Comparison of Skin Structural and Functional Parameters in Well-Nourished and Moderately Undernourished Infants

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Keywords

Skin development · Nutrition · Infant skin · Structural skin parameters · Functional skin parameters · Fatty acids · Skin barrier function

Abstract

Background: Little is known about the impact of nutrition on the development of skin structure and function in infants.

Methods: We investigated epidermal, dermal, and subcutis parameters of aged-matched well-nourished and moderately undernourished infants in this single-center, cross-sectional, noninterventional study using noninvasive methods (skin caliper, 20-MHz sonography, transepidermal water loss, skin pH, and corneometry). Plasma fatty acids were determined as an indicator of nutritional differences. 310 infants from different age groups, i.e., 1 week, 4 weeks, and 6, 9, 12, 24, and 36 months were included. Approximately half of each age group was well-nourished (WHO reference values weight-for-height/length Z score: $-0.75 \leq Z \leq 0.75$) and the other half was moderately undernourished ($-3 \leq Z < -2$).

Results: Structural maturational differences in the deeper dermis and subcutis regions of the skin and subtle functional changes in the epidermis were observed in moderately

undernourished infants without notable clinical symptoms. Reduced skin barrier function or skin hydration were not observed in the undernourished infants, and skin pH shifted to more acidic values in this group. **Conclusion:** These findings reveal a greater impact of moderate undernutrition on the development of the dermis and subcutis and suggest that critical epidermal functions such as skin barrier and pH are mostly maintained.

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Published by S. Karger AG, Basel

Introduction

Our knowledge about the role of nutrition in the development and maintenance of healthy skin stems largely from observations of clinical skin changes accompanying undernutrition such as scaly dermatosis and skin lesions exhibiting hyperkeratosis [1–3]. Little is known about the impact of nutrition on the maturation of skin structure and function from birth and through the first years of life.

This work was carried out in Santa Domingo in the Dominican Republic.

A better understanding is required to facilitate the care of infants with nutritional deficiencies and to protect against potential impairment of the skin barrier, reduced thermoregulatory properties, and resistance to skin infections [4].

The skin of healthy infants is inherently physiologically fragile compared to adults with a lower resistance to aggressions [5]. The maturation process of the skin from birth through the first year of life has been studied extensively using noninvasive biophysical measurement methods concentrated on the stratum corneum and the physical development of skin barrier function [5–8]. It is generally believed that the skin barrier is competent in full-term infants at birth, based on measurements of transepidermal water loss (TEWL) [5, 9]; however, the water-handling properties of the stratum corneum do not appear to be fully developed until at least the end of the first year [5, 7]. Indeed, recent evidence based on the water-holding and transport properties of the stratum corneum suggest that skin barrier maturation continues into the fourth year of life [8, 10]. This development appears to be dependent on the anatomical site, with TEWL and conductance measurements taken in the less environmentally exposed inner upper arm being higher and taking longer to decrease to adult values than in the more exposed dorsal forearm [8]. Capacitance, an indirect parameter of skin hydration state, increases steeply in the first days or weeks after birth, reflecting increasing skin hydration [6, 7]. Skin surface pH is higher in neonates and decreases steeply in the first few days after birth, and more gradually thereafter [6, 11]. Structurally infant skin has a thinner epidermis and stratum corneum than adult skin [5].

Differences from the skin of adults have also been noted in the structure of the deeper skin layers, i.e., the dermis and subcutis. Studies on dermal thickness in infants are very limited, particularly in infants <2 years old. These studies demonstrate that children's skin is thinner than that of adults and there are also variations in thickness depending on body region, as seen in adults [12, 13]. The subcutaneous fat layer (subcutis) increases steeply in the first few months after birth and has been investigated in studies of the body composition and nutritional status of infants [14, 15].

To gain an insight into the effect of nutrition on skin maturation and development, we compared structural and functional differences in the skin of well-nourished and moderately undernourished infants from 1 week to 3 years of age by using noninvasive biophysical measurement methods. By carefully age-matching the well-nour-

ished and undernourished groups, we not only have a reliable basis for the comparison between the 2 groups but can also add to the knowledge base of normal skin development in age groups which have been underrepresented in existing studies. Since a number of the cutaneous clinical symptoms seen in protein energy malnutrition (PEM) such as dry scaly skin and rashes are associated with fatty acid (FA) deficiencies [16, 17], blood FAs were also examined. Together, this information is a step toward establishing a better scientific rationale for the components of an optimal internal nutritional supplement as well as topical treatment of undernourished infants.

Methods

Participants

This single-center, noninterventional study was conducted at the Department of Infectious Diseases, Robert Reid Cabral Children's Hospital, Santa Domingo, Dominican Republic. Subjects were recruited from among children visiting the clinic with a non-serious complaint or were siblings of other patients visiting the clinic.

A total of 310 eligible subjects were divided into 7 age groups; approximately half of each group was moderately undernourished (WHO reference values for weight-for-height/length Z score: $-3 \leq Z < -2$) and the other half was well-nourished ($-0.75 \leq Z \leq 0.75$). The groups were 1 week $\pm$ 5 days old (well-nourished: $n = 21$, undernourished: $n = 22$), 4 weeks $\pm$ 7 days old (well-nourished: $n = 23$, undernourished: $n = 22$), 6 months $\pm$ 20 days old (well-nourished: $n = 24$, undernourished: $n = 22$), 9 months $\pm$ 20 days old (well-nourished: $n = 22$, undernourished: $n = 22$), 12 months $\pm$ 20 days old (well-nourished: $n = 22$, undernourished: $n = 22$), 24 months $\pm$ 84 days old (well-nourished: $n = 22$, undernourished: $n = 22$), and 36 months $\pm$ 84 days old (well-nourished: $n = 22$, undernourished: $n = 22$). Children who were born preterm and/or had skin disorders or other diseases that might influence skin health were excluded.

A physical examination including the measurement of vital signs, body temperature, height, and weight was conducted; a 5-day diet record was completed by parents or guardians; a full body photograph was made; a clinical assessment of the skin was made which included erythema, dryness, scaling, edema, pigmentation, and skin gloss (none [0] to 3 [severe]); noninvasive measurements of the skin were made; and blood was drawn for laboratory tests (HIV quick test, hematology, and clinical chemistry) and FA analyses.

Biophysical Measurement Methods

Prior to conducting TEWL measurements and corneometry, stable climatic conditions were achieved by having the subjects remain for at least 30 min (sitting or lying) in an air-conditioned room at $20 \pm 2^\circ\text{C}$ and $50 \pm 10\%$ humidity with loose-fitting clothes or a light blanket to prevent undercooling.

The biophysical measurement methods included TEWL using an AquaFlux AF200 (on the cheek and volar forearm); full skin thickness using a DermaScan® C USB Ultrasound 20 MHz (on the

cheek, volar forearm, thigh, and calf); capacitance of stratum corneum using Corneometer® CM 825 (on the cheek, calf, and volar forearm); skin surface pH using a Skin-pH-Meter® PH 905 (on the cheek, forehead, and volar forearm); and a caliper for skin folds as an indicator of subcutaneous fat (in the subscapular and triceps areas). Altogether, the measurement series usually lasted approximately 1.5–2 h. Measurements were not taken if the infants were crying, and, in a few cases, a longer break was taken to allow the infants to calm before proceeding.

Fatty Acids

FAs were analyzed by Synelvia SAS (Labège, France). The determination of total FAs was performed using gas chromatography with mass spectrometric detection. Extraction of FAs from plasma was performed using a hydrolysis step followed by liquid/liquid extraction. Samples were then methylated before analysis.

Identification of methylated fatty acids was performed by retention time and comparison with a mixture of standard reference solution. The quantification of compounds of interest was performed using a calibration curve of external standards with an internal standard for methylation step, and TriAcylGlycerol (TAG) as a second internal standard to evaluate the performance of the hydrolysis. The range of linearity was determined at different concentrations (range 1–500 µg/mL).

The total fatty acid methyl esters were analyzed using an Agilent 7890A gas chromatograph, equipped with a 100-meter-long SLB-IL111 fused silica capillary of 0.2-µm film thickness and coupled by an Agilent 5975C mass spectrometer.

Statistical Analyses

The impact of nutritional condition on skin parameters was assessed for each measurement area separately within a two-way ANOVA model, including the main and interaction effects of the factors “age group” and “nutrition condition”. The global nutrition effect was evaluated only if the interaction of the main factors was not significant at a level of 10%. The evaluation of nutrition effects within each age group and measurement area was performed by contrasts within the ANOVA model.

A total clinical assessment score was determined for each subject as the sum of the individual clinical assessment scores (erythema, dryness, scaling, edema, pigmentation, and skin gloss). The impact of the nutrition condition was assessed for each age group and area separately, applying the Wilcoxon rank sum test. The impact of the nutrition condition on the individual clinical assessment scores was assessed analogously.

Results and Discussion

Description of Subjects and Diet

A total of 310 infants aged 1 week to 3 years were included in this noninterventional study. There were 7 age-matched nutritional groups of well-nourished and moderately undernourished infants defined according to the respective WHO reference (Z) scores. Demographic data are listed in Table 1. With the exception of 1 black baby in the 6-month-old undernourished group, all infants

were mulatto (black and white). Analyses according to gender were not made as differences in skin structure were only expected with the onset of hormonal changes at puberty [13, 18].

In both the 1- and 4-week-old well-nourished and undernourished groups, >80% of babies were breast-fed. Fewer infants were breast-fed as the infants grew older: 67–41% in the well-nourished groups and 50–32% in the undernourished groups aged 6–12 months. At the age of 24 and 36 months, none of the well-nourished infants were breast-fed but 14 and 5%, respectively, of the undernourished infants were still breast-fed (online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000499434). In older children, the reported composition of solid food in the 5 days preceding the study visit did not vary between nourishment groups. The basic foods in both groups were rice, beans, different grains, and potatoes. Dishes with meat and eggs were also recorded frequently. Milk, juice, and soup were the most frequently recorded liquids for the older children. Since there was no obvious difference in the type of food consumed in the 2 nourishment groups, it appears that the difference in nutritional status can be attributed to the amount of food consumed and the resulting differences in protein and caloric intake. The amount of food was not recorded as part of the study as reliable data could not be obtained retrospectively at the time of the study visit.

In general, the skin of the babies and children in both nourishment groups appeared healthy. Observations of erythema, edema, or dryness were noted in both groups, with findings in 34% of well-nourished and 44% of undernourished infants.

Changes in Skin Structure during Development in Both Nutritional Groups

Measurements of skin-fold thickness (SFT) measured by caliper are an indicator of subcutaneous fat [14]. In the well-nourished infants, the lowest values for SFT were noted in the 1-week-old babies, with higher values at ≥4 weeks of age in both the subscapular (Fig. 1a) and triceps (Fig. 1b) areas. This is in agreement with another study reporting a rapid increase in subcutaneous fat in infants up to 3–5 months of age [14]. Beyond 12 months of age, a decrease in SFT was noted in the subscapular region (Fig. 1a). The observation of proportionately greater subcutaneous fat mass at the extremities compared to the trunk has been reported by other authors [14, 15].

The SFT was significantly lower in the undernourished than in the well-nourished groups at all ages (Fig. 1). A notable increase in SFT occurred later in undernourished

Table 1. Demographic characteristics of the 310 infants included in the study

Age group	N	Age	Height, cm	Weight, g	Z score	Sex, <i>n</i>	
						male	female
1 week							
Well-nourished	21	1.3±0.3 wk	50.0±2.0	3,460.5±420.8	0.2±0.5	11	10
Undernourished	22	1.2±0.3 wk	46.8±1.8	2,264.3±291.1	-2.3±0.4	11	11
4 weeks							
Well-nourished	23	4.3±0.3 wk	52.8±1.5	4,116.6±413.7	0.3±0.5	10	13
Undernourished	22	3.9±0.7 wk	48.1±2.5	2,471.8±441.1	-2.3±0.4	14	8
6 months							
Well-nourished	24	6.0±0.2 mo*	66.0±3.4	7,522.8±978.2	0.1±0.5	14	10
Undernourished	22	6.3±0.3 mo**	62.7±3.9	5,412.0±826.5	-2.4±0.3	10	12
9 months							
Well-nourished	22	9.2±0.2 mo**	70.3±2.6	8,341.6±719.6	-0.1±0.6	16	6
Undernourished	22	9.1±0.3 mo	66.1±4.3	6,063.3±911.9	-2.4±0.3	10	12
12 months							
Well-nourished	22	12.2±0.4 mo**	74.4±3.2	9,124.4±755.3	-0.1±0.5	9	13
Undernourished	22	12.3±0.4 mo	70.5±3.7	6,917.8±741.8	-2.3±0.3	12	10
24 months							
Well-nourished	22	24.4±0.8 mo	86.1±3.6	11,597.1±1,176.6	-0.1±0.6	10	12
Undernourished	22	23.7±3.0 mo	82.8±4.5	9,066.4±916.3	-2.3±0.3	10	12
36 months							
Well-nourished	22	36.9±0.8 mo	94.7±4.1	13,490.8±1,224.5	-0.2±0.5	8	14
Undernourished	22	37.4±1.6 mo	89.9±4.6	10,442.9±1,000.8	-2.3±0.3	12	10

Values are expressed as mean ± SD, unless otherwise indicated. In 5 subjects, the exact date of birth was not documented leading to different data for the age calculation, i.e., * *n* = 22, ** *n* = 21. wk, weeks; mo, months.

infants, being first observed at 6 months (Fig. 1) compared to at 4 weeks in well-nourished infants. In contrast to the well-nourished infants, the slight decrease in values from 6 months onward was more similar in the subscapular and triceps regions (Fig. 1a, b).

Variance in SFT patterns in developing infants led Schlüter et al. [14] to conclude that feeding habits and caloric intake may be responsible for developmental differences in subcutaneous fat in the trunk and extremities. Our results confirm this finding and highlight the importance of nutrition as a factor, not only with regard to the amount but also the distribution of body fat. Even in moderately undernourished infants, there is an impact on the subcutaneous fat storage layer which protects organs and bones, plays a key role in temperature regulation, and serves as an energy reservoir.

Skin thickness was measured using 20-MHz sonography, a frequency which allows depiction of the dermis but not separate resolution of the epidermis. Regional and maturational differences in skin thickness have been reported in adults and in children aged ≥2 [12] and 12 years [18], and in Chinese children aged 0–12 years [13]. These

differences have been primarily attributed to dermal thickness and collagen content [12, 13]. In this study, 4 different anatomical areas were measured: cheek, volar forearm, thigh, and calf. To our knowledge, this is the first time that defined age groups rather than pooled values have been measured during the first and second years of life.

In the well-nourished infants, skin thickness values were highest at all locations at 1 week of age (Fig. 2). Step-wise lower values were measured in the cheek and forearm regions at 4 weeks and 6 months, at which point a plateau was reached (Fig. 2a, b). In the thigh and calf, a plateau was already reached at 4 weeks (Fig. 2c, d). It can be speculated that the initial high values can be attributed to measurement anomalies related to tissue water as the skin adapted to a dry extrauterine environment, and not primarily to collagen content as is the case in older children and adults.

In 1- and 4-week-old infants, skin thickness was greater in undernourished than in well-nourished infants. Differences between the 2 groups were not significant in the 1-week old groups, but at the age of

Fig. 1. Comparison of skin-fold thickness in well-nourished and undernourished infants in the 7 age groups. Values are shown as mean + SD. The number in each group is shown beneath the respective bar. *** $p < 0.001$.

4 weeks, the values in undernourished infants were significantly greater than in well-nourished infants in the cheek, forearm, and calf (Fig. 2a, b, d). This suggests a delayed adaptive response of the skin to the dry, extra-uterine environment in the undernourished infants after birth. Skin thickness values had decreased in undernourished infants by 6 months, with lower values than in well-nourished infants in the groups ≥ 6 months measured at the volar forearm, thigh, and calf (Fig. 2b–d). In the cheek area, skin thickness was similar in the 2 nourishment groups from 6 to 24 months (Fig. 2a). At 36 months, skin thickness values were significantly lower in undernourished children at all locations, including the cheek (Fig. 2).

It seems likely that lower values of dermal skin thickness in undernourished children at ≥ 6 months are related to reduced collagen content. Thavaraj and Sesikaran [3] reported dermal edema with a reduction in collagen and increased melanin in the basal layer in a study of the histopathological changes in children with PEM. Vasantha [19] demonstrated decreased soluble collagen and retardation of collagen maturation in rats exposed to protein and caloric deficiency.

Changes in Skin Physiological Parameters during Development in Both Nutritional Groups

TEWL, a widely accepted surrogate marker of skin barrier function, was measured on the cheek and volar

Fig. 2. Comparison of dermal thickness in well-nourished and undernourished infants in the 7 age groups. The values are shown as mean + SD. The number in each group is shown beneath the respective bar. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

(Figure continued on next page.)

forearm. In the well-nourished groups, a gradual increase in the TEWL values was noted up to the age of 6 months (Fig. 3). Mean values varied between age groups but all values were within the normal range for TEWL for the device used. This finding was expected as it is generally accepted that skin barrier function is already developed in full-term infants shortly after birth [5, 20]. Furthermore, there is a large interperson variability in TEWL in young infants compared to in older children and adults [7]. This may have affected the ability to determine differences between groups.

TEWL values were lower in the undernourished children except in those aged 1 week, and 12 and 36 months

(Fig. 3). However, all mean values were within the normal range. This suggests a functioning skin barrier regardless of whether dermis and subcutis development has been altered as a consequence of undernutrition. However, it should be kept in mind that other dynamic measures of water handling by the stratum corneum, e.g., high frequency conductance [8] or absorption and desorption to test water-holding capacity [7], were not included in this study and might have led to a different interpretation. Measurements in other body regions such as the upper inner arm may also have produced other results [8].

An acidic skin surface is important for the integrity of the skin barrier, as several key enzymes necessary for syn-

thesis and maintenance of the barrier are pH-dependent [11] and pH is critical for cutaneous antimicrobial defense [21]. Measurements of skin pH on the cheek and volar forearm were comparable in all well-nourished groups, ranging from 5.2 to 5.9, with no discernible pattern related to age (Fig. 4a, b). In contrast, on the forehead only the values in the 1- and 4-week-old babies were similar to those at the other locations, with lower values being measured in all age groups ≥ 6 months (4.8–5.0) (Fig. 4c).

Similar patterns were noted at the same locations in the undernourished groups up to the age of 12 months (Fig. 4). In the 24- and 36-month-old groups, the pH was lower in the undernourished infants at all locations

(Fig. 4). It can be speculated that lower pH may have an effect on enzymatic reactions in the skin, e.g., those necessary for the integrity of the skin barrier. However, a shift in pH to more acidic values in moderately undernourished infants would likely have less detrimental impact on skin health and microbial resistance than increased pH.

Skin surface hydration was assessed by corneometry on the cheek, calf, and volar forearm. The highest hydration values in both nutritional groups were noted in the cheek (range 38.5–62.9, and 28.2–36.8 and 35.5–49.5 in the calf and forearm, respectively). Hydration values increased in the well-nourished groups from 1 to 4 weeks (35% higher in the cheek, 23% in the calf, and 26% in the

Fig. 3. Comparison of TEWL values in well-nourished and undernourished infants in the 7 age groups. To enable a reliable measurement of TEWL in the infants, it was necessary to make the measurement interval as short as possible. The close-chambered device used allowed for cutting off the measurement at a target precision of 0.3 gm²/h standard deviation, a setting which led to a systematic overestimation of TEWL, but which was consistent across all groups. The values are shown as mean + SD. The number in each group is shown beneath the respective bar. * $p < 0.05$, ** $p < 0.01$

forearm). An increase was also noted in the undernourished groups, but the maximal effect was delayed to 6 months (57, 22, and 17% in the cheek, calf, and forearm, respectively). This increase in the weeks after birth agrees with previous reports [6, 7]. In the 4-week-old infants, corneometry values ($p < 0.05$) in the cheek and forearm were significantly lower in the undernourished infants than in the well-nourished infants. Otherwise, there were no significant differences between nutritional groups (online suppl. Fig. S5).

Plasma FA Differences between Nutritional Groups

Essential FAs (EFAs) are a type of polyunsaturated (PU)FA that cannot be synthesized in our bodies and

must therefore be obtained from the diet. EFAs have documented roles in both the dermal and epidermal layers of the skin. There are 2 classes: ω -6 and ω -3. Linoleic acid (LA) is the parent compound of the ω -6 PUFAs; α -linolenic acid (ALA) is the parent compound of the ω -3 PUFAs. From these 2 parent compounds, the body synthesizes longer-chain derivatives that also have important functions in skin health. LA and derivatives of the ω -6 pathway play a central role in maintaining skin barrier integrity whereas ALA and derivatives of the ω -3 pathway serve primarily as immune modulators [22]. We did not determine skin levels of FAs, but plasma levels can be considered a good indicator of availability to the skin for LA and ALA as well as those derivatives which cannot be

Fig. 4. Comparison of skin pH in well-nourished and undernourished infants in the 7 age groups. The values are shown as mean + SD. The number in each group is shown beneath the respective bar. $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 2. Plasma fatty acids expressed as a percentage of total fatty acids in well-nourished and moderately undernourished infants in the 7 age groups

Fatty acid	Age						
	1 wk	4 wk	6 mo	9 mo	12 mo	24 mo	36 mo
Linoleic acid							
Well-nourished	6.72±2.8	10.62±1.1	11.19±1.6	10.40±2.8	10.15±3.3	11.79±1.9	12.71±2.1
Undernourished	5.18±2.0	7.46±2.1	9.46±3.0	8.90±3.2	9.69±2.6	10.04±2.6	9.64±3.0
<i>p</i> value	0.1300	<0.0001	0.0301	0.1247	0.6299	0.0158	0.0005
γ-Linolenic acid							
Well-nourished	0.27±0.1	0.21±0.1	0.22±0.1	0.20±0.1	0.26±0.2	0.38±0.2	0.36±0.2
Undernourished	0.30±0.2	0.30±0.1	0.32±0.2	0.30±0.2	0.44±0.3	0.42±0.2	0.43±0.2
<i>p</i> value	0.6742	0.0408	0.0490	0.0621	0.0187	0.4512	0.3640
Di-homo-γ-linolenic acid							
Well-nourished	3.35±3.4	2.66±2.7	2.03±2.0	1.97±2.0	2.57±2.6	2.93±2.9	2.41±2.4
Undernourished	3.38±1.2	4.27±1.7	2.52±1.1	2.52±1.0	2.57±0.8	3.40±1.1	3.77±1.5
<i>p</i> value	0.9590	0.0025	0.0819	0.0319	0.9978	0.1242	0.0010
Arachidonic acid							
Well-nourished	11.53±4.6	11.74±2.5	10.45±3.5	10.19±3.0	10.60±3.6	11.92±2.4	12.67±2.8
Undernourished	14.17±4.4	9.90±2.3	9.36±3.3	8.78±2.5	9.10±3.0	9.98±3.3	9.73±3.4
<i>p</i> value	0.1623	0.0328	0.3085	0.1186	0.1685	0.0323	0.0045
α-Linolenic acid							
Well-nourished	1.11±0.6	1.40±0.4	1.50±0.4	1.05±0.4	1.08±0.5	0.90±0.3	0.96±0.4
Undernourished	1.32±0.7	1.46±0.7	1.30±0.4	1.32±0.4	1.21±0.4	1.35±0.7	1.46±0.5
<i>p</i> value	0.4458	0.8014	0.1400	0.0505	0.4267	0.0124	0.0015
Eicosapentaenoic acid							
Well-nourished	0.39±0.2	0.40±0.2	0.42±0.2	0.45±0.2	0.53±0.2	0.59±0.3	0.64±0.3
Undernourished	0.43±0.1	0.45±0.1	0.45±0.2	0.44±0.2	0.50±0.3	0.57±0.4	0.55±0.2
<i>p</i> value	0.5190	0.3771	0.6895	0.8719	0.7786	0.8193	0.2943
Docosahexaenoic acid							
Well-nourished	4.88±1.2	4.60±1.1	4.12±1.4	3.94±1.8	4.45±1.7	4.08±1.0	4.68±1.3
Undernourished	5.03±1.3	4.78±0.9	3.83±1.4	3.51±0.9	3.64±1.4	4.12±1.1	4.28±1.3
<i>p</i> value	0.7806	0.6124	0.5009	0.3522	0.1178	0.9040	0.3453
Palmitoleic acid							
Well-nourished	2.50±1.0	0.88±0.4	0.91±0.6	1.04±0.4	1.54±1.0	1.18±0.4	1.02±0.4
Undernourished	2.86±1.2	2.68±1.3	1.93±1.3	2.18±1.4	1.80±1.1	2.40±1.0	2.60±1.3
<i>p</i> value	0.4345	<0.0001	0.0041	0.0026	0.5424	<0.0001	<0.0001
Myristic acid							
Well-nourished	1.34±0.7	1.44±0.5	1.14±0.6	1.53±0.8	1.26±0.5	1.18±0.5	0.99±0.6
Undernourished	1.17±0.4	1.13±0.4	1.14±0.4	1.12±0.4	1.11±0.5	1.04±0.4	1.04±0.3
<i>p</i> value	0.4570	0.0664	0.9568	0.0538	0.3873	0.3096	0.7339
Palmitic acid							
Well-nourished	39.84±3.6	34.86±4.3	36.48±5.1	39.85±3.7	38.67±5.6	35.64±3.8	34.47±5.0
Undernourished	38.04±6.7	37.91±5.2	38.99±4.4	39.79±4.1	39.91±7.1	38.51±5.5	38.96±6.3
<i>p</i> value	0.4236	0.0783	0.0987	0.9629	0.5625	0.0518	0.0156
Stearic acid							
Well-nourished	14.84±2.0	17.07±2.2	16.16±2.1	15.12±2.0	15.46±1.7	15.84±1.8	16.09±1.6
Undernourished	14.23±1.9	16.60±1.9	15.42±1.5	15.36±2.1	15.44±2.7	15.12±1.5	15.04±1.9
<i>p</i> value	0.4578	0.5136	0.1916	0.7199	0.9841	0.1716	0.0639
Oleic acid							
Well-nourished	10.84±2.4	12.24±2.2	13.47±3.0	12.47±2.6	11.69±2.5	12.07±1.5	11.51±2.0
Undernourished	11.26±2.6	10.60±3.0	13.22±3.5	13.71±2.1	12.99±2.1	11.26±2.0	10.39±2.1
<i>p</i> value	0.6791	0.0932	0.8093	0.1179	0.0936	0.1423	0.0897

Values are listed as mean ± SD. *p* values in bold type are significant. 1 wk: well-nourished *n* = 12, undernourished *n* = 12; 4 wk: well-nourished *n* = 19, undernourished *n* = 15; 6 mo: well-nourished *n* = 21, undernourished *n* = 20; 9 mo: well-nourished *n* = 19, undernourished *n* = 20; 12 mo: well-nourished *n* = 21, undernourished *n* = 17; 24 mo: well-nourished *n* = 22, undernourished *n* = 22; 36 mo: well-nourished *n* = 20, undernourished *n* = 21. wk, week/weeks; mo, months.

synthesized in the skin. These include the long-chain metabolites γ -linolenic acid, arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid [23]. Even though statistical differences between the nutritional and age groups were not always found, broader trends were evident for a number of the ω -6 and ω -3 EFAs that play a key role in skin health.

The percent contribution of LA was lower in all age groups of undernourished children (Table 2). LA, the most abundant ω -6 PUFA in the epidermis, is inserted into ceramides and plays a specific role in barrier function [24]. The intermediate product γ -linolenic acid was higher in these groups, and the subsequent conversion product di-homo- γ -linolenic acid was also higher in most of the age groups of undernourished children. With the exception of the 1-week-old undernourished babies, arachidonic acid was consistently lower in all undernourished infants. Arachidonic acid is the second-most abundant ω -6 PUFA in the epidermis, and is associated with inflammation, growth regulation, and differentiation [23]. ALA was higher in older undernourished children, with significant differences in the 2- and 3-year-olds. There were no apparent differences in the ω -3 derivatives eicosapentaenoic acid and docosahexaenoic acid.

Plasma levels of a number of other nonessential FAs which are also found in the epidermis [25] were also determined (Table 2). Palmitoleic acid was significantly increased ($p < 0.01$) and myristic acid was decreased (ns) in most of the age groups of undernourished children. Palmitic acid was slightly higher in most of the undernourished groups, but the difference was only significant at 36 months ($p < 0.05$). There were no apparent differences in stearic and oleic acid levels between the nutritional groups.

The LA and arachidonic acid results are in agreement with those of studies on children with PEM, in whom lower values are the most consistent finding [2, 16]. Similar to our findings in moderate PEM, Decsi et al. [16] reported higher levels of di-homo- γ -linolenic acid in severe PEM in Romanian children. In contrast, Kozletzko et al. [2] reported decreased values of this derivative in severely undernourished Nigerian children. In most reports, ALA values remain unaffected by PEM [16]. Differences in findings regarding the FA composition in plasma lipids of PEM children may be partly attributed to differences in the severity of PEM as well as between the malnourishment types marasmus, kwashiorkor, or the mixed forms of marasmus-kwashiorkor [2, 16].

Conclusion

Our results stress the importance of nutrition in the development and maintenance of healthy skin. Structural abnormalities in deeper regions of the skin as well as subtle functional changes in the epidermis were observed in moderately undernourished infants prior to clinically relevant skin changes. It can be speculated that it is crucial for the epidermal layer of the skin to functionally compensate and maintain a skin barrier in the face of certain nutritional deficiencies such as reduced EFAs, but that this ability will have its limits.

Even though it was beyond the scope of this study, the possible role of additional factors such as carotenoid antioxidants and the time course of their depletion from a potential reservoir in an infant's subcutaneous fatty tissue could provide valuable insights into the skin's ability to compensate for nutritional deficiencies [26]. Carotenoids are known to play a key protective role in the skin against the increased formation of free radicals associated with system stress; term newborns have maximal levels which decrease over time and are directly related to nutritional conditions [26].

It is important to keep in mind that the layers of the skin are in constant interaction with each other, and that perturbations of the dermis or epidermis, e.g., by infectious or immunological challenge, can impact the functionality of the skin as a whole. This underscores the importance of timely recognition and correction of nutritional deficiencies in infants to protect against skin disease in this fragile population.

Acknowledgements

The authors would like to thank the study staff from the investigational site and the colleagues from the data management and statistics group of bioskin GmbH for their support. This work was supported by Nestec Ltd., Vevey, Switzerland.

Statement of Ethics

The study was approved by Hospital's Ethics Committee and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant's responsible parent or legal guardian before inclusion in the study.

Disclosure Statement

The authors state no conflicts of interest.

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