*, 2012).

12
13
14 848 Although pain sensitivity exists at birth, nerve injury occurring during infancy or childhood
15
16 849 does not induce chronic pain sensitivity unlike in adults. This probably results from a
17
18 850 'default' neuroimmune response skewed in an anti-inflammatory direction, suppressing the
19
20 851 excitation of dorsal horn neurons during childhood, whereas in adolescents and adults it is
21
22 852 biased in a pro-inflammatory direction (Fitzgerald & McKelvey, 2016).

23
24
25 853 Overall, newborn sensitivity is very different from that of adults. As peripheral injury during
26
27 854 this period seems to alter sensory function and prevent the appropriate development of spinal
28
29 855 dorsal horn circuits (Jankowski *et al.*, 2014), special care in newborn pain treatment is
30
31 856 needed. Further investigations are required to understand better (1) how immature fibre
32
33 857 endings react when pressure or shear forces are applied, (2) to what extent they can induce
34
35 858 PIV and protect newborn skin against PI formation, and (3) whether a neuroimmune response
36
37 859 different from that of adults results in variations concerning PI aetiology.
38
39
40
41
42
43

44 860

45 861 **IV. CONCLUSIONS**

46
47 862 (1) Although highly different in appearance, newborn and elderly skin share common features
48
49 863 responsible for their physiological fragility and resulting in a higher risk of skin damage or PI
50
51 864 formation.

52
53 865 (2) At the structural level, they share: (a) a thinner epidermis; (b) a thinner dermis containing
54
55 866 a less-resistant collagen network, a higher collagen III:collagen I ratio and less elastin; (c) a
56
57 867 flatter DEJ with weaker anchoring systems; and (d) a thinner hypodermis. These
58
59
60

1
2
3 868 characteristics induce lower mechanical resistance to skin damage under pressure or shear
4
5 869 forces.

6
7 870 (3) At the epidermis level, a higher pH increases serine protease activity (kallikrein 5 and 7).
8
9 871 This leads to corneodesmosome and lipid-processing enzyme degradation, and a lower
10
11 872 activity of key enzymes such as β -glucocerebrosidase and acidic sphingomyelinase involved
12
13 873 in the synthesis of ceramides. Consequently, the cohesion of corneocytes is decreased and the
14
15 874 lipid-rich extracellular matrix is altered, putting the SC barrier at higher risk of disruption
16
17 875 under shear forces, chemical trauma, invasion of microorganisms and infections, all of which
18
19 876 may induce PI formation or prevent wound healing.

20
21 877 (4) Correlated with immature ESGs and lower ESG activity in young newborn skin and a
22
23 878 progressive decrease of ESG function and lipid production in aged skin, some data suggest
24
25 879 that SC hydration is lower in both age groups. In the newborn, skin surface dehydration is
26
27 880 more significant when vernix caseosa is missing (preterm and post-term newborns).

28
29 881 (5) Flattening of the DEJ not only decreases mechanical resistance but also the nutritional
30
31 882 exchanges and signalling between the dermis and epidermis. Moreover, the protein network is
32
33 883 modulated and this may have an effect not only on the mechanical characteristics of the DEJ,
34
35 884 but also on (a) the number of interfollicular epidermal stem cells or their activation potential
36
37 885 and therefore on epidermis turnover, or (b) pain sensitivity and the control of sensory axon
38
39 886 branching behaviour. Further studies are needed to understand these effects in detail.

40
41 887 (6) At the dermis level, TGF β /Smad signalling plays a key role in ECM formation as it
42
43 888 stimulates the synthesis of several key structural molecules such as collagen, fibronectin,
44
45 889 decorin and versican. It also inhibits matrix-degrading MMPs and stimulates their inhibitors.
46
47 890 As TGF β signalling and the production of its receptor T β RII is lower in both newborns and
48
49 891 the elderly, we speculate that this may be a key reason why dermal ECM is mechanically
50
51 892 more fragile in both cases. In addition, as structural molecules including decorin and versican
52
53
54
55
56
57
58
59
60

1
2
3 893 are also involved in various physiological processes such as collagenesis and elastogenesis
4
5 894 but also in wound repair, angiogenesis, and in cell proliferation, adhesion and migration, we
6
7
8 895 also speculate that PI formation may result from a decrease of the skin's ability to repair
9
10 896 damage induced by pressure or friction.

11
12 897 (7) The microvasculature of newborn skin presents a horizontal plexus with a capillary
13
14 898 network that is not yet organized into capillary loops compared to adult skin, whereas ageing
15
16
17 899 skin is associated with a reduced number and size of blood vessels. We speculate that this
18
19 900 lower-level organization will lead to less-efficient or less finely regulated responses following
20
21 901 pressure or shear force application.

22
23
24 902 (8) Concerning the PIV mechanisms which allow the skin to resist light pressures, a decrease
25
26 903 in responsiveness to NO and prostaglandin signalling pathways and an increase in
27
28 904 responsiveness to TSP1, which limits the ability of NO to relax blood vessels, are correlated
29
30 905 with skin ageing, explaining the observed decrease in the PIV response in the elderly
31
32 906 correlated to a higher PI prevalence. Although we have few data for newborns, several
33
34 907 observations suggest that the NO pathway is not directly or fully functional at birth in human
35
36 908 skin and that TSP1 is more abundant around the endothelial cells of the newborn. This may
37
38 909 result in a greater sensitivity of skin to pressure and a higher risk of PI, especially in preterm
39
40 910 neonates.

41
42
43
44 911 (9) Sensory perception and PIV induction are both significantly decreased during skin ageing
45
46 912 with a reduced number of Meissner's corpuscles, Merkel cell neurite complexes and nerve
47
48 913 fibre endings and reduced nerve myelination and conduction. At birth, skin sensitivity is also
49
50 914 different and is less finely controlled compared to that of adults, due to immature sensory
51
52 915 receptors, sensory fibres, connections between neurons and a drastically different
53
54 916 neuroimmune response. The ability of the nervous system to induce PIV remains to be
55
56 917 investigated.
57
58
59
60

918

919 **V. REFERENCES**

920

921 ABMAN, S.H., CHATFIELD, B.A., RODMAN, D.M., HALL, S.L. & MCMURTRY, I.F. (1991).

922 Maturational changes in endothelium-derived relaxing factor activity of ovine pulmonary
923 arteries in vitro. *American Journal of Physiology* **260**(4), L280–L285.

924

925 AGACHE, P., BLANC, D., BARRAND, C. & LAURENT, R. (1980). Sebum levels during the first
926 year of life. *British Journal of Dermatology* **103**(6), 643–650.

927

928 AKAMATSU, H., HASEGAWA, S., YAMADA, T., MIZUTANI, H., NAKATA, S., YAGAMI, A. &

929 MATSUNAGA, K. (2016). Age-related decrease in CD271(+) cells in human skin. *The Journal*
930 *of Dermatology* **43**, 311–313.

931

932 AKDENIZ, M., GABRIEL, S., LICHTERFELD-KOTTNER, A., BLUME-PEYTAVI, U. & KOTTNER, J.
933 (2018a). Transepidermal water loss in healthy adults: a systematic review and meta-analysis
934 update. *British Journal of Dermatology* **179**(5), 1049–1055.

935

936 AKDENIZ, M., TOMOVA-SIMITCHIEVA, T., DOBOS, G., BLUME-PEYTAVI, U. & KOTTNER, J.
937 (2018b). Does dietary fluid intake affect skin hydration in healthy humans? A systematic
938 literature review. *Skin Research and Technology* **00**, 1–7.

939

940 ALGOTSSON, A., NORDBERG, A. & WINBLAD, B. (1995). Influence of age and gender on skin
941 vessel reactivity to endothelium-dependent and endothelium-independent vasodilators tested

942

943

944

945

- 1
2
3 942 with iontophoresis and a laser Doppler perfusion imager. *The Journal of Gerontology Series*
4
5 943 *A Biological Sciences and Medical Sciences* **50**(2), M121–M127.
6
7 944
8
9
10 945 ALI, S.M. & YOSIPOVITCH, G. (2013). Skin pH: from basic science to basic skin care. *Acta*
11
12 946 *Dermato- Venereologica* **93**(3), 261–267.
13
14 947
15
16
17 948 AMANO, S. (2016). Characterization and mechanisms of photoageing-related changes in skin.
18
19 949 Damages of basement membrane and dermal structures. *Experimental Dermatology* **25**, 14–
20
21 950 19.
22
23
24 951
25
26 952 AMANO, S., NISHIYAMA, T. & BURGESSON, R.E. (1999). A specific and sensitive ELISA for
27
28 953 laminin 5. *Journal of Immunological Methods* **224**, 161–169
29
30 954
31
32
33 955 AMLUNG, S.R., MILLER, W.L. & BOSLEY, L.M. (2001). The 1999 National Pressure Ulcer
34
35 956 Prevalence Survey: a benchmarking approach. *Advances in Skin & Wound Care* **14**, 297–301.
36
37 957
38
39
40 958 ARAI, K.Y., HARA, T., NAGATSUKA, T., KUDO, C., TSUCHIYA, S., NOMURA, Y. & NISHIYAMA,
41
42 959 T. (2017). Postnatal changes and sexual dimorphism in collagen expression in mouse skin.
43
44 960 *PLoS One* **11**, 12–15
45
46
47 961
48
49 962 AUGUST, D.L., EDMONDS, L., BROWN, D.K., MURPHY, M. & KANDASAMY, Y. (2014). Pressure
50
51 963 injuries to the skin in a neonatal unit: fact or fiction. *Journal of Neonatal Nursing* **20**(3), 129–
52
53 964 137.
54
55
56 965
57
58
59
60

- 1
2
3 966 AVŞAR, P. & KARADAĞ, A. (2018). Efficacy and cost-effectiveness analysis of evidence-based
4
5 967 nursing interventions to maintain tissue integrity to prevent pressure ulcers and incontinence-
6
7 968 associated dermatitis. *Worldviews on Evidence Based Nursing* **15**(1), 54–61.
9
10 969
11
12 970 BARBOLLAT-BOUTRAND, L., JOLY-TONETTI, N., DOS SANTOS, M., METRAL, E., BOHER, A.,
13
14 971 MASSE, I., BERTHIER-VERGNES, O., BERTOLINO, P., DAMOUR, O. & LAMARTINE, J. (2017).
15
16 972 MicroRNA-23b-3p regulates human keratinocyte differentiation through repression of TGIF1
17
18 973 and activation of the TGF- β -SMAD2 signalling pathway. *Experimental Dermatology* **26**(1),
19
20 974 51–57.
21
22
23
24 975
25
26 976 BERGER-KULEMANN, V., BRUGGER, P.C., REISEGGER, M., KLEIN, K., HACHEMIAN, N.,
27
28 977 KOELBLINGER, C., WEBER, M. & PRAYER, D. (2012). Quantification of the subcutaneous fat
29
30 978 layer with MRI in fetuses of healthy mothers with no underlying metabolic disease vs. fetuses
31
32 979 of diabetic and obese mothers. *Journal of Perinatal Medicine* **40**(2), 179–184.
33
34
35 980
36
37 981 BERNABE, K.Q. (2012). Pressure ulcers in the pediatric patient. *Current Opinion in Pediatrics*
38
39 982 **24**, 352–356.
40
41
42 983
43
44 984 BETSHOLTZ, C., LINDBLOM, P. & GERHARDT, H. (2005). Role of pericytes in vascular
45
46 985 morphogenesis. *Mechanisms of Angiogenesis*. **94**, 115–125.
47
48
49 986
50
51 987 BLUME-PEYTAVI, U., HAUSER, M., STAMATAS, G.N., PATHIRANA, D. & GARCIA BARTELS, N.
52
53 988 (2012). Skin care practices for newborns and infants: review of the clinical evidence for best
54
55 989 practices. *Pediatric Dermatology* **29**(1), 1–14.
56
57
58 990
59
60

- 1
2
3 991 BLUME-PEYTAVI, U., TAN, J., TENNSTEDT, D., BORALEVI, F., FABBROCINI, G., TORRELO, A.,
4
5 992 SOARES-OLIVEIRA, R., HAFTEK, M., ROSSI, A.B., THOUVENIN, M.D., MANGOLD, J., GALLIANO,
6
7 993 M.F., HERNANDEZ-PIGEON, H., ARIES, M.F., ROUVRAIS, C., *ET AL.* (2016) Fragility of
8
9 994 epidermis in newborns, children and adolescents. *Journal of the European Academy of*
10
11 995 *Dermatology and Venereology* **4**, 3–56.
12
13
14 996
15
16 997 BOEGEHOLD M.A. (2010). Endothelium-dependent control of vascular tone during early
17
18 998 postnatal and juvenile growth. *Microcirculation* **17**(5), 394–406.
19
20
21 999
22
23 1000 BONAMY, A.K., MARTIN, H., JÖRNESKOG, G. & NORMAN, M. (2007). Lower skin capillary
24
25 1001 density, normal endothelial function and higher blood pressure in children born preterm.
26
27 1002 *Journal of Internal Medicine* **262**(6), 635–642.
28
29
30 1003
31
32 1004 BOUWSTRA, J.A., GROENINK, H.W., KEMPENAAR, J.A., ROMEIJN, S.G. & PONEC, M. (2008).
33
34 1005 Water distribution and natural moisturizer factor content in human skin equivalents are
35
36 1006 regulated by environmental relative humidity. *Journal of Investigative Dermatology* **128**(2),
37
38 1007 378–388.
39
40
41 1008
42
43 1009 BOWDEN, J.L. & McNULTY, P.A. (2013). Age-related changes in cutaneous sensation in the
44
45 1010 healthy human hand. *AGE* **35**(4), 1077–1089.
46
47
48 1011
49
50 1012 BRADEN, B. & BERGSTROM, N. (1987). A conceptual schema for the study of the etiology of
51
52 1013 pressure sores. *Rehabilitation Nursing* **12**(1), 8–12, 16
53
54
55 1014
56
57
58
59
60

- 1
2
3 1015 BRAVERMAN, I.M. & FONFERKO, E. (1982). Studies in cutaneous ageing: I. The elastic fiber
4
5 1016 network. *Journal of Investigative Dermatology* **78**, 434–443.
6
7 1017
8
9 1018 BREIJ, L.M., KERKHOF, G.F., DE LUCIA ROLFE, E., ONG, K.K., ABRAHAMSE-BERKEVELD, M.,
10
11 1019 ACTON, D. & HOKKEN-KOELEGA, A.C.S. (2017) Longitudinal fat mass and visceral fat during
12
13 1020 the first 6 months after birth in healthy infants: support for a critical window for adiposity in
14
15 1021 early life. *Pediatric Obesity* **12**(4), 286–294.
16
17 1022
18
19 1023 CANTA, A., CHIORAZZI, A., CAROZZI, V.A., MEREGALLI, C., OGGIONI, N., BOSSI, M.,
20
21 1024 RODRIGUEZ-MENENDEZ, V., AVEZZA, F., CRIPPA, L., LOMBARDI, R., DE VITO, G., PIAZZA, V.,
22
23 1025 CAVALETTI, G. & MARMIROLI, P. (2016). Age-related changes in the function and structure of
24
25 1026 the peripheral sensory pathway in mice. *Neurobiology of Ageing* **45**, 136–148.
26
27 1027
28
29 1028 CARTLIDGE, P. (2000). The epidermal barrier. *Seminars in Neonatology* **5**, 273–280.
30
31 1029
32
33 1030 CASPERS, P.J., LUCASSEN, G.W., CARTER, E.A., BRUINING, H.A. & PUPPELS, G.J. (2001). In
34
35 1031 vivo confocal Raman microspectroscopy of the skin: noninvasive determination of molecular
36
37 1032 concentration profiles. *Journal of Investigative Dermatology* **116**, 434–442.
38
39 1033
40
41 1034 CENIZO, V., ANDRÉ, V., REYMERMIER, C., SOMMER, P., DAMOUR, O. & PERRIER, E. (2006).
42
43 1035 LOXL as a target to increase the elastin content in adult skin: a dill extract induces the LOXL
44
45 1036 gene expression. *Experimental Dermatology* **15**(8), 574–581.
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1038 CHANG, F., FLAVAHAN, S. & FLAVAHAN, N.A. (2016). Immature endothelial cells initiate
4
5 1039 endothelin-mediated constriction of newborn arteries. *The Journal of Physiology* **594**(17),
6
7 1040 4933–4944.
8
9 1041
10
11 1042 CHARRUYER, A., BARLAND, C.O., YUE, L., WESSENDORF, H.B., LU, Y., LAWRENCE, H.J.,
12
13 1043 MANCIANTI, M.L. & GHADIALLY, R. (2009). Transit-amplifying cell frequency and cell cycle
14
15 1044 kinetics are altered in aged epidermis. *Journal of Investigative Dermatology* **129**(11), 2574–
16
17 1045 2583.
18
19 1046
20
21
22
23 1047 CHENG, W., YAN-HUA, R., FANG-GANG, N. & GUO-AN, Z. (2011). The content and ratio of
24
25 1048 type I and III collagen in skin differ with age and injury. *African Journal of Biotechnology* **10**,
26
27 1049 2524–2529.
28
29 1050
30
31
32 1051 CHIANG, L.Y., POOLE, K., OLIVEIRA, B.E., DUARTE, N., SIERRA, Y.A., BRUCKNER-TUDERMAN,
33
34 1052 L., KOCH, M., HU, J. & LEWIN, G.R. (2011). Laminin-332 coordinates mechanotransduction
35
36 1053 and growth cone bifurcation in sensory neurons. *Nature Neuroscience* **14**(8), 993–1000.
37
38 1054
39
40
41 1055 CHITTOCK, J., COOKE, A., LAVENDER, T., BROWN, K., WIGLEY, A., VICTOR, S., CORK, M.J. &
42
43 1056 DANBY, S.G. (2016). Development of stratum corneum chymotrypsin-like protease activity
44
45 1057 and natural moisturising factors from birth to 4 weeks of age compared to adults. *British*
46
47 1058 *Journal of Dermatology* **175**(4), 713–720.
48
49 1059
50
51
52 1060 CHUNG, J.H., YANO, K., LEE, M.K., YOUN, C.S., SEO, J.Y., KIM, K.H., CHO, K.H., EUN, H.C. &
53
54 1061 DETMAR, M. (2002). Differential effects of photoageing vs intrinsic ageing on the
55
56 1062 vascularization of human skin. *Archives of Dermatology* **138**, 1437–1442.
57
58
59
60

- 1
2
3 1063
4
5 1064 COFFMAN, J.D. (1994). Effects of endothelium-derived nitric oxide on skin and digital blood
6
7 1065 flow in humans. *American Journal of Physiology* **267**(6 Pt 2), H2087–H2090.
8
9 1066
10
11 1067 COLEMAN, S., NIXON, J., KEEN, J., WILSON, L., MCGINNIS, E., DEALEY, C., STUBBS, N.,
12
13 1068 FARRIN, A., DOWDING, D., SCHOLS, J.M., CUDDIGAN, J., BERLOWITZ, D., JUDE, E., VOWDEN,
14
15 1069 P., SCHOONHOVEN, L., *ET AL.* (2014). A new pressure ulcer conceptual framework. *Journal of*
16
17 1070 *Advanced Nursing* **70**(10), 2222–2234.
18
19 1071
20
21
22 1072 COMPER, C., KINOSIAN, B.P., RATCLIFFE, S.J. & BAUMGARTEN, M. (2007). Obesity reduces
23
24 1073 the risk of pressure ulcers in elderly hospitalized patients. *The journals of gerontology. Series*
25
26 1074 *A, Biological sciences and medical sciences* **62**(11), 1310–1312.
27
28
29 1075
30
31 1076 COOLEN, N.A., SCHOUTEN, K.C.W.M., MIDDELKOOP, E. & ULRICH, M.M.W. (2010).
32
33 1077 Comparison between human fetal and adult skin. *Archives of Dermatological Research*
34
35 1078 **302**(1), 47–55.
36
37
38 1079
39
40 1080 COX, J. (2011). Predictors of pressure ulcers in adult critical care patients. *American Journal*
41
42 1081 *of Critical Care* **20**(5), 364–375.
43
44
45 1082
46
47 1083 DESAI, H. (1997). Ageing and wounds. Part 2: Healing in old age. *Journal of Wound Care*
48
49 1084 **6**(5), 237–239.
50
51
52 1085
53
54
55
56
57
58
59
60

- 1
2
3 1086 DE SOUZA, I.M.F., VITRAL, G.L.N. & REIS, Z.S.N. (2019). Skin thickness dimensions in
4
5 1087 histological section measurement during late-fetal and neonatal developmental period: A
6
7 1088 systematic review. *Skin Research & Technology* **25**(6),793–800.
9
10 1089
11
12 1090 DIMRI, G.P., LEE, X., BASILE, G., ACOSTA, M., SCOTT, G., ROSKELLEY, C., MEDRANO, E.E.,
13
14 1091 LINSKENS, M., RUBELJ, I. & PEREIRA-SMITH, O. (1995). A biomarker that identifies senescent
15
16 1092 human cells in culture and in ageing skin in vivo. *Proceedings of the National Academy of*
17
18 1093 *Sciences* **92**(20), 9363–9367.
19
20 1094
21
22 1095 DOS SANTOS, M., MICHPOULOU, A., ANDRÉ-FREI, V., BOULESTEIX, S., GUICHER, C., DAYAN,
23
24 1096 G., WHITELOCK, J., DAMOUR, O. & ROUSSELLE, P. (2016). Perlecan expression influences the
25
26 1097 keratin 15-positive cell population fate in the epidermis of aging skin. *Aging (Albany NY)*
27
28 1098 **8**(4), 751–768.
29
30 1099
31
32 1100 EDSBERG, L.E., BLACK, J.M., GOLDBERG, M., MCNICHOL, L., MOORE, L. & SIEGGREEN, M.
33
34 1101 (2016). Revised National Pressure Ulcer Advisory Panel pressure injury staging system.
35
36 1102 *Journal of Wound Ostomy & Continence Nursing* **43**, 585–597.
37
38 1103
39
40 1104 ELIAS, P.M., GOERKE, J. & FRIEND, D.S. (1977). Mammalian epidermal barrier layer lipids:
41
42 1105 Composition and influence on structure. *Journal of Investigative Dermatology* **69**, 535–546.
43
44 1106
45
46 1107 ELIAS, P.M., WILLIAMS, M.L., CRUMRINE, D. & SCHMUTH, M. (2010). Ichthyoses: Clinical,
47
48 1108 biochemical, pathogenic and diagnostic assessment. Introduction. *Current Problems in*
49
50 1109 *Dermatology* **39**, 1–29.
51
52 1110
53
54
55
56
57
58
59
60

- 1
2
3 1111 ELLISON, J. & GARROD, D.R. (1984). Anchoring filaments of the amphibian epidermal-dermal
4
5 1112 junction traverse the basal lamina entirely from the plasma membrane of hemidesmosomes to
6
7 1113 the dermis. *Journal of Cell Science* **72**, 163–172.
8
9 1114
10
11 1115 EMERY, M.M., HEBERT, A.A., AGUIRRE VILA-CORO, A. & PRAGER, T.C. (1991). The
12
13 1116 relationship between skin maturation and electrical skin impedance. *Journal of*
14
15 1117 *Dermatological Science* **2**(5), 336–340.
16
17 1118
18
19 1119 EPSTEIN, E.H. JR. (1974). (Alpha1(3))3 human skin collagen. Release by pepsin digestion and
20
21 1120 preponderance in fetal life. *Journal of Biological Chemistry* **249**(10), 3225–3231.
22
23 1121
24
25 1122 EUROPEAN PRESSURE ULCER ADVISORY PANEL (EPUAP), NATIONAL PRESSURE INJURY
26
27 1123 ADVISORY PANEL (NPIAP), AND PAN PACIFIC PRESSURE INJURY ALLIANCE (PPPIA) (2019)
28
29 1124 Prevention and Treatment of Pressure Ulcers/Injuries: Clinical Practice Guideline, E. Haesler,
30
31 1125 Editor. *European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel,*
32
33 1126 *Pan Pacific Pressure Injury Alliance.*
34
35 1127
36
37 1128 EVANS, N.J. & RUTTER N. (1986). Development of the epidermis in the newborn. *Biology of*
38
39 1129 *the Neonate* **49**, 74–80.
40
41 1130
42
43 1131 FAIRLEY, J.A. & RASMUSSEN, J.E. (1983). Comparison of stratum corneum thickness in
44
45 1132 children and adults. *Journal of the American Academy of Dermatology* **8**, 652–654.
46
47 1133
48
49 1134 FARAGE, M.A., MILLER, K.W., ELSNER, P. & MAIBACH, H.I. (2013). Characteristics of the
50
51 1135 Ageing Skin. *Advances in Wound Care (New Rochelle)* **2**(1), 5–10.
52
53
54
55
56
57
58
59
60

- 1
2
3 1136
4
5 1137 FEITO, J., GARCÍA-SUÁREZ, O., GARCÍA-PIQUERAS, J., GARCÍA-MESA, Y., PÉREZ-SÁNCHEZ, A.,
6
7 1138 SUAZO, I., CABO, R., SUÁREZ-QUINTANILLA, J., COBO, J. & VEGA, J.A. (2018). The
8
9 1139 development of human digital Meissner's and Pacinian corpuscles. *Annals of Anatomy* **219**, 8–
10
11 24.
12
13 1140
14
15 1141
16
17 1142 FERREIRA, A.P., DA SILVA JUNIOR, J.R., FIGUEIROA, J.N. & ALVES, J.G. (2014). Abdominal
18
19 1143 subcutaneous and visceral fat thickness in newborns: correlation with anthropometric and
20
21 1144 metabolic profile. *Journal of Perinatology* **34**(12), 932–935.
22
23
24 1145
25
26 1146 FESTA, E., FRETZ, J., BERRY, R., SCHMIDT, B., RODEHEFFER, M., HOROWITZ, M. & HORSLEY,
27
28 1147 V. (2011). Adipocyte lineage cells contribute to the skin stem cell niche to drive hair cycling.
29
30 1148 *Cell* **146**, 761–771.
31
32
33 1149
34
35 1150 FISCHER, C., BERTELLE, V., HOHLFELD, J., FORCADA-GUEX, M., STADELMANN-DIAW, C. &
36
37 1151 TOLSA, J.-F. (2010). Nasal trauma due to continuous positive airway pressure in neonates.
38
39 1152 *Archives of Disease in Childhood - Fetal and Neonatal Edition* **95**(6), F447–F451.
40
41
42 1153
43
44 1154 FISHER, G.J., SHAO, Y., HE, T., QIN, Z., PERRY, D., VOORHEES, J.J. & QUAN, T. (2016).
45
46 1155 Reduction of fibroblast size/mechanical force down-regulates TGF- β type II receptor:
47
48 1156 implications for human skin aging. *Aging Cell* **15**(1), 67–76.
49
50
51 1157
52
53 1158 FITZGERALD, M. & MCKELVEY, R. (2016). Nerve injury and neuropathic pain - A question of
54
55 1159 age. *Experimental Neurology* **275 Pt 2**, 296–302.
56
57
58 1160
59
60

- 1
2
3 1161 FLAVAHAN S & FLAVAHAN NA (2014). The atypical structure and function of newborn
4
5 1162 arterial endothelium is mediated by Rho/Rho kinase signaling. *American Journal of*
6
7 1163 *Physiology-Heart and Circulatory Physiology* **307**, H628–H632.
8
9 1164
10
11
12 1165 FLAVAHAN, S., MOZAYAN, M.M., LINDGREN, I. & FLAVAHAN, N.A. (2013). Pressure-induced
13
14 1166 maturation of endothelial cells on newborn mouse carotid arteries. *American Journal of*
15
16 1167 *Physiology-Heart and Circulatory Physiology* **305**, H321–H329.
17
18
19 1168
20
21 1169 FLUHR, J.W., DARLENSKI, R., TAIEB, A., HACHEM, J.P., BAUDOUIN, C., MSIKA, P., DE
22
23 1170 BELILOVSKY, C. & BERARDESCA, E. (2010). Functional skin adaptation in infancy - almost
24
25 1171 complete but not fully competent. *Experimental Dermatology* **19**(6), 483–492.
26
27 1172
28
29
30 1173 FLUHR, J.W., KAO, J., JAIN, M., AHN, S.K., FEINGOLD, K.R. & ELIAS, P.M. (2001). Generation
31
32 1174 of free fatty acids from phospholipids regulates stratum corneum acidification and integrity.
33
34 1175 *Journal of Investigative Dermatology* **117**, 44– 51.
35
36 1176
37
38
39 1177 FOSTER, K.G., HEY, E.N. & KATZ, G. (1969) The response of the sweat glands of the newborn
40
41 1178 baby to thermal stimuli and to intradermal acetylcholine. *The Journal of Physiology* **203**(1),
42
43 1179 13–29.
44
45 1180
46
47
48 1181 FOUCHARD, M., MISERY, L., LE GARREC, R., SIGAUDO-ROUSSEL, D. & FROMY, B. (2019).
49
50 1182 Alteration of pressure-induced vasodilation in ageing and diabetes, a neuro-vascular damage.
51
52 1183 *Frontiers in Physiology* **10**, 862.
53
54
55 1184
56
57
58
59
60

- 1
2
3 1185 FOX, C., NELSON, D. & WAREHAM, J. (1998). The timing of skin acidification in very low
4
5 1186 birth weight infants. *Journal of Perinatology* **18**(4), 272–275.
6
7 1187
8
9
10 1188 FOX, M.D. (2011). Wound care in the neonatal intensive care unit. *Neonatal Network* **30**(5),
11
12 1189 291–303.
13
14 1190
15
16 1191 FROMY, B., ABRAHAM, P. & SAUMET, J.-L. (1998). Non-nociceptive capsaicin sensitive nerve
17
18 1192 terminal stimulation allows for an original vasodilatory reflex in the human skin. *Brain*
19
20 1193 *Research* **811**, 166–168.
21
22 1194
23
24 1195 FROMY, B., LINGUEGLIA, E., SIGAUDO-ROUSSEL, D., SAUMET, J.L. & LAZDUNSKI, M. (2012).
25
26 1196 Asic3 is a neuronal mechanosensor for pressure-induced vasodilation that protects against
27
28 1197 pressure ulcers. *Nature Medicine* **18**(8), 1205–1207.
29
30 1198
31
32 1199 FROMY, B., SIGAUDO-ROUSSEL, D., GAUBERT-DAHAN, M.-L., ROUSSEAU, P., ABRAHAM, P.,
33
34 1200 BENZONI, D., BERRUT, G. & SAUMET, J.L. (2010). Ageing-associated sensory neuropathy
35
36 1201 alters pressure induced vasodilation in humans. *Journal of Investigative Dermatology* **130**,
37
38 1202 849–855.
39
40 1203
41
42 1204 FUJII, K., SUGAMA, J., OKUWA, M., SANADA, H. & MIZOKAMI, Y. (2010). Incidence and risk
43
44 1205 factors of pressure ulcers in seven neonatal intensive care units in Japan: a multisite
45
46 1206 prospective cohort study. *International Wound Journal* **7**(5), 323–328.
47
48 1207
49
50 1208 GARCÍA-PIQUERAS, J., GARCÍA-MESA, Y., CÁRCABA, L., FEITO, J., TORRES-PAREJO, I.,
51
52 1209 MARTÍN-BIEDMA, B., COBO, J., GARCÍA-SUÁREZ, O. & VEGA, J.A. (2019). Ageing of the
53
54
55
56
57
58
59
60

- 1
2
3 1210 somatosensory system at the periphery: age-related changes in cutaneous mechanoreceptors.
4
5 1211 *Journal of Anatomy* **234**(6), 839–852.
6
7 1212
8
9
10 1213 GAUBERT, M.L., SIGAUDO-ROUSSEL, D., TARTAS, M., BERRUT, G., SAUMET, J.L. & FROMY, B.
11
12 1214 (2007). Endothelium-derived hyperpolarizing factor as an in vivo back-up mechanism in the
13
14 1215 cutaneous microcirculation in old mice. *The Journal of Physiology* **585**(Pt 2), 617–626.
16
17 1216
18
19 1217 GEFEN, A., ALVES, P., CIPRANDI, G., COYER, F., MILNE, C.T., OUSEY, K., OHURA, N.,
20
21 1218 WATERS, N. & WORSLEY, P. (2020). Device-related pressure ulcers: SECURE prevention.
22
23 1219 *Journal of Wound Care* **29**(Sup2a), S1–S52.
25
26 1220
27
28 1221 GEFEN, A. & SOPPI, E. (2020). What is new in our understanding of pressure injuries: the
29
30 1222 inextricable association between sustained tissue deformations and pain and the role of the
31
32 1223 support surface. *Wound Practice and Research* **28**(2), 58–65.
34
35 1224
36
37 1225 GEFEN, A. (2018). The future of pressure ulcer prevention is here: Detecting and targeting
38
39 1226 inflammation early. *EWMA Journal* **19**(2), 7–13.
41
42 1227
43
44 1228 GENZEL-BOROVICZÉNY, O., CHRIST, F. & GLAS, V. (2004). Blood transfusion increases
45
46 1229 functional capillary density in the skin of anemic preterm infants. *Pediatric Research* **56**(5),
47
48 1230 751–755.
50
51 1231
52
53 1232 GESSIN, J.C., BROWN, L.J., GORDON, J.S. & BERG, R.A. (1993). Regulation of collagen
54
55 1233 synthesis in human dermal fibroblasts in contracted collagen gels by ascorbic acid, growth
56
57 1234 factors, and inhibitors of lipid peroxidation. *Experimental Cell Research* **206**(2), 283–290.
58
59
60

- 1
2
3 1235
4
5 1236 GIANGRECO, A., GOLDIE, S.J., FAILLA, V., SAINTIGNY, G. & WATT, F.M. (2010). Human skin
6
7 1237 ageing is associated with reduced expression of the stem cell markers beta1 integrin and
8
9 1238 MCSP. *Journal of Investigative Dermatology* **130**(2), 604–608.
10
11
12 1239
13
14 1240 GIANGRECO, A., QIN, M., PINTAR, J.E. & WATT, F.M. (2008). Epidermal stem cells are
15
16 1241 retained in vivo throughout skin aging. *Aging Cell* **7**(2), 250–259.
17
18
19 1242
20
21 1243 GIUSTI, F., MARTELLA, A., BERTONI, L. & SEIDENARI, S. (2001). Skin barrier, hydration, and
22
23 1244 pH of the skin of infants under 2 years of age. *Pediatric Dermatology* **18**, 93–96.
24
25
26 1245
27
28 1246 GLUCKMAN, P.D., HANSON, M.A., COOPER, C. & THORNBURG, K.L. (2008). Effect of in utero
29
30 1247 and early-life conditions on adult health and disease. *The New England Journal of Medicine*
31
32 1248 **359**(1), 61–73.
33
34
35 1249
36
37 1250 GRAFF, M. K., BRYANT, J. & BEINLICH, N. (2000). Preventing Heel Breakdown. *Orthopaedic*
38
39 1251 *Nursing* **19**(5), 63–70.
40
41
42 1252
43
44 1253 GREY, J.E., HARDING, K.G. & ENOCH, S. (2006). Pressure ulcers. *British Medical Journal*
45
46 1254 **332**(7539), 472–475.
47
48
49 1255
50
51 1256 GRUNNET, L.G., LUND, A.Q., LAIGAARD, K.K., ALIBEGOVIC, A.C., JENSEN, R.T., HENRIKSEN,
52
53 1257 N.S., ASTRUP, A., VAAG, A. & BRØNS, C. (2019). Abdominal fat distribution measured by
54
55 1258 ultrasound and aerobic fitness in young Danish men born with low and normal birth weight.
56
57 1259 *Obesity Research & Clinical Practice* **13**(6), 529–532.
58
59
60

1
2
3 1260
4
5 1261 HACHEM, J.P., MAN, M.Q., CRUMRINE, D., UCHIDA, Y., BROWN, B.E., ROGIERS, V., ROSEEUW,
6
7 1262 D., FEINGOLD, K.R. & ELIAS, P.M. (2005). Sustained serine proteases activity by prolonged
8
9 1263 increase in pH leads to degradation of lipid processing enzymes and profound alterations of
10
11 1264 barrier function and stratum corneum integrity. *Journal of Investigative Dermatology* **125**(3),
12
13 1265 510–520.
14
15
16

17 1266
18
19 1267 HACHEM, J., ROELANDT, T., SCHÜRER, N., PU, X., FLUHR, J., GIDDELO, C., MAN, M.Q.,
20
21 1268 CRUMRINE, D., ROSEEUW, D., FEINGOLD, K.R., MAURO, T. & ELIAS, P.M. (2010). Acute
22
23 1269 acidification of stratum corneum membrane domains using polyhydroxyl acids improves lipid
24
25 1270 processing and inhibits degradation of corneodesmosomes. *Journal of Investigative*
26
27 1271 *Dermatology* **130**, 500–510.
28
29
30

31 1272
32
33 1273 HARPIN, V.A & RUTTER, N. (1983). Barrier properties of the newborn infant's skin. *The*
34
35 1274 *Journal of Pediatrics* **102**, 419–425.
36
37
38

39 1275
40 1276 HARPIN, V.A. & RUTTER, N. (1982). Sweating in preterm babies. *The Journal of Pediatrics*
41
42 1277 **100**(4), 614–619.
43
44
45

46 1278
47 1279 HATJE, L.K., RICHTER, C.; BLUME-PEYTAVI, U. & KOTTNER, J. (2015). Blistering time as a
48
49 1280 parameter for the strength of dermoepidermal adhesion: a systematic review and meta-
50
51 1281 analysis. *British Journal of Dermatology* **172**(2), 323–330.
52
53
54

55 1282
56
57
58
59
60

- 1
2
3 1283 HELMBOLD, P., LAUTENSCHLAGER, C., MARSCH, W. & NAYAK, R.C. (2006). Detection of a
4
5 1284 physiological juvenile phase and the central role of pericytes in human dermal microvascular
6
7 1285 ageing. *Journal of Investigative Dermatology* **126**, 1419–1421.
8
9 1286
10
11
12 1287 HENDERSON, C.A., TAYLOR, J. & CUNLIFFE, W.J. (2000). Sebum excretion rates in mothers
13
14 1288 and neonates. *British Journal of Dermatology* **142**(1), 110–111.
15
16
17 1289
18
19 1290 HOEGER, P.H. & ENZMANN, C.C. (2002). Skin physiology of the neonate and young infant: a
20
21 1291 prospective study of functional skin parameters during early infancy. *Pediatric Dermatology*
22
23 1292 **19**, 256–262.
24
25
26 1293
27
28 1294 HOLBROOK, K.A. (1982). A histologic comparison of infant and adult skin. In: Maibach HI,
29
30 1295 Boisits EK, eds. Neonatal Skin: Structure and Function. New York: Marcel Dekker, Inc.,
31
32 1296 1982, 3–31.
33
34
35 1297
36
37 1298 HOLBROOK, K. (2000). Embryogenesis of skin. In: Harper, J., Oranje, A. & Prose, N.S. eds:
38
39 1299 Textbook of pediatric dermatology. Oxford: Blackwell Science; 2000, 3–42.
40
41
42 1300
43
44 1301 HOLOWATZ, L.A., THOMPSON, C.S., MINSON, C.T. & KENNEY, W.L. (2005). Mechanisms of
45
46 1302 acetylcholine-mediated vasodilatation in young and aged human skin. *The Journal of*
47
48 1303 *Physiology* **563**(Pt 3), 965–973.
49
50
51 1304
52
53 1305 IJZERMAN, R.G., DE JONGH, R.T., BEIJK, M.A., VAN WEISSENBRUCH, M.M., DELEMARRE-VAN
54
55 1306 DE WAAL, H.A., SERNÉ, E.H. & STEHOUWER, C.D. (2003). Individuals at increased coronary
56
57
58
59
60

- 1
2
3 1307 heart disease risk are characterized by an impaired microvascular function in skin. *European*
4
5 1308 *Journal of Clinical Investigation* **33**(7), 536–542.
6
7 1309
8
9
10 1310 ISENBERG, J.S., QIN, Y., MAXHIMER, J.B., SIPES, J.M., DESPRES, D., SCHNERMANN, J.,
11
12 1311 FRAZIER, W.A & ROBERTS, D.D. (2009). Thrombospondin-1 and CD47 regulate blood
13
14 1312 pressure and cardiac responses to vasoactive stress. *Matrix Biology* **28**(2), 110–119.
15
16 1313
17
18
19 1314 JACKSON, D., SARKI, A.M., BETTERIDGE, R. & BROOKE, J. (2019). Medical device-related
20
21 1315 pressure ulcers: A systematic review and meta-analysis. *International Journal of Nursing*
22
23 1316 *Studies*. **92**, 109–120.
24
25 1317
26
27
28 1318 JAMES, M.A., TULLETT, J., HEMSLEY, A.G. & SHORE, A.C. (2006). Effects of ageing and
29
30 1319 hypertension on the microcirculation. *Hypertension* **47**(5), 968–974.
31
32 1320
33
34
35 1321 JANKOWSKI, M.P., ROSS, J.L., WEBER, J.D., LEE, F.B., SHANK, A.T. & HUDGINS, R.C. (2014)
36
37 1322 Age-dependent sensitization of cutaneous nociceptors during developmental inflammation.
38
39 1323 *Molecular Pain* **10**, 34.
40
41 1324
42
43
44 1325 JAN, Y.K., STRUCK, B.D., FOREMAN, R.D. & ROBINSON, C. (2009). Wavelet analysis of sacral
45
46 1326 skin blood flow oscillations to assess soft tissue viability in older adults. *Microvascular*
47
48 1327 *Research* **78**(2), 162–168.
49
50 1328
51
52
53 1329 JENNY, C., LÜTSCHG, J. & BROSER, P.J. (2020). Change in cross-sectional area of the median
54
55 1330 nerve with age in neonates, infants and children analyzed by high-resolution ultrasound
56
57 1331 imaging. *European Journal of Paediatric Neurology* **29**, 137–143.
58
59
60

- 1
2
3 1332
4
5 1333 JOBANPUTRA, R.D., BOYLE, C.J., DINI, D. & MASEN, M.A. (2020). Modelling the effects of
6
7 1334 age-related morphological and mechanical skin changes on the stimulation of tactile
8
9 1335 mechanoreceptors. *Journal of the Mechanical Behavior of Biomedical Materials* **112**, 104073.
10
11 1336
12
13
14 1337 JOHNSON, J.M., MINSON, C.T. & KELLOGG, D.L. JR. (2014). Cutaneous vasodilator and
15
16 1338 vasoconstrictor mechanisms in temperature regulation. *Comprehensive Physiology* **4**(1), 33–
17
18 1339 89.
19
20
21 1340
22
23
24 1341 KADOYA, K., SASAKI, T., KOSTKA, G., TIMPL, R., MATSUZAKI, K., KUMAGAI, N., SAKAI, L.Y.,
25
26 1342 NISHIYAMA, T. & AMANO, S. (2005). Fibulin-5 deposition in human skin: decrease with
27
28 1343 ageing and ultraviolet B exposure and increase in solar elastosis. *British Journal of*
29
30 1344 *Dermatology* **153**(3), 607–612.
31
32
33 1345
34
35 1346 KAHATA, K., DADRAS, M.S. & MOUSTAKAS, A. (2018) TGF- β family signaling in epithelial
36
37 1347 differentiation and epithelial-mesenchymal transition. *Cold Spring Harbor Perspectives in*
38
39 1348 *Biology* **10**(1), a022194.
40
41
42 1349
43
44 1350 KASHIBUCHI, N., HIRAI, Y., O'GOSHI, K. & TAGAMI, H. (2002). Three-dimensional analyses of
45
46 1351 individual corneocytes with atomic force microscope: morphological changes related to age,
47
48 1352 location and to the pathologic skin conditions. *Skin Research and Technology* **8**, 203–211.
49
50
51 1353
52
53
54 1354 KASZA, I., SUH, Y., WOLLNY, D., CLARK, R.J., ROOPRA, A., COLMAN, R.J., MACDOUGALD,
55
56 1355 O.A., SHEDD, T.A., NELSON, D.W., YEN, M.I., YEN, C.L. & ALEXANDER, C.M. (2014).
57
58
59
60

- 1
2
3 1356 Syndecan-1 Is Required to Maintain Intradermal Fat and Prevent Cold Stress. *PLoS Genetics*
4
5 1357 **10**(8), e1004514.
6
7
8 1358
9
10 1359 KEL, J.M., GIRARD-MADOUX, M.J., REIZIS, B. & CLAUSEN, B.E. (2010). TGF-beta is required
11
12 1360 to maintain the pool of immature Langerhans cells in the epidermis. *Journal of Immunology*
13
14 1361 **185**(6), 3248–3255.
15
16
17 1362
18
19 1363 KELLY, R.I., PEARSE, R., BULL, R.H., LEVEQUE, J.L., DE RIGAL, J. & MORTIMER, P.S. (1995).
20
21 1364 The effects of ageing on the cutaneous microvasculature. *Journal of the American Academy of*
22
23 1365 *Dermatology* **33**, 749–756.
24
25
26 1366
27
28 1367 KEYES, B.E., SEGAL, J.P., HELLER, E., LIEN, W.H., CHANG, C.Y., GUO, X., ORISTIAN, D.S.,
29
30 1368 ZHENG, D. & FUCHS, E. (2013). Nfatc1 orchestrates aging in hair follicle stem cells.
31
32 1369 *Proceedings of the National Academy of Sciences of the United States of America* **110**(51),
33
34 1370 E4950–E4959.
35
36
37 1371
38
39
40 1372 KILIC, A., MASUR, C., REICH, H., KNIE, U., DÄHNHARDT, D., DÄHNHARDT-PFEIFFER, S. &
41
42 1373 ABELS, C. (2019). Skin acidification with a water-in-oil emulsion (pH 4) restores disrupted
43
44 1374 epidermal barrier and improves structure of lipid lamellae in the elderly. *The Journal of*
45
46 1375 *Dermatology* **46**(6), 457–465.
47
48
49 1376
50
51 1377 KLIGMAN, A.M. (1979). Perspectives and problems in cutaneous gerontology. *Journal of*
52
53 1378 *Investigative Dermatology* **73**, 39–46.
54
55
56 1379
57
58
59
60

- 1
2
3 1380 KOBAYASHI, N. & SAKAI, T. (1994). Postnatal reorganization of actin filaments and
4
5 1381 differentiation of intercellular boundaries in the rat aortic endothelial cells. *Cell and Tissue*
6
7 1382 *Research* **278**(3), 471–482.
8
9 1383
10
11
12 1384 KOCH, S.C., TOCHIKI, K.K., HIRSCHBERG, S. & FITZGERALD, M. (2012). C-fiber activity-
13
14 1385 dependent maturation of glycinergic inhibition in the spinal dorsal horn of the postnatal rat.
15
16 1386 *Proceedings of the National Academy of Sciences* **109**(30), 12201–12206.
17
18 1387
19
20
21 1388 KOTTNER, J., CUDDIGAN, J., CARVILLE, K., BALZER, K., BERLOWITZ, D., LAW, S., LITCHFORD,
22
23 1389 M., MITCHELL, P., MOORE, Z., PITTMAN, J., SIGAUDDO-ROUSSEL, D., YEE, C.Y. & HAESLER, E.
24
25 1390 (2019). Prevention and treatment of pressure ulcers/injuries: The protocol for the second
26
27 1391 update of the international Clinical Practice Guideline. *Journal of Tissue Viability* **28**(2), 51–
28
29 1392 58.
30
31 1393
32
33 1394 KRAMER, R.H., FUH, G.M., BENSCH, K.G. & KARASEK, M.A. (1985). Synthesis of
34
35 1395 extracellular matrix glycoproteins by cultured microvascular endothelial cells isolated from
36
37 1396 the dermis of neonatal and adult skin. *Journal of Cellular Physiology* **123**(1), 1–9.
38
39 1397
40
41
42
43
44 1398 KUTLUBAY, Z., TANAKOL, A., ENGÝN, B., ONEL, C., SÝMSEK, E., SERDAROGLU, S., TUZUN, Y.,
45
46 1399 YILMAZ, E. & EREN, B. (2017). Newborn Skin: Common Skin Problems. *Maedica (Bucur)*
47
48 1400 **12**(1), 42–47.
49
50 1401
51
52
53 1402 LABEAU SO, AFONSO E, BENBENISHTY J, BLACKWOOD B, BOULANGER C, BRETT SJ, CALVINO-
54
55 1403 GUNTHER S, CHABOYER W, COYER F, DESCHEPPER M, FRANÇOIS G, HONORE PM, JANKOVIC
56
57 1404 R, KHANNA AK, LLAURADO-SERRA M, *ET AL.* (2021). Prevalence, associated factors and
58
59
60

- 1
2
3 1405 outcomes of pressure injuries in adult intensive care unit patients: the DecubICUs study.
4
5 1406 *Intensive Care Medicine* **47**(2), 160–169.
6
7 1407
8
9
10 1408 LAVKER, R.M. (1995). Cutaneous ageing: Chronologic versus photoageing. In Photodamage
11
12 1409 (ed. Gilchrest BA), pp. 123–135. Blackwell Science, Cambridge, MA.
13
14 1410
15
16 1411 LAVKER, R.M., ZHENG, P. & DONG, G. (1987). Aged skin: a study by light, transmission
17
18 1412 electron, and scanning electron microscopy. *Journal of Investigative Dermatology* **88**(3), 44s–
19
20 1413 51s.
21
22 1414
23
24 1415 LAVKER, R.M., ZHENG, P.S. & DONG, G. (1989). Morphology of aged skin. *Clinics in*
25
26 1416 *Geriatric Medicine* **5**, 53–67.
27
28 1417
29
30 1418 LEVAKOV, A., VUCKOVIĆ, N., DOLAI, M., KAĆANSKI, M.M. & BOZANIĆ, S. (2012). Age-
31
32 1419 related skin changes. *Medicinski Pregled* **65**(5-6), 191–195.
33
34 1420
35
36 1421 LEWANDOWSKI, A.J., DAVIS, E.F., YU, G., DIGBY, J.E., BOARDMAN, H., WHITWORTH, P.,
37
38 1422 SINGHAL, A., LUCAS, A., MCCORMICK, K., SHORE, A.C. & LEESON, P. (2015). Elevated blood
39
40 1423 pressure in preterm-born offspring associates with a distinct antiangiogenic state and
41
42 1424 microvascular abnormalities in adult life. *Hypertension* **65**(3), 607–614.
43
44 1425
45
46 1426 LEWIN, G.R. & MENDELL, L.M. (1994). Regulation of cutaneous C-fiber heat nociceptors by
47
48 1427 nerve growth factor in the developing rat. *Journal of Physiology* **71**(3), 941–949.
49
50 1428
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1429 LIARTE, S., BERNABÉ-GARCÍA, Á. & NICOLÁS, F. J. (2020). Role of TGF- β in Skin Chronic
4
5 1430 Wounds: A Keratinocyte Perspective. *Cells* **9**(2), 306.
6
7
8 1431
9
10 1432 LOERAKKER, S., MANDERS, E., STRIJKERS, G.J., NICOLAY, K., BAALJENS, F.P., BADER, D.L. &
11
12 1433 OOMENS, C.W. (2011) The effects of deformation, ischemia, and reperfusion on the
13
14 1434 development of muscle damage during prolonged loading. *Journal of Applied Physiology*
15
16 1435 **111**(4), 1168–77.
17
18
19 1436
20
21 1437 LORD, M. S., TANG, F., RNJAK-KOVACINA, J., SMITH, J. G. W., MELROSE, J. & WHITELOCK, J.
22
23 1438 M. (2018). The multifaceted roles of perlecan in fibrosis. *Matrix Biology* **68-69**, 150–166.
24
25
26 1439
27
28 1440 LOVELL, C.R., SMOLENSKI, K.A., DUANCE, V.C., LIGHT, N.D., YOUNG, S. & DYSON, M.
29
30 1441 (1987). Type I and III collagen content and fibre distribution in normal human skin during
31
32 1442 ageing. *British Journal of Dermatology* **117**(4), 419–428.
33
34
35 1443
36
37 1444 LUDRIKSONE, L., GARCIA BARTELS, N., KANTI, V., BLUME-PEYTAVI, U. & KOTTNER, J. (2014).
38
39 1445 Skin barrier function in infancy: a systematic review. *Archives of Dermatological Research*
40
41 1446 **306**(7), 591–599.
42
43
44 1447
45
46 1448 LUEBBERDING, S., KRUEGER, N. & KERSCHER, M. (2014). Age-related changes in male skin:
47
48 1449 quantitative evaluation of one hundred and fifty male subjects. *Skin Pharmacology and*
49
50 1450 *Physiology* **27**(1), 9–17.
51
52
53
54 1451
55
56
57
58
59
60

- 1
2
3 1452 LUEBBERDING, S., KRUEGER, N. & KERSCHER, M. (2013). Age-related changes in skin barrier
4
5 1453 function—Quantitative evaluation of 150 female subjects. *International Journal of Cosmetic*
6
7 1454 *Science* **35**, 183–190.
8
9 1455
10
11
12 1456 LUND, C.H. & OSBORNE, J.W. (2004). Validity and reliability of the neonatal skin condition
13
14 1457 score. *Journal of Obstetric, Gynecologic & Neonatal Nursing* **33**(3), 320–327.
15
16
17 1458
18
19 1459 LUND, C., KULLER, J., LANE, A., LOTT JW & RAINES DA. (1999). Neonatal skin care: the
20
21 1460 scientific basis for practice. *Neonatal Network* **18**, 15–27.
22
23
24 1461
25
26 1462 LUTON, A., HERNANDEZ, J., PATTERSON, C.R., NIELSEN-FARRELL, J., THOMPSON, A. &
27
28 1463 KAISER, J.R. (2017). Preventing Pressure Injuries in Neonates Undergoing Therapeutic
29
30 1464 Hypothermia for Hypoxic-Ischemic Encephalopathy: An Interprofessional Quality
31
32 1465 Improvement Project. *Advances in Neonatal Care* **17**(4), 237–244.
33
34
35 1466
36
37 1467 MAITI, R., GERHARDT, L.C., LEE, Z.S, BYERS, R.A., WOODS, D., SANZ-HERRERA, J.A.,
38
39 1468 FRANKLIN, S.E, LEWIS, R., MATCHER, S.J. & CARRÉ, M.J. (2016). In vivo measurement of skin
40
41 1469 surface strain and sub-surface layer deformation induced by natural tissue stretching. *Journal*
42
43 1470 *of the Mechanical Behavior of Biomedical Materials* **62**, 556–569.
44
45
46
47 1471
48
49 1472 MANI, V., BROMLEY, S.K., ÄIJÖ, T., MORA-BUCH, R., CARRIZOSA, E., WARNER, R.D., HAMZE,
50
51 1473 M., SEN, D.R., CHASSE, A.Y., LORANT, A., GRIFFITH, J.W., RAHIMI, R.A., MCENTEE, C.P.,
52
53 1474 JEFFREY, K.L., MARANGONI, F., ET AL. (2019). Migratory DCs activate TGF- β to precondition
54
55 1475 naïve CD8⁺ T cells for tissue-resident memory fate. *Science* **366**(6462), eaav5728.
56
57
58 1476
59
60

- 1
2
3 1477 MAN, M.Q., XIN, S.J., SONG, S.P., CHO, S.Y., ZHANG, X.J., TU, C.X., FEINGOLD, K.R. &
4
5 1478 ELIAS, P.M. (2009). Variation of skin surface pH, sebum content and stratum corneum
6
7 1479 hydration with age and gender in a large Chinese population. *Skin Pharmacology and*
8
9 1480 *Physiology* **22**, 190–199.
10
11
12 1481
13
14 1482 MANZANO, F., NAVARRO, M.J., ROLDÁN, D., MORAL, M.A., LEYVA, I., GUERRERO, C.,
15
16 1483 SANCHEZ, M.A., COLMENERO, M. & FERNÁNDEZ-MONDEJAR, E.; GRANADA UPP GROUP.
17
18 1484 (2010). Pressure ulcer incidence and risk factors in ventilated intensive care patients. *Journal*
19
20 1485 *of Critical Care* **25**(3), 469–476.
21
22
23 1486
24
25 1487 MARANGONI, R.G., KORMAN, B.D., WEI, J., WOOD, T.A., GRAHAM, L.V., WHITFIELD, M.L.,
26
27 1488 SCHERER, P.E., TOURTELLOTTE, W.G. & VARGA, J. (2015). Myofibroblasts in murine
28
29 1489 cutaneous fibrosis originate from adiponectin-positive intradermal progenitors. *Arthritis &*
30
31 1490 *Rheumatology* **67**, 1062–1073.
32
33
34 1491
35
36 1492 MARTIN, H., GAZELIUS, B. & NORMAN, M. (2000). Impaired acetylcholine-induced vascular
37
38 1493 relaxation in low birth weight infants: implications for adult hypertension? *Pediatric*
39
40 1494 *Research* **47**(4 Pt 1), 457–462.
41
42
43 1495
44
45 1496 MCALEER, M. A., JAKASA, I., RAJ, N., O'DONNELL, C., LANE, M. E., RAWLINGS, A. V.,
46
47 1497 VOEGELI, R., MCLEAN, W., KEZIC, S. & IRVINE, A. D. (2018). Early-life regional and temporal
48
49 1498 variation in filaggrin-derived natural moisturizing factor, filaggrin-processing enzyme
50
51 1499 activity, corneocyte phenotypes and plasmin activity: implications for atopic dermatitis. *The*
52
53 1500 *British journal of dermatology* **179**(2), 431–441.
54
55
56 1501
57
58
59
60

- 1
2
3 1502 MEDOW, M.S., GLOVER, J.L. & STEWART, J.M. (2008). Nitric oxide and prostaglandin
4
5 1503 inhibition during acetylcholine-mediated cutaneous vasodilation in humans. *Microcirculation*
6
7
8 1504 **15**(6), 569–579.
9
10 1505
11
12 1506 MERVIS, J.S. & PHILLIPS, T.J. (2019). Pressure ulcers: Pathophysiology, epidemiology, risk
13
14 1507 factors, and presentation. *Journal of the American Academy of Dermatology* **81**(4), 881–890.
15
16
17 1508
18
19 1509 MICHEL, M., L'HEUREUX, N., AUGER, F.A. & GERMAIN, L. (1997). From newborn to adult:
20
21 1510 phenotypic and functional properties of skin equivalent and human skin as a function of donor
22
23 1511 age. *Journal of Cellular Physiology* **171**(2), 179–189.
24
25
26 1512
27
28 1513 MICHEL, M., TÖRÖK, N., GODBOUT, M.J., LUSSIER, M., GAUDREAU, P., ROYAL, A. &
29
30 1514 GERMAIN, L. (1996). Keratin 19 as a biochemical marker of skin stem cells in vivo and in
31
32 1515 vitro: keratin 19 expressing cells are differentially localized in function of anatomic sites, and
33
34 1516 their number varies with donor age and culture stage. *Journal of Cell Science* **109** (Pt 5),
35
36 1517 1017–1028.
37
38
39 1518
40
41
42 1519 MIYAUCHI, Y., SHIMAOKA, Y., FUJIMURA, T., KOIKE, Y., YATABE, M., NISHIKAWA, M.,
43
44 1520 HAYASHI, M., SUGATA, K., MORIWAKI, S. & HATAMOCHI, A. (2016). Developmental changes
45
46 1521 in neonatal and infant skin structures during the first 6 months: in vivo observation. *Pediatric*
47
48 1522 *Dermatology* **33**(3), 289–295.
49
50
51 1523
52
53 1524 MLOSEK, R.K., MALINOWSKA, S., SIKORA, M., DEBOWSKA, R., STĘPIEŃ, A., CZEKAJ, K. &
54
55 1525 DĄBROWSKA, A. (2013). The use of high frequency ultrasound imaging in skin moisturization
56
57 1526 measurement. *Skin research and Technology* **19**(2), 169–175.
58
59
60

- 1
2
3 1527
4
5 1528 MLOSEK, R.K., MALINOWSKA, S., STĘPIEŃ, A., CZEKAJ, K. & DĄBROWSKA, A. (2011).
6
7 1529 Changes in the high frequency skin ultrasound associated with ageing. *Ultra-sonography* **47**,
8
9 1530 22–27.
10
11 1531
12
13 1532 MOHAMMED, J., BEURA, L. K., BOBR, A., ASTRY, B., CHICOINE, B., KASHEM, S. W., WELTY,
14
15 1533 N. E., IGYÁRTÓ, B. Z., WIJEYESINGHE, S., THOMPSON, E. A., MATTE, C., BARTHOLIN, L.,
16
17 1534 KAPLAN, A., SHEPPARD, D., BRIDGES, A. G., *ET AL.* (2016). Stromal cells control the epithelial
18
19 1535 residence of DCs and memory T cells by regulated activation of TGF- β . *Nature immunology*
20
21 1536 **17**(4), 414–421.
22
23 1537
24
25 1538 MORAGAS, A., CASTELLS, C. & SANS, M. (1993). Mathematical morphologic analysis of
26
27 1539 ageing-related epidermal changes. *Analytical and Quantitative Cytology and Histology* **15**(2),
28
29 1540 75–82.
30
31 1541
32
33 1542 MULLER-DELP, J.M., SPIER, S.A., RAMSEY, M.W. & DELP, M.D. (2002). Aging impairs
34
35 1543 endothelium-dependent vasodilation in rat skeletal muscle arterioles. *The American Journal*
36
37 1544 *of Physiology-Heart and Circulatory Physiology* **283**(4), H1662–H1672.
38
39 1545
40
41 1546 NAKAGAWA, N., MATSUMOTO, M. & SAKAI, S. (2010). In vivo measurement of the water
42
43 1547 content in the dermis by confocal Raman spectroscopy. *Skin Research Technology* **16**(2),
44
45 1548 137–141.
46
47 1549
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1550 NAKANO, A., CHAO, S.C., PULKKINEN, L., MURRELL, D., BRUCKNER-TUDERMAN, L.,
4
5 1551 PFENDNER, E. & UITTO, J. (2002). Laminin 5 mutations in junctional epidermolysis bullosa:
6
7 1552 molecular basis of Herlitz vs. non-Herlitz phenotypes. *Human Genetics* **110**, 41–51.
8
9
10 1553
11
12 1554 NAMER, B. (2010). Age related changes in human C-fiber function. *Neuroscience Letters*
13
14 1555 **470**(3), 185-187.
15
16
17 1556
18
19 1557 NASSAJI, M., ASKARI, Z. & GHORBANI, R. (2014). Cigarette smoking and risk of pressure ulcer
20
21 1558 in adult intensive care unit patients. *International Journal of Nursing Practice* **20**, 418–423.
22
23
24 1559
25
26 1560 NEIDIG, J. R., KLEIER, C. & OPPLIGER, R. A. (1989). Risk factors associated with pressure
27
28 1561 ulcers in the pediatric patient following open-heart surgery. *Progress in Cardiovascular*
29
30 1562 *Nursing* **4**(3), 99–106.
31
32
33 1563
34
35 1564 NEWTON, V.L., BRADLEY, R.S., SEROUL, P., CHEREL, M., GRIFFITHS, C.E., RAWLINGS, A.V.,
36
37 1565 VOEGELI, R., WATSON, R.E. & SHERRATT, M.J. (2017). Novel approaches to characterize age-
38
39 1566 related remodeling of the dermal-epidermal junction in 2D, 3D and in vivo. *Skin Research*
40
41 1567 *and Technology* **23**(2), 131–148.
42
43
44 1568
45
46 1569 NIKOLOVSKI, J., STAMATAS, G., KOLLIAS, N. & WIEGAND, B.C. (2008). Barrier function and
47
48 1570 water-holding and transport properties of infant stratum corneum are different from adult and
49
50 1571 continue to develop through the first year of life. *Journal of Investigative Dermatology* **128**,
51
52 1572 1728–1736.
53
54
55 1573
56
57
58
59
60

- 1
2
3 1574 NPUAP, EPUAP & PPPIA (2014). Prevention and treatment of Pressure Ulcers: Quick
4
5 1575 reference Guide. Emily Haesler (Ed.). Cambridge Media : Perth, Australia.
6
7
8 1576
9
10 1577 O'BRIEN, D.D., SHANKS, A.M., TALSMA, A., BRENNER, P.S. & RAMACHANDRAN, S.K. (2014).
11
12 1578 Intraoperative risk factors associated with postoperative pressure ulcers in critically ill
13
14 1579 patients: a retrospective observational study. *Critical Care Medicine* **42**(1), 40–47.
15
16
17 1580
18
19 1581 OOMENS, C.W., BADER, D.L., LOERAKKER, S. & BAAIJENS, F. (2015). Pressure induced deep
20
21 1582 tissue injury explained. *Annals of Biomedical Engineering*. 43(2), 297–305.
22
23
24 1583
25
26 1584 ORSSO, C.E., COLIN-RAMIREZ, E., FIELD, C.J., MADSEN, K.L., PRADO, C.M. & HAQQ, A.M.
27
28 1585 (2020). Adipose tissue development and expansion from the womb to adolescence: an
29
30 1586 overview. *Nutrients* **12**(9), 2735.
31
32
33 1587
34
35 1588 PABLOS, J.L., CARREIRA, P.E., SERRANO, L., DEL CASTILLO, P. & GOMEZ-REINO, J.J. (1997).
36
37 1589 Apoptosis and proliferation of fibroblasts during postnatal skin development and scleroderma
38
39 1590 in the tight-skin mouse. *Journal of Histochemistry & Cytochemistry* **45**(5), 711–719.
40
41
42 1591
43
44 1592 PALMER, A.K. & KIRKLAND, J.L. (2016). Aging and adipose tissue: potential interventions for
45
46 1593 diabetes and regenerative medicine. *Experimental Gerontology* **86**, 97–105
47
48
49 1594
50
51 1595 PANOUTSOPOULOU, I.G., WENDELSCHAFFER-CRABB, G., HODGES, J.S. & KENNEDY, W.R.
52
53 1596 (2009). Skin blister and skin biopsy to quantify epidermal nerves: a comparative study.
54
55 1597 *Neurology* **72**(14), 1205–1210.
56
57
58 1598
59
60

- 1
2
3 1599 PARK, K.H. & KIM, K.S. (2014). Effect of a structured skin care regimen on patients with fecal
4
5 1600 incontinence: a comparison cohort study. *Journal of Wound Ostomy & Continence Nursing*
6
7
8 1601 **41**(2), 161–167.
9
10 1602
11
12 1603 PASQUALI-RONCHETTI, I. & BACCARANI-CONTRI, M. (1997). Elastic fiber during development
13
14 1604 and aging. *Microscopy Research and Technique* **38**(4), 428–435.
15
16 1605
17
18
19 1606 PEETERS, E., DE HERTOOGH, G., JUNGE, K., KLINGE, U. & MISEREZ, M. (2014). Skin as marker
20
21 1607 for collagen type I/III ratio in abdominal wall fascia. *Hernia* **18**(4), 519–525.
22
23 1608
24
25
26 1609 PERERA, P., KURBAN, A.K. & RYAN, T.J. (1970). The development of the cutaneous
27
28 1610 microvascular system in the newborn. *British Journal of Dermatology* **82**, 86–91.
29
30 1611
31
32
33 1612 PERIN, F., PITTET, J.C., SCHNEBERT, S., PERRIER, P., TRANQUART, F. & BEAU, P. (2000).
34
35 1613 Ultrasonic assessment of variations in thickness of subcutaneous fat during the normal
36
37 1614 menstrual cycle. *European Journal of Ultrasound* **11**(1), 7–14.
38
39 1615
40
41
42 1616 PICARDO, M., OTTAVIANI, M., CAMERA, E. & MASTROFRANCESCO, A. (2009). Sebaceous
43
44 1617 gland lipids. *Dermatoendocrinology* **1**(2), 68–71.
45
46 1618
47
48
49 1619 PIENTA, K. & COFFEY, D.S. (1990). Characterization of the subtypes of cell motility in ageing
50
51 1620 human skin fibroblasts. *Mechanisms of Ageing and Development* **56**(2), 99–105.
52
53 1621
54
55
56
57
58
59
60

- 1
2
3 1622 PLIKUS, M.V., GUERRERO-JUAREZ, C.F., ITO, M., LI, Y.R., DEDHIA, P.H., ZHENG, Y., SHAO,
4
5 1623 M., GAY, D.L., RAMOS, R. & HIS, T.C. (2017). Regeneration of fat cells from myofibroblasts
6
7 1624 during wound healing. *Science* **355**, 748–752.
8
9
10 1625
11
12 1626 POCHI, P.E., STRAUSS, J.S. & DOWNING, D.T. (1979) Age-related changes in sebaceous gland
13
14 1627 activity. *Journal of Investigative Dermatology* **73**(1), 108–111.
15
16
17 1628
18
19 1629 POULIOT, N., SAUNDERS, N. A. & KAUR, P. (2002). Laminin 10/11: an alternative adhesive
20
21 1630 ligand for epidermal keratinocytes with a functional role in promoting proliferation and
22
23 1631 migration. *Experimental Dermatology*, **11**(5), 387–397.
24
25
26 1632
27
28 1633 PROKSCH, E. (2018). Buffering capacity. *Current Problems in Dermatology* **54**, 11–18.
29
30 1634
31
32 1635 PROKSCH, E., BRANDNER, J.M. & JENSEN, J.M. (2008). The skin: an indispensable barrier.
33
34 1636 *Experimental Dermatology* **17**, 1063–1072.
35
36 1637
37
38 1638 PRZYBYSZ, P., JACKOWSKA, T., WILIŃSKA, M., MALINOWSKA, S., WÓJTOWICZ, J. & MLOSEK,
39
40 1639 R.K. (2021). Ultrasound image of healthy skin in newborns in the first 24 hours of life.
41
42 1640 *Journal of Ultrasonography* **20**(83), e242–e247.
43
44
45 1641
46
47 1642 QUAN, T. & FISHER, G.J. (2015). Role of age-associated alterations of the dermal extracellular
48
49 1643 matrix microenvironment in human skin ageing: a mini-review. *Gerontology* **61**(5), 427–434.
50
51
52 1644
53
54
55
56
57
58
59
60

- 1
2
3 1645 RAHMANI, N., MOHSENI-BANDPEI, M.A., SALAVATI, M., VAMEGHI, R. & ABDOLLAHI, I.
4
5 1646 (2018). Normal values of abdominal muscles thickness in healthy children using
6
7 1647 ultrasonography. *Musculoskeletal Science and Practice* **34**, 54–58.
8
9 1648
10
11
12 1649 RAWLINGS A.V. (2017) The Stratum Corneum and Aging. In: Farage M., Miller K., Maibach
13
14 1650 H. (eds) *Textbook of Aging Skin*. Springer, Berlin, Heidelberg, 67–90.
15
16
17 1651
18
19 1652 RAZMUS, I., LEWIS, L. & WILSON, D. (2008). Pressure ulcer development in infants: State of
20
21 1653 the science. *The Journal of Healthcare Quality* **30**(5), 36–42.
22
23
24 1654
25
26 1655 REED, R.C., JOHNSON, D.E. & NIE, A.M. (2021). Preterm infant skin structure is qualitatively
27
28 1656 and quantitatively different from that of term newborns. *Pediatric and Developmental*
29
30 1657 *Pathology* **24**(2), 96–102.
31
32
33 1658
34
35 1659 RIRIE, D.G. & EISENACH, J.C. (2006). Age-dependent responses to nerve injury-induced
36
37 1660 mechanical allodynia. *Anesthesiology* **104**(2), 344–350.
38
39
40 1661
41
42 1662 RITTER, A.M., LEWIN, G.R., KREMER, N.E & MENDELL, L.M. (1991). Requirement for nerve
43
44 1663 growth factor in the development of myelinated nociceptors in vivo. *Nature* **350**(6318), 500–
45
46 1664 502.
47
48
49 1665
50
51 1666 RITTER, A.M., LEWIN, G.R. & MENDELL, L.M. (1993). Regulation of myelinated nociceptor
52
53 1667 function by nerve growth factor in neonatal and adult rats. *Brain Research Bulletin* **30**(3-4),
54
55 1668 245–249.
56
57
58 1669
59
60

- 1
2
3 1670 RITTIÉ, L. & FISHER, G.J. (2015). Natural and sun-induced ageing of human skin. *Cold Spring*
4
5 1671 *Harbor Perspectives in Medicine* **5**(1), a015370.
6
7 1672
8
9 1673 ROGERS, N.M., ROBERTS, D.D. & ISENBERG, J.S. (2013). Age-associated induction of cell
10
11 1674 membrane CD47 limits basal and temperature-induced changes in cutaneous blood flow.
12
13 1675 *Annals of Surgery* **258**(1), 184–191.
14
15 1676
16
17 1677 ROSENBLOOM, J., ABRAMS, W.R. & MECHAM, R. (1993). Extracellular matrix 4: the elastic
18
19 1678 fiber. *FASEB Journal* **7**, 1208–1218.
20
21
22 1679
23
24 1680 ROSSI, M., CUPISTI, A., MARIANI, S., SANTORO, G. & PENTIMONE, F. (2002) Endothelium
25
26 1681 dependent and endothelium-independent skin vasoreactivity in the elderly. *Aging Clinical and*
27
28 1682 *Experimental Research* **14**, 343–346.
29
30
31 1683
32
33 1684 ROUSSELLE, P. & BECK, K. (2013). Laminin 332 processing impacts cellular behavior. *Cell*
34
35 1685 *Adhesion & Migration* **7**(1), 122–134.
36
37
38 1686
39
40 1687 ROUSSELLE, P., KEENE, D.R., RUGGIERO, F., CHAMPLIAUD, M.F., REST, M. & BURGESSON, R.E.
41
42 1688 (1997). Laminin 5 binds the NC-1 domain of type VII collagen. *Journal of Cell Biology* **138**,
43
44 1689 719–728.
45
46
47 1690
48
49 1691 ROUSSELLE, P., LUNSTRUM, G.P., KEENE, D.R. & BURGESSON, R.E. (1991) Kalinin : an
50
51 1692 epithelium-specific basement membrane adhesion molecule that is a component of anchoring
52
53 1693 filaments. *Journal of Cell Biology* **114**, 567–576).
54
55
56 1694
57
58
59
60

- 1
2
3 1695 RUIZ MARTÍNEZ, M.A., PERALTA GALISTEO, S., CASTÁN, H. & MORALES HERNÁNDEZ, M.E.
4
5 1696 (2020). Role of proteoglycans on skin ageing: a review. *International Journal of Cosmetic*
6
7 1697 *Science* **42**(6), 529-535.
8
9
10 1698
11
12 1699 SAKAI, L.Y., KEENE, D.R. & ENGVALL, E. (1986). Fibrillin, a new 350-kD glycoprotein, is a
13
14 1700 component of extracellular microfibrils. *Journal of Cell Biology* **103**, 2499–2509.
15
16
17 1701
18
19 1702 SAIJO, S. & TAGAMI, H. (1991). Dry skin of newborn infants: functional analysis of the stratum
20
21 1703 corneum. *Pediatric Dermatology* **8**, 155–159.
22
23
24 1704
25
26 1705 SCHLÜER, A.B., HALFENS, R.J. & SCHOLS, J.M. (2012). Pediatric pressure ulcer prevalence: a
27
28 1706 multicenter, cross-sectional, point prevalence study in Switzerland. *Ostomy Wound Manage*
29
30 1707 **58**(7), 18-31.
31
32
33 1708
34
35 1709 SCHLÜER, A.B., SCHOLS, J.M. & HALFENS, R.J. (2014) Risk and associated factors of pressure
36
37 1710 ulcers in hospitalized children over 1 year of age. *Journal for Specialists in Pediatric Nursing*
38
39 1711 **19**(1), 80-89.
40
41
42 1712
43
44 1713 SCHMIDT, B.A. & HORSLEY, V. (2013). Intradermal adipocytes mediate fibroblast recruitment
45
46 1714 during skin wound healing. *Development* **140**, 1517–1527.
47
48
49 1715
50
51 1716 SCHREML, S., ZELLER, V., MEIER, R.J., KORTING, H.C., BEHM, B., LANDTHALER, M. &
52
53 1717 BABILAS, P. (2012). Impact of age and body site on adult female skin surface pH.
54
55 1718 *Dermatology* **224**(1), 66-71.
56
57
58 1719
59
60

- 1
2
3 1720 SEO, J.E., KIM, S., SHIN, M.H., KIM, M.S., EUN, H.C., PARK, C.H. & CHUNG, J.H. (2010).
4
5 1721 Ultraviolet irradiation induces thrombospondin-1 which attenuates type I procollagen
6
7 1722 downregulation in human dermal fibroblasts. *Journal of Dermatological Science* **59**(1), 16–
8
9 1723 24.
10
11
12 1724
13
14 1725 SGONC, R. & GRUBER, J. (2013). Age-related aspects of cutaneous wound healing: a mini-
15
16 1726 review. *Gerontology* **59**(2), 159–164.
17
18
19 1727
20
21 1728 SHAPIRO, S. D., ENDICOTT, S. K., PROVINCE, M. A., PIERCE, J. A. & CAMPBELL, E. J. (1991).
22
23 1729 Marked longevity of human lung parenchymal elastic fibers deduced from prevalence of D-
24
25 1730 aspartate and nuclear weapons-related radiocarbon. *The Journal of clinical investigation*
26
27 1731 **87**(5), 1828–1834.
28
29
30 1732
31
32 1733 SHIN, J.W., KWON, S.H., CHOI, J.Y., NA, J.I., HUH, C.H., CHOI, H.R. & PARK, K.C. (2019).
33
34 1734 Molecular Mechanisms of Dermal Ageing and Antiageing Approaches. *International Journal*
35
36 1735 *of Molecular Sciences* **20**(9), 2126.
37
38
39 1736
40
41 1737 SHIOHARA, T., MIZUKAWA, Y., SHIMODA-KOMATSU, Y. & AOYAMA, Y. (2018). Sweat is a
42
43 1738 most efficient natural moisturizer providing protective immunity at points of allergen entry.
44
45 1739 *Allergology International* **67**(4), 442–447.
46
47
48 1740
49
50 1741 SHUSTER, S., BLACK, M.M. & MCVITIE, E. (1975). The influence of age and sex on skin
51
52 1742 thickness, skin collagen and density. *British Journal of Dermatology* **93**(6), 639– 643.
53
54
55 1743
56
57
58
59
60

- 1
2
3 1744 SHUTTLEWORTH, C.A. & FORREST, L. (1975). Changes in guinea-pig dermal collagen during
4
5 1745 development. *Biochemical Society Transactions* **3**(1), 147–149.
6
7 1746
8
9
10 1747 SMITH, L.T., HOLBROOK, K.A. & MADRI, J.A. (1986). Collagen types I, III, and V in human
11
12 1748 embryonic and fetal skin. *American Journal of Anatomy* **175**(4), 507–521.
13
14 1749
15
16
17 1750 SOKOLNICKI, L.A., STROM, N.A., ROBERTS, S.K., KINGSLEY-BERG, S.A., BASU, A. &
18
19 1751 CHARKOUDIAN, N. (2009). Skin blood flow and nitric oxide during body heating in type 2
20
21 1752 diabetes mellitus. *Journal of Applied Physiology* **106**(2), 566–570.
22
23 1753
24
25
26 1754 STAMATAS, G. N., ESTANISLAO, R. B., SUERO, M., RIVERA, Z. S., LI, J., KHAJAT, A. &
27
28 1755 KOLLIAS, N. (2006). Facial skin fluorescence as a marker of the skin's response to chronic
29
30 1756 environmental insults and its dependence on age. *British Journal of Dermatology* **154**(1),
31
32 1757 125–132.
33
34 1758
35
36
37 1759 STAMATAS, G.N., NIKOLOVSKI, J., LUEDTKE, M.A., KOLLIAS, N. & WIEGAND, B.C. (2010).
38
39 1760 Infant skin microstructure assessed in vivo differs from adult skin in organization and at the
40
41 1761 cellular level. *Pediatric Dermatology* **27**, 125–131.
42
43 1762
44
45
46 1763 SWEE, M.H., PARKS, W.C. & PIERCE, R.A. (1995). Developmental regulation of elastin
47
48 1764 production. Expression of tropoelastin pre-mRNA persists after down-regulation of steady-
49
50 1765 state mRNA levels. *The Journal of Biological Chemistry* **270**(25), 14899–14906.
51
52 1766
53
54
55
56
57
58
59
60

- 1
2
3 1767 TAGAMI, H. (2008). Functional characteristics of the stratum corneum in photoaged skin in
4
5 1768 comparison with those found in intrinsic aging. *Archive of Dermatological Research*. **300**
6
7
8 1769 (Suppl 1), S1-S6.
9
10 1770
11
12 1771 TAN, C.Y., STATHAM, B., MARKS, R. & PAYNE, P.A. (1982). Skin thickness measurement by
13
14 1772 pulsed ultrasound: its reproducibility, validation and variability. *British Journal of*
15
16
17 1773 *Dermatology* **106**, 657– 667.
18
19 1774
20
21 1775 TAO, J., JIN, Y.F., YANG, Z., WANG, L.C., GAO, X.R., LUI, L. & MA. H. (2004). Reduced
22
23 1776 arterial elasticity is associated with endothelial dysfunction in persons of advancing age:
24
25 1777 comparative study of noninvasive pulse wave analysis and laser Doppler blood flow
26
27 1778 measurement. *American Journal of Hypertension* **17**(8), 654– 659.
28
29
30 1779
31
32
33 1780 TAYEM, R., NIEMANN, C., PESCH, M., MORGNER, J., NIESSEN, C.M., WICKSTRÖM, S.A. &
34
35 1781 AUMAILLEY, M. (2021). Laminin 332 is indispensable for homeostatic epidermal
36
37 1782 differentiation programs. *Journal of Investigative Dermatology* **141**, 2602– 2610.
38
39
40 1783
41
42 1784 TAYYIB, N., COYER, F. & LEWIS, P. (2016) Saudi Arabian adult intensive care unit pressure
43
44 1785 ulcer incidence and risk factors: a prospective cohort study. *International Wound Journal*
45
46 1786 **13**(5), 912–919.
47
48
49 1787
50
51 1788 TÉLLEZ-SOTO, C.A., PEREIRA SILVA, M.G., DOS SANTOS, L., MENDES, T.DE O., SINGH, P.,
52
53 1789 FORTES, S.A., FAVERO, P. & MARTIN, A.A. (2021). In vivo determination of dermal water
54
55 1790 content in chronological skin aging by confocal Raman spectroscopy. *Vibrational*
56
57 1791 *Spectroscopy* **112**, 103196.
58
59
60

- 1
2
3 1792
4
5 1793 TELOFSKI, L.S., MORELLO, A.P., MACK CORREA, C. & STAMATAS, G.N. (2012). The infant
6
7 1794 skin barrier: can we preserve, protect, and enhance the barrier? *Dermatology Research and*
8
9 1795 *Practice* **2012**, 1–18.
10
11
12 1796
13
14 1797 TEW, G.A., KLONIZAKIS, M., MOSS, J., RUDDOCK, A.D., SAXTON, J.M. & HODGES, G.J. (2011).
15
16 1798 Role of sensory nerves in the rapid cutaneous vasodilator response to local heating in young
17
18 1799 and older endurance-trained and untrained men. *Experimental Physiology* **96**(2), 163–170.
19
20
21 1800
22
23 1801 TOUWSLAGER, R. N. H., HOUBEN, A. J. H. M., GIELEN, M., ZEEGERS, M. P., STEHOUWER, C. D.
24
25 1802 A., ZIMMERMANN, L. J., KESSELS, A.G., GERVER, W.J., BLANCO, C.E. & MULDER, A. L. M.
26
27 1803 (2012). Endothelial vasodilatation in newborns is related to body size and maternal
28
29 1804 hypertension. *Journal of Hypertension* **30**(1), 124–131.
30
31
32 1805
33
34 1806 TRIANTAFYLLOU, C., CHORIANOPOULOU, E., KOURKOUNI, E., ZAOUTIS, T.E. & KOURLABA, G.
35
36 1807 (2021) Prevalence, incidence, length of stay and cost of healthcare-acquired pressure ulcers in
37
38 1808 pediatric populations: A systematic review and meta-analysis. *Int J Nurs Stud.* **115**, 103843.
39
40
41 1809
42
43 1810 VALLE-ORERO, J., RIVAS-PARDO, J.A., TAPIA-ROJO, R., POPA, I., ECHELMAN, D.J., HALDAR, S.
44
45 1811 & FERNÁNDEZ, J.M. (2017). Mechanical Deformation Accelerates Protein Ageing.
46
47 1812 *Angewandte Chemie International Edition* **56**(33), 9741–9746.
48
49
50 1813
51
52 1814 VAN MÜLDER, T.J.S., DE KOEIJER, M., THEETEN, H., WILLEMS, D., VAN DAMME, P.,
53
54 1815 DEMOLDER, M., DE MEYER, G., BEYERS, K.C.L. & VANKERCKHOVEN, V. (2017). High
55
56 1816 frequency ultrasound to assess skin thickness in healthy adults. *Vaccine* **35**(14), 1810–1815.
57
58
59
60

- 1
2
3 1817
4
5 1818 VARANI, J., SPEARMAN, D., PERONE, P., FLIGIEL, S.E., DATTA, S.C., WANG, Z.Q., SHAO, Y.,
6
7 1819 KANG, S., FISHER, G.J. & VOORHEES, J.J. (2001). Inhibition of type I procollagen synthesis by
8
9 1820 damaged collagen in photoaged skin and by collagenase-degraded collagen in vitro. *The*
10
11 1821 *American Journal of Pathology* **158**(3), 931–942.
12
13
14 1822
15
16 1823 VERDIER-SÉVRAIN & S., BONTÉ, F. (2007). Skin hydration: a review on its molecular
17
18 1824 mechanisms. *Journal of Cosmetic Dermatology* **6**(2), 75–82.
19
20
21 1825
22
23 1826 VILLONE, D., FRITSCH, A., KOCH, M., BRUCKNER-TUDERMAN, L., HANSEN, U. & BRUCKNER,
24
25 1827 P. (2008). Supramolecular interactions in the dermo-epidermal junction zone: anchoring
26
27 1828 fibril-collagen VII tightly binds to banded collagen fibrils. *Journal of Biological Chemistry*
28
29 1829 **283**(36), 24506–24513.
30
31
32 1830
33
34 1831 VISSCHER, M.O., ADAM, R., BRINK, S. & ODIO, M. (2015). Newborn infant skin: physiology,
35
36 1832 development, and care. *Clinical Dermatology* **33**(3), 271–280.
37
38
39 1833
40
41 1834 VISSCHER, M.O., BARAI, N., LARUFFA, A.A., PICKENS, W.L., NARENDRAN, V. & HOATH, S.B.
42
43 1835 (2011*a*). Epidermal barrier treatments based on vernix caseosa. *Skin Pharmacology*
44
45 1836 *Physiology* **24**(6), 322–329.
46
47
48 1837
49
50 1838 VISSCHER, M.O., CHATTERJEE, R., MUNSON, K.A., PICKENS, W.L. & HOATH, S.B. (2000).
51
52 1839 Changes in diapered and nondiapered infant skin over the first month of life. *Pediatric*
53
54 1840 *Dermatology* **17**, 45–51.
55
56
57 1841
58
59
60

- 1
2
3 1842 VISSCHER, M.O., NARENDRAN, V., PICKENS, W.L., LARUFFA, A.A., MEINZEN-DERR, J.,
4
5 1843 ALLEN, K. & HOATH, S.B. (2005). Vernix caseosa in neonatal adaptation. *Journal of*
6
7 1844 *Perinatology* **25**, 440–446.
8
9
10 1845
11
12 1846 VISSCHER, M.O., UTTURKAR, R., PICKENS, W.L., LARUFFA, A.A., ROBINSON, M., WICKETT,
13
14 1847 R.R., NARENDRAN, V. & HOATH, S.B. (2011*b*). Neonatal skin maturation--vernix caseosa and
15
16 1848 free amino acids. *Pediatric Dermatology* **28**(2), 122–132.
17
18
19 1849
20
21 1850 VITELLARO-ZUCCARELLO, L., CAPPELLETTI, S., DAL POZZO ROSSI, V. & SARI-GORLA M.
22
23 1851 (1994). Stereological analysis of collagen and elastic fibers in the normal human dermis:
24
25 1852 variability with age, sex, and body region. *Anatomical Record* **238**(2), 153–162.
26
27
28 1853
29
30 1854 VITRAL, G.L.N., AGUIAR, R.A.P.L., DE SOUZA, I.M.F., REGO, M.A.S., GUIMARÃES, R.N. &
31
32 1855 REIS, Z.S.N. (2018). Skin thickness as a potential marker of gestational age at birth despite
33
34 1856 different fetal growth profiles: A feasibility study. *PLoS One* **13**(4), e0196542.
35
36
37 1857
38
39 1858 VOUILLARMET, J., JOSSET-LAMAUGARNY, A., MICHON, P., SAUMET, J. L., KOITKA-WEBER, A.,
40
41 1859 HENNI, S., FROMY, B. & SIGAUDO-ROUSSEL, D. (2019). Neurovascular response to pressure in
42
43 1860 patients with diabetic foot ulcer. *Diabetes* **68**, 832–836.
44
45
46 1861
47
48 1862 WALLER, J.M. & MAIBACH, H.I. (2005). Age and skin structure and function, a quantitative
49
50 1863 approach (I): blood flow, pH, thickness, and ultrasound echogenicity. *Skin Research &*
51
52 1864 *Technology* **11**(4), 221–235.
53
54
55
56 1865
57
58
59
60

- 1
2
3 1866 WARREN, J.B. (1994). Nitric oxide and human skin blood flow responses to acetylcholine and
4
5 1867 ultraviolet light. *FASEB Journal* **8**(2), 247–251.
6
7
8 1868
9
10 1869 WOLLINA, U., WETZKER, R., ABDEL-NASER, M.B. & KRUGLIKOV, I.L. (2017). Role of adipose
11
12 1870 tissue in facial aging. *Clinical Interventions in Aging* **12**, 2069–2076.
13
14
15 1871
16
17 1872 XU, H., FONSECA, M., WOLNER, Z., CHUNG, E., WU, X., GELLER, S., DUSZA, S.W., DEROSA,
18
19 1873 A.P., MARGHOOB, A.A., BUSAM, K.J., HALPERN, A.C. & MARCHETTI, M.A. (2017). Reference
20
21 1874 values for skin microanatomy: A systematic review and meta-analysis of ex vivo studies.
22
23
24 1875 *Journal of the American Academy of Dermatology* **77**(6), 1133-1144.e4.
25
26 1876
27
28 1877 YAMADA, T., HASEGAWA, S., MIYACHI, K., DATE, Y., INOUE, Y., YAGAMI, A., ARIMA, M.,
29
30 1878 IWATA, Y., YAMAMOTO, N., NAKATA, S., MATSUNAGA, K., SUGIURA, K. & AKAMATSU, H.
31
32 1879 (2018). Laminin-332 regulates differentiation of human interfollicular epidermal stem cells.
33
34 1880 *Mechanisms of Ageing and Development* **171**, 37–46.
35
36 1881
37
38 1882 YA-XIAN, Z., SUETAKE, T. & TAGAMI, H. (1999). Number of cell layers of the stratum
39
40 1883 corneum in normal skin – relationship to the anatomical location on the body, age, sex and
41
42 1884 physical parameters. *Archives of Dermatology Research* **291**, 555–559.
43
44
45 1885
46
47 1886 YOSIPOVITCH, G., MAAYAN-METZGER, A., MERLOB, P. & SIROTA, L. (2000). Skin barrier
48
49 1887 properties in different body areas in neonates. *Pediatrics* **106**, 105–108.
50
51
52 1888
53
54 1889 ZELLERS, T.M. & VANHOUTTE, P.M. (1991). Endothelium-dependent relaxations of piglet
55
56 1890 pulmonary arteries augment with maturation. *Pediatric Research* **30**, 176–180.
57
58
59
60

- 1
2
3 1891
4
5 1892 ZHANG, L.J., CHEN, S.X., GUERRERO-JUAREZ, C.F., LI, F., TONG, Y., LIANG, Y., LIGGINS, M.,
6
7 1893 CHEN, X., CHEN, H., LI, M., HATA, T., ZHENG, Y., PLIKUS, M.V. & GALLO, R.L. (2019). Age-
8
9
10 1894 related loss of innate immune antimicrobial function of dermal fat is mediated by
11
12 1895 transforming growth factor beta. *Immunity* **50**(1), 121–136.
13
14 1896
15
16 1897 ZHANG, L.J., GUERRERO-JUAREZ, C.F., HATA, T., BAPAT, S.P., RAMOS, R., PLIKUS, M.V. &
17
18 1898 GALLO, R.L. (2015). Dermal adipocytes protect against invasive *Staphylococcus aureus* skin
19
20 1899 infection. *Science* **347**, 67–71.
21
22
23 1900
24
25 1901 ŽIVICOVÁ, V., LACINA, L., MATEU, R., SMETANA, K. JR, KAVKOVÁ, R., DROBNÁ KREJČÍ, E.,
26
27 1902 GRIM, M., KVASILOVÁ, A., BORSKÝ, J., STRNAD, H., HRADILOVÁ, M., ŠÁCHOVÁ, J., KOLÁŘ, M.
28
29 & DVOŘÁNKOVÁ, B. (2017). Analysis of dermal fibroblasts isolated from neonatal and child
30
31 1903 cleft lip and adult skin: Developmental implications on reconstructive surgery. *International*
32
33 1904 *Journal of Molecular Medicine* **40**(5), 1323–1334.
34
35
36
37 1906
38
39
40 1907
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **1908 Figure legends**
4

5 **1909 Fig. 1.** Comparison of skin structure in newborn, adult and elderly skin. BL, basal layer; CL,
6
7
8 **1910** capillary loop; DEJ, dermal–epidermal junction; ECM, extracellular matrix; ESG, eccrine
9
10 **1911** sweat gland; GL, granular layer; SC, stratum corneum; SL, spinous layer.
11

12 **1912**
13
14 **1913 Fig. 2.** The key role of transforming growth factor beta (TGF β) signalling in skin. This
15
16
17 **1914** pathway is not fully functional in newborn skin and is impaired during skin ageing. MMP,
18
19 **1915** metalloproteinase; ROS, reactive oxygen species; Smad, suppressor of mothers against
20
21 **1916** decapentaplegic; T β RII, TGF β receptor II; TIMP, metalloproteinase inhibitor.
22

23
24 **1917**
25
26 **1918 Fig. 3.** Effects of a higher pH on skin barrier function.
27

28
29 **1919**
30
31 **1920 Fig. 4.** Comparison of the pressure-induced vasodilation (PIV) mechanism in young adult and
32
33 **1921** ageing skin. ASIC3, acid-sensing ion channel 3; CGRP, calcitonin gene-related peptide;
34
35 **1922** EDHF, endothelium-derived hyperpolarizing factor; NO, nitric oxide; PACAP, pituitary
36
37 **1923** adenylyl cyclase activating peptide; PGE2, prostaglandin E2; ROS, reactive oxygen species;
38
39 **1924** TSP1, thrombospondin-1; VIP, vasoactive intestinal peptide.
40

41
42 **1925**
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

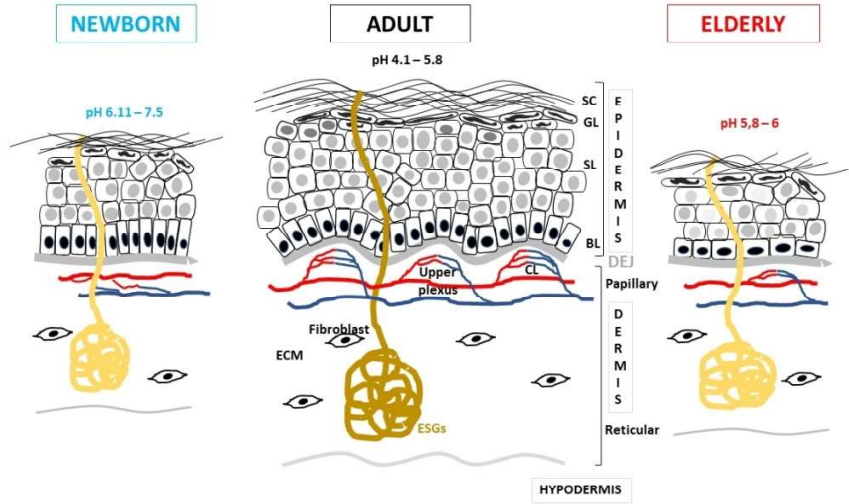


Fig. 1. Comparison of skin structure in newborn, adult and elderly skin. BL, basal layer; CL, capillary loop; DEJ, dermal-epidermal junction; ECM, extracellular matrix; ESG, eccrine sweat gland; GL, granular layer; SC, stratum corneum; SL, spinous layer.

338x190mm (96 x 96 DPI)

Table 1. Comparison of skin structure and barrier functionality in newborn, young adult and elderly skin. Text entries for newborn and elderly skin are compared with that of young adults. BMI, body mass index; coll, collagen; DEJ, dermal–epidermal junction; ESG, eccrine sweat gland; NMF, natural moisturizing factor; PIV, pressure-induced vasodilation; SC, stratum corneum.

NEWBORN	YOUNG ADULT	ELDERLY
<p>Thin SC (~30%) (Ya Xian <i>et al.</i>, 1999; Stamatas <i>et al.</i>, 2010)</p> <p>Very thin SC for preterm (Razmus <i>et al.</i>, 2008)</p>	<p>Thick SC (Fairley & Rasmussen, 1983; Holbrook, 2000)</p>	<p>SC thickness similar to young adult or thicker depending on anatomical region (Waller & Maibach, 2005; Newton <i>et al.</i>, 2017; Rawlings, 2017)</p>
<p>Thin epidermis (~20%) (Evans & Rutter, 1986; Stamatas <i>et al.</i>, 2010; Przybysz <i>et al.</i>, 2021)</p> <p>Very thin epidermis for preterm (Razmus <i>et al.</i>, 2008)</p>	<p>Thick epidermis (Mlosek <i>et al.</i>, 2011)</p>	<p>Thin epidermis (~10 to ~50%) (Xu <i>et al.</i>, 2017)</p>
<p>Very high cell proliferation and stem cell number and/or activation potential (Michel <i>et al.</i>, 1997; Hoeger & Enzmann, 2002; Stamatas <i>et al.</i>, 2010)</p>	<p>High cell proliferation</p>	<p>Low cell proliferation and stem cell number and/or activation potential (Kligman, 1979; Moragas <i>et al.</i>, 1993; Lavker, 1995; Michel <i>et al.</i>, 1997; Stamatas <i>et al.</i>, 2006; Giangreco <i>et al.</i>, 2008, 2010; Charruyer <i>et al.</i>, 2009; Keyes <i>et al.</i>, 2013)</p>
<p>pH 6.11–7.5 => Lower skin barrier function (Yosipovitch <i>et al.</i>, 2000; Ludriksone <i>et al.</i>, 2014)</p>	<p>pH 4.1–5.8 => High barrier function (Yosipovitch <i>et al.</i>, 2000; Fluhr <i>et al.</i>, 2001; Ali & Yosipovitch, 2013; Proksch, 2018)</p>	<p>Higher pH, increasing with age => Lower skin barrier function (Man <i>et al.</i>, 2009; Schreml <i>et al.</i>, 2012; Ali & Yosipovitch, 2013; Rittié & Fisher, 2015; Kilic <i>et al.</i>, 2019)</p>
<p>Low SC hydration and dry and rough skin surface (0–2 weeks of age) (Saijo & Tagami, 1991; Visscher <i>et al.</i>, 2000; Giusti <i>et al.</i>, 2001; Yosipovitch <i>et al.</i>, 2000; Hoeger & Enzmann, 2002; Nikolovski <i>et al.</i>, 2008; Chittock <i>et al.</i>, 2016)</p> <p>Missing vernix caseosa (preterm or post-term) => higher dehydration and impaired skin barrier function (Visscher <i>et al.</i>, 2005; Telofski <i>et al.</i>, 2012)</p>	<p>High SC hydration and smooth surface</p>	<p>Low SC hydration (at least for some anatomical regions) and dry and rough skin surface (Kligman, 1979; Tagami, 2008; Man <i>et al.</i>, 2009; Luebbberding <i>et al.</i>, 2014)</p>
<p>Immature ESGs, low sebum production and less NMF (Foster <i>et al.</i>, 1969; Agache <i>et al.</i>, 1980; Saijo & Tagami, 1991; Emery <i>et al.</i>, 1991; Henderson <i>et al.</i>, 2000; Chittock <i>et al.</i>, 2016; McAleer <i>et al.</i>, 2018)</p> <p>No sweating for premature <36GA (Harpin & Rutter, 1982)</p>	<p>Functional ESGs and high sebum production => Well-hydrated skin (surface and SC)</p>	<p>Decreased activity of ESGs, low sebum production and less NMF (Pochi <i>et al.</i>, 1979; Man <i>et al.</i>, 2009; Luebbberding <i>et al.</i>, 2013; Farage <i>et al.</i>, 2013; Rittié & Fisher, 2015)</p>

<p>Less-undulating DEJ with fewer anchoring fibrils => Reduced nutritional exchanges and higher mechanical fragility (Evans & Rutter, 1986; Cartlidge, 2000; Razmus <i>et al.</i>, 2008; Miyauchi <i>et al.</i>, 2016)</p> <p>Flat DEJ for preterm babies (Holbrook, 1982; Cartlidge, 2000)</p>	<p>Undulating DEJ => Normal nutritional exchanges</p>	<p>Less-undulating DEJ => Reduced nutritional exchanges and higher mechanical fragility (Lavker <i>et al.</i>, 1987, 1989; Moragas <i>et al.</i>, 1993; Desai, 1997; Giangreco <i>et al.</i>, 2010; Farage <i>et al.</i>, 2013; Hatje <i>et al.</i>, 2015; Newton <i>et al.</i>, 2017)</p>
<p>Thin dermis with gradual transition between papillary and reticular dermis (Holbrook, 1982; Tan <i>et al.</i>, 1982; Vitellaro-Zuccarello <i>et al.</i>, 1994; Stamatias <i>et al.</i>, 2010; Przybysz <i>et al.</i>, 2021; Reed <i>et al.</i>, 2021)</p>	<p>Thick dermis with clear separation between papillary and reticular dermis (Mlosek <i>et al.</i>, 2011)</p>	<p>Thin dermis (except in sun-exposed area) with clear transition between papillary and reticular dermis (Shuster <i>et al.</i>, 1975; Giangreco <i>et al.</i>, 2010)</p>
<p>Low fibroblast density Immature and highly proliferative, they maintain keratinocyte immaturity (Pablos <i>et al.</i>, 1997; Živicová <i>et al.</i>, 2017)</p>	<p>High fibroblast density Mature and proliferative fibroblasts</p>	<p>Low fibroblast density High senescence and low motility (Pienta & Coffey, 1990; Dimri <i>et al.</i>, 1995; Sgonc & Gruber, 2013)</p>
<p>Low collagen synthesis (Arai <i>et al.</i>, 2017) Collagen fibrils smaller in preterm neonates than at full-term (Holbrook, 1982)</p>	<p>High collagen synthesis</p>	<p>Fragmented and coarsely distributed collagen I => Decreased mechanical tension in fibroblasts (Quan & Fisher, 2015; Fisher <i>et al.</i>, 2016; Shin <i>et al.</i>, 2019)</p>
<p>High coll III/coll I ratio (Epstein, 1974; Shuttleworth & Forest, 1975; Cheng <i>et al.</i>, 2011)</p>	<p>Low coll III/coll I ratio</p>	<p>High coll III/coll I ratio (Lovell <i>et al.</i>, 1987)</p>
<p>Low density of elastin network => Lower elasticity (Swee <i>et al.</i>, 1995; Pasquali-Ronchetti & Baccarani-Contri, 1997)</p>	<p>High density of elastin network => High elasticity</p>	<p>Elastic fibre decrease and alteration => Low elasticity (Braverman & Fonferko, 1982; Lavker <i>et al.</i>, 1989; Swee <i>et al.</i>, 1995; Valle-Orero <i>et al.</i>, 2017; Shin <i>et al.</i>, 2019)</p>
<p>Horizontal plexus with a capillary network not well organized (Perera <i>et al.</i>, 1970; Miyauchi <i>et al.</i>, 2016) Lower capillary density for preterm infants (Bonamy <i>et al.</i>, 2007)</p>	<p>Well-organized capillary network with papillary loops</p>	<p>Significant reduction of papillary loops and blood vessel number and size Increased volume fraction in horizontal vessels Sparse and tortuous vessels (Kligman, 1979; Kelly <i>et al.</i>, 1995; Chung <i>et al.</i>, 2002; Betsholtz <i>et al.</i>, 2005; Helmbold <i>et al.</i>, 2006)</p>
<p>Immature Meissner's and Pacini's corpuscles, immature AΔ- & C-fibres Lower withdrawal threshold to mechanical stimulation, but lower proportion of heat-sensitive C fibres and immature synaptic connections in the dorsal horn => Sensitivity, but underlying mechanisms are different from adults (Ritter <i>et al.</i>, 1991, 1993; Ririe & Eisenach, 2006; Koch <i>et al.</i>, 2012; Jankowski <i>et al.</i>, 2014; Fitzgerald & McKelvey, 2016; Feito <i>et al.</i>, 2018)</p>	<p>High density of functional sensory fibres => High and regulated sensitivity</p>	<p>Decreased number of Meissner's corpuscles, Merkel cell neurite complexes and free nerve fibres, including mechano-sensitive C-fibres => Lower & impaired sensitivity and decreased PIV (Panoutsopoulou <i>et al.</i>, 2009; Fromy <i>et al.</i>, 2010; Namer, 2010; Tew <i>et al.</i>, 2011; Bowden & McNulty, 2013; Garcia-Piqueras <i>et al.</i>, 2019)</p>

<p>Low nerve conduction and myelination degree (Canta <i>et al.</i>, 2016; Jenny <i>et al.</i>, 2020)</p>	<p>High nerve conduction and myelination degree (Canta <i>et al.</i>, 2016)</p>	<p>Decreased nerve conduction and myelination degree (Canta <i>et al.</i>, 2016)</p>
<p>Thin hypodermis => Lower shock attenuation (Fereira <i>et al.</i>, 2014) Very thin or no hypodermis in preterm infants (Fox, 2011; Orsso <i>et al.</i>, 2020)</p>	<p>Thicker hypodermis => Higher shock attenuation (Perin <i>et al.</i>, 2000; Grunnet <i>et al.</i>, 2019)</p>	<p>Thinner hypodermis (normal BMI) => Lower shock attenuation (Levakov <i>et al.</i>, 2012; Rittié & Fisher, 2015)</p>

For Review Only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

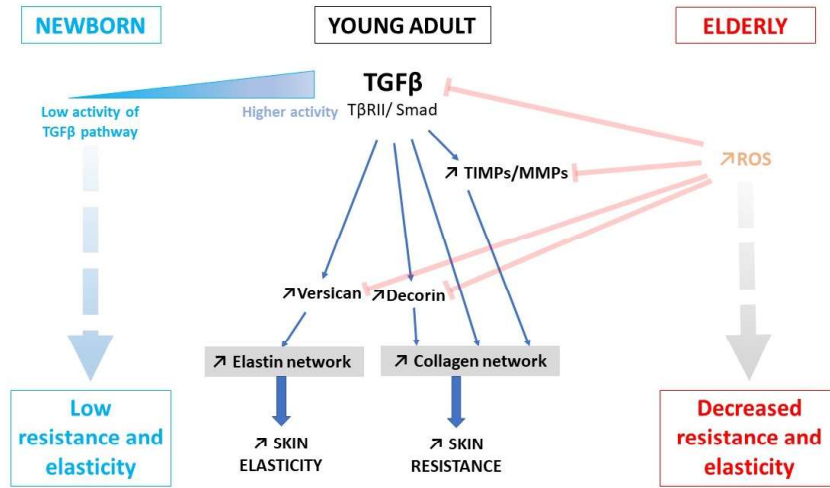


Fig. 2. The key role of transforming growth factor beta (TGFβ) signalling in skin. This pathway is not fully functional in newborn skin and is impaired during skin ageing. MMP, metalloproteinase; ROS, reactive oxygen species; Smad, suppressor of mothers against decapentaplegic; TβRII, TGFβ receptor II; TIMP, metalloproteinase inhibitor.

338x190mm (96 x 96 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

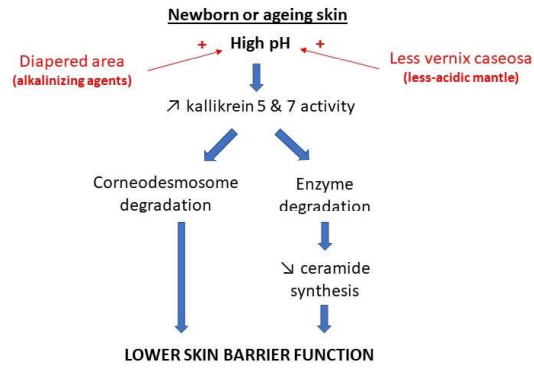


Fig. 3. Effects of a higher pH on skin barrier function.

338x190mm (96 x 96 DPI)

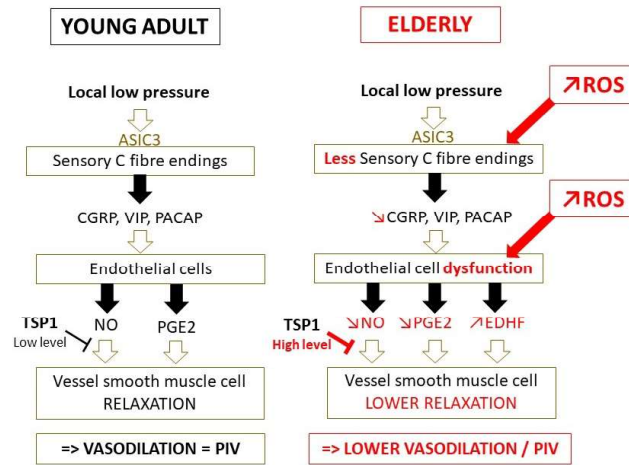


Fig. 4. Comparison of the pressure-induced vasodilation (PIV) mechanism in young adult and ageing skin. ASIC3, acid-sensing ion channel 3; CGRP, calcitonin gene-related peptide; EDHF, endothelium-derived hyperpolarizing factor; NO, nitric oxide; PACAP, pituitary adenylyl cyclase activating peptide; PGE2, prostaglandin E2; ROS, reactive oxygen species; TSP1, thrombospondin-1; VIP, vasoactive intestinal peptide.

338x190mm (96 x 96 DPI)