Developmental Changes in Skin Barrier and Structure during the First 5 Years of Life

Russel M. Walters    Preeya Khanna    Melissa Chu    M. Catherine Mack

Johnson & Johnson Consumer Inc., Skillman, N.J., USA

Introduction

The skin serves the critical function of providing a protective barrier between the body’s viscera and the external world. The top layer of the skin, the stratum corneum (SC), is largely responsible for regulating the transport of water and other substances through the skin. Water loss through the skin is a significant health concern in preterm infants, and a better understanding of how skin barrier function evolves and reacts towards external factors is the first step to developing solutions for improved infant skin health [1–3].

To quantify these differences, the barrier function of the skin is commonly assessed by measuring water holding and transport properties, specifically the rate of water flux through the SC (transepidermal water loss, TEWL) and SC thickness, was measured on the upper inner arm and dorsal forearm in subjects aged 3 months to 4 years (n = 171) and a subset of mothers (n = 44). The rate of skin surface area expansion as a function of age peaked before birth (~90 cm²/week) and declined to a steady plateau (~10 cm²/week) by 1 year of age. SC thickness increased and TEWL decreased, but did not reach adult values until 3–4 years of age. A better understanding of how skin hydration changes after birth suggests that barrier function may be related mechanistically to skin surface area expansion.

Key Words
Stratum corneum · Skin barrier · Skin conductance · Surface area expansion · Water loss

Abstract
The structure of the stratum corneum (SC) and the corresponding skin barrier develops from before birth up to about 4 years of age. Large subject-to-subject variability within an age group requires a large population to observe trends in skin barrier properties over time. Barrier function, quantified by transepidermal water loss (TEWL) and SC thickness, was measured on the upper inner arm and dorsal forearm in subjects aged 3 months to 4 years (n = 171) and a subset of mothers (n = 44). The rate of skin surface area expansion as a function of age peaked before birth (~90 cm²/week) and declined to a steady plateau (~10 cm²/week) by 1 year of age. SC thickness increased and TEWL decreased, but did not reach adult values until 3–4 years of age. A better understanding of how skin hydration changes after birth suggests that barrier function may be related mechanistically to skin surface area expansion.

© 2016 S. Karger AG, Basel
searchers found that in the first 15 days of life skin hydration is significantly lower compared with older infants and adults [11–13]. Approximately 2 weeks after birth, skin hydration has been observed to increase and even exceed values found in adults [7]; however, postnatal skin hydration development differs depending on the anatomical area [3, 14, 15]. Over the first years of life, skin hydration decreases to adult-like values [3, 12, 16–18].

Measurements of water content as a function of depth in the skin are greater in infants than adults [7, 12]. Inconsistent changes with age in natural moisturizing factor (NMF) have been reported by several groups. NMF has been observed to be lower in infants up to 1 year of age than in adults [7]. However, another study contradicts this by reporting that infant NMF levels are not lower than adult levels [12]. NMF levels have been shown to be higher in newborns (1–15 days of age) than at 6 weeks or 6 months of age [12], which may represent a mechanism evolved to maintain skin hydration during this period of rapid adaptation.

TEWL varies by body site within subjects and can be variable within similar subject populations [7, 10, 19, 20]. There have been differing trends of TEWL with age reported in the literature [9, 12, 21]. In general, TEWL tends to be greater shortly after birth and tends to decrease towards adult values with age depending on the anatomical area [3, 12, 21–23].

While a number of studies have considered age-dependent changes in TEWL and SC hydration and potential skin proteins (e.g. NMF) that may cause these changes, the literature has barely addressed geometric changes in skin or considered how body growth and skin surface area growth may contribute to changing skin barrier properties [24]. However, there is converging evidence that these geometric properties may indeed be significant to barrier formation and functionality. Notably, during prenatal barrier formation, at specific differentiation sites, including the head/scalp and palmar/plantar skin [25], upper layers of the epidermis differentiate into granular keratinocytes that grow in size and eventually transform into corneocytes (flat, anucleated, nonpermeable protein-filled cells). Lipid sheets form between cells, creating a laminar barrier. As specific sites differentiate, cells spread like a front across the surface area of the developing infant [26]. The structure of the SC, including the aspect ratio of the corneocytes, lipid-to-corneocyte thickness ratio and offset ratio of corneocytes, affect TEWL as they influence the path length of water diffusion through the SC [27]. Such developmental changes could potentially be encapsulated by a gross metric such as the calculated skin surface area.

Due to inter- and intrapersonal variability, assessing the skin barrier change with age requires a large number of subjects and preferably multiple body sites. In this study, we sought to determine how the SC structure and the resultant skin barrier properties change with a child’s age and with changes in gross geometric skin properties as a child grows.

Materials and Methods

Study Design

Infants and toddlers [3–49 months old, Caucasian (n = 83) and African American (n = 88)] and a subset of their mothers [25–40 years, Caucasian Fitzpatrick skin type I–III (n = 25) and African American (n = 19)] were enrolled between July and September 2010 in Skillman (N.J., USA). Children and mothers refrained from using topical products and cosmetics for at least 24 h prior to the study evaluations.

TEWL and high-frequency conductance measurements (indicative of moisture content in the SC [28]) were obtained from the dorsal forearm and upper inner arm, enabling assessments of the effect of age and the environment (e.g. temperature, humidity, dew point, etc.) on SC water holding and transport. TEWL was measured using a VapoMeter (Delfin Technologies Ltd., Kuopio, Finland). The VapoMeter uses the closed-chamber measurement principle to determine the evaporation rate of water from skin [29]. High-frequency skin conductance was measured using the Skicon-200EX® (IBS Co. Ltd., Hamamatsu, Japan) skin surface hygrometer. All measurements were performed in triplicate at each body site. Measurements were performed in a temperature- and humidity-controlled environment after a 30-min acclimatization period.

Reflectance confocal image stacks were collected from the skin of a subset of subjects using a Vivascope® 1500 (Caliber I.D. Inc., Rochester, N.Y., USA). Image stacks (a series of images from individual subjects) were collected from the dorsal forearm and upper inner arm of 44 adult subjects. Useable image stacks of the upper inner arm measurement site were collected in 142 infant subjects, and usable image stacks of the dorsal arm measurement sites were collected in 151 infant subjects. SC thickness was calculated through visual inspection of the image stacks.

Body Surface Area Calculations

For prenatal baby, infant and toddler data, the body surface area (BSA) was calculated with the Ahn mean BSA and weight (Neo-BSA_w) equation [30]:

\[
BSA = 10.602 \times \text{weight}^{0.6561}.
\]

(1)

Although there are a number of related equations to calculate BSA (e.g. Haycock et al. [31], Dubois and Dubois [32] and Mosteller [33]), the Neo-BSA_w was specifically designed for infant and prenatal populations within 400–7,000 g. Average weights and lengths for neonates ranging from 24 to 42 gestational weeks were used to calculate average BSAs. These weights and heights were collected from Ahn [30] and the 50th percentile of the World Health Orga-
BSAs were calculated using the Haycock equation calculated from Hadlock et al. [35] as follows:

\[
\text{Fetal weight (g)} = \exp(0.578 + 0.332 \times \text{gestational age} - 0.00354 \times \text{gestational age}^2).
\]

(2)

For ages in which weights fell in the 400–7,000-gram range, the Neo-BSA<sub>w</sub> equation was used to calculate average BSA. Adult BSAs were calculated using the Haycock equation [31]:

\[
\text{BSA (m}^2\rangle = 0.024265 \times \text{weight (kg)}^{0.5378} \times \text{height (cm)}^{0.3964}.\]

(3)

The BSA calculations were completed in Matlab® (Mathworks, Natick, Mass., USA) where a locally weighted linear regression, Lowess method (Matlab), was used to fit a smooth curve to BSA versus gestational age data. A similar procedure was used to fit a curve to the rate of change of BSA.

Results

TEWL was elevated in infants compared with adults. Figure 1 shows the dorsal forearm TEWL from 225 subjects, and the upper inner arm TEWL from 221 subjects as a function of the subject age (shown as weeks after conception). The upper inner arm TEWL is generally greater than the dorsal forearm TEWL across all ages. Both locations exhibit a decrease in TEWL with subject age from birth until about 4 years of age. After the age of 4 years, TEWL appears to stop decreasing and to become similar to adult TEWL.

Averaging by age eliminates some of the variability of the TEWL measurement between subjects and more clearly illustrates the decreasing trend of TEWL with age until about 4 years of age. For this analysis, we grouped data from multiple subjects into age bins in which average subject TEWL and average subject age are shown with large diamond and large circle markers (fig. 1a). In order to have a similar number of subjects in each bin, seven infant age bins of variable age width (mean of 23 subjects per age bin) were defined. Since there were fewer young infants, the youngest age bins are wider in age. All 44 adults (average age 32 years) were placed into one age bin.

Figure 1b shows dorsal forearm SC thickness from 108 subjects and the upper inner arm SC thickness from 71 subjects as a function of the subject age (weeks after conception). The SC thickness increases with age until 4 years of age, at which point the SC thickness is similar to that of adults. All subject data are shown in the small points. Large data points are age-bin averages, similar to the previous figure. There was a median of 11 subjects per bin for dorsal forearm SC thickness, and 7 subjects per bin for upper inner arm SC thickness. The SC thickness of the upper inner arm and dorsal forearm are similar, unlike the TEWL from the two sites which differ consistently.

Figure 1c shows SC thickness plotted against TEWL at the dorsal forearm location, as well as the upper inner arm location for all age groups combined. The large circles and diamonds represent the same age bins from figures 1a and b; however, in figure 1b not all subjects had SC thickness measurements. Therefore, data used in the analysis were included only when both SC and TEWL data were available for the same subject. With increasing SC thickness, a decrease in TEWL was observed for both the upper inner arm and the dorsal forearm. Since the SC is the primary source of the skin’s barrier properties, a thicker SC was expected to be associated with a decrease in TEWL. Figure 1c also shows that upper inner arm TEWL is higher than dorsal forearm locations at equivalent SC thicknesses. The low TEWL of adults (fig. 1c, larger diamonds with TEWL <10 g/m²/h) in the upper inner arm area suggests that decreasing TEWL may be due to a mechanism other than increased SC thickness for subjects older than 4 years of age. The relationship between SC thickness and TEWL is likely more complex than a linear regression.

Figure 2 shows BSA versus age in gray, where age is in weeks after conception and extends back before birth. As described previously, the BSA is calculated from average height and weight data at each age and a curve has been fitted to these calculated points. As the child grows from an embryo to an infant its BSA increases rapidly and continues to increase beyond 2 years of age through puberty, though at a lesser rate.

The secondary vertical axis in figure 2 is the rate of change of BSA as a function of age. The calculated rate of change of the BSA peaks just prior to birth. After birth, the rate of BSA slows, mirroring the slowing of height and weight growth, which eventually plateaus. Not shown in the figure is the relatively rapid growth in height and weight seen during puberty. The changes at puberty do not result in a rapid increase in the rate of BSA growth. Since the infant already has a relatively high BSA, the rate of change in surface area at puberty is only slightly above the rate achieved at the age of 2 years.

In figure 2, the infant BSA growth rate appears to be approximately logistical, modeled by the following growth rate equation:

\[
\frac{d\text{BSA}}{dt} = r \times \text{BSA} \times \left(1 - \frac{\text{BSA}}{K}\right),
\]

(4)

in which \(r\) is a growth rate and \(K\) is the final adult BSA reached. The shape of logistic growth is initially (when

Developmental Changes in Infant Skin

Skin Pharmacol Physiol 2016;29:111–118
DOI: 10.1159/000444805
BSA is much smaller than K) exponential with a growth rate of $r$. As BSA reaches K, the growth slows, becoming limited by the $(1 - \text{BSA}/K)$ term until BSA reaches K and growth approaches zero. Since BSA is a function of height and weight, the growth is reflective of the logistic nature in both of these values. A fetus begins with high height and weight growth rates that slow as it develops.

The values from figure 1 are replotted on figure 3 to show that TEWL reaches more adult-like values at least 1 year after the plateau in the rate of BSA expansion. This time lag suggests a mechanism may come into play after rapid body surface expansion to stabilize the skin barrier, a process that is completed approximately 1 year after the reduction in expansion. Contributing to the water loss, infants also have a higher surface area to body mass ratio than adults. Figure 4 displays the mass of water lost through the skin per day as a percentage of total body mass as a function of age. Young infants lose three to four times more water than adults, when calculated as a function of total body mass.
Discussion

In these studies, we determined that infants do indeed lose more water mass per day than adults in the measured body areas, and that the metrics of TEWL and SC thickness reflect this reduced skin barrier function (fig. 1, 4). However, TEWL also shows different postnatal development in other body areas [23]. In particular, we noted a decreased TEWL with increasing age from birth to adulthood concomitant with an SC thickness increase from birth to adulthood. Both parameters changed rapidly over the first years of life and stabilized at values close to those found in the adult by 3–5 years of age. Potentially foreshadowing these changes, BSA increased with age as expected [34] until BSA began to decrease over the first year and plateaued by 1–2 years of age. The decrease in TEWL was approximately linearly proportional to the increase in SC thickness.

SC thickness increased similarly in upper inner arm skin and dorsal forearm skin. However, TEWL was greater in upper inner arm skin than on the dorsal forearm. The reason(s) for the reduced barrier function in the upper inner arm are unclear, but could include structural factors relating to overall growth, such as overall skin thickness including non-SC layers (not measured in these studies), biological factors such as lipid distribution within the different skin locations, changes in NMF production and a greater environmental exposure of the dorsal forearm.
forearm than the upper inner arm. In adults, resistance to water permeability was shown to be greater for the upper inner arm than the dorsal forearm, with no significant difference in TEWL between sites [10, 20].

There are a number of reported processes that accompany barrier formation that could potentially take months to years to progress. It is known that both the protein and lipid components play roles in maintaining proper water balance in the SC, and NMF helps to retain water within corneocytes. Changes in the composition of the lipid matrix of ceramides, fatty acids and cholesterol have been shown to impact TEWL [36–38]. In addition, disordering the lipid matrix through increasing temperature or applying exogenous species, such as sodium lauryl sulfate or oleic acid, result in increased TEWL [37–39].

Perhaps the reduced barrier to transport observed in infant SC represents a necessary trade-off with the rapid expansion of the skin surface area that is required in the early stages of life. Then, as the rapid surface area expansion slows and the skin matures over the first few years, the SC structure stabilizes to create a more robust barrier, which results in a reduction in TEWL.

Recent studies in the areas of pediatric tissue expansion for surgical reconstruction by Zollner et al. [40] suggest that as the skin expands in response to controlled long-term stretch, one achieves an increase in skin surface area with constant epidermal thickness (because of increased keratinocyte mitosis) while maintaining a similar collagenous microstructure to unexpanded skin. These findings would suggest that changes in permeability may be unrelated to changes in skin surface area alone. It is conceivable that the changes in TEWL and skin hydration are due to age-related changes (e.g. maturation) in skin function rather than skin surface area-related factors.

In conclusion, these data indicate that maturation of the skin barrier (reduction of TEWL, reduction of the rate of water mass loss, increase in SC thickness) takes place after the period of most rapid skin surface area expansion, corresponding to the second through to the fourth year of life, on the dorsal forearm and upper inner arm [23]. Mature skin barrier function is characterized by values in these parameters that are similar to those in adults. From a clinical perspective, these data provide additional rationale for protecting the young child from conditions that might result in a depletion of water mass and/or damage to the already fragile skin barrier.

Acknowledgements

These studies were fully supported by Johnson & Johnson Consumer Inc., Skillman, N.J., USA. Medical writing and editorial support was provided by Alex Loeb, PhD, CMPP, Evidence Scientific Solutions, Philadelphia, Pa., USA, and was funded by Johnson & Johnson Consumer Inc.
Statement of Ethics

The Allendale Investigational Review Board (Old Lyme, Conn., USA) approved the study protocol. Written, informed consent was obtained from all adult subjects and from the parents or legal guardians of all child subjects.

Disclosure Statement

The authors declare no conflicts of interest in this work. The authors are all employees of Johnson & Johnson Consumer Inc.

References


