Abnormalities in Stratum Corneum Function in Patients Recovered from Leprosy


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Key Words
Barrier function  Leprosy  pH  Stratum corneum hydration

Abstract
Background and Objectives: Leprosy involves both the skin and peripheral nervous system. Leprosy patients display an increased incidence of xerosis and altered sensory thresholds, which persist in previously active skin sites. We assessed here whether alterations in stratum corneum (SC) function persist in cured leprosy, and the relationship of epidermal functional abnormalities to each clinical subtype of leprosy.

Methods: A total of 43 cured leprosy subjects and 29 normal control subjects were enrolled in this study. Basal skin surface pH, SC hydration, permeability barrier function as well as barrier recovery rates were measured over previously involved skin sites with a skin physiology monitor. One-way ANOVA and two-tailed Student’s t test were used to determine the significance between 2 groups and 3 or more groups, respectively.

Results: Competent barrier function was observed in all subtypes of cured leprosy subjects. All cured leprosy subjects except those with the borderline tuberculoid type exhibited a significantly lower SC hydration in comparison with normal subjects. Conclusions: A varied spectrum of alterations in SC function remains in all subjects who have recovered from leprosy, but the spectrum of SC functional abnormalities varies with disease subtype.

Introduction

Key stratum corneum (SC) functions include maintenance of permeability barrier homeostasis, SC hydration and SC integrity (the converse of desquamation), which all play important roles in cutaneous function. Studies have demonstrated that permeability barrier function regulates (1) epidermal proliferation, (2) epidermal lipid synthesis and epidermal lipid processing, (3) primary cytokine release, the initial stage of cutaneous inflammation, (4) epidermal antimicrobial peptide expression, (5) and epidermal terminal differentiation (cornification), signaled in part by changes in the epidermal calcium gradient [1–10]. Moreover, SC hydration has been shown to regulate epidermal proliferation, differentiation, inflammation, melanin content, as well as serving as a ‘driver’
of epidermal permeability barrier function [11–16]. The acidic pH of SC serves as a type of functional superre- 
ulator, influencing epidermal permeability barrier homeo- 
stasis, desquamation, skin infections, initiation of in-
flammation in the skin, antimicrobial defense produc-
tion and primary cytokine release [17–22]. SC functions 
are also regulated by a variety of local and systemic sig-
naling mechanisms. For example, the epidermal calcium 
gradient and cytokines are critical regulators of epider-
mal lamellar body secretion, lipid synthesis and DNA 
synthesis [23–27]. Not only changes in barrier function, 
but also a number of environmental stressors, such as in-
creased psychological stress, can alter epidermal struc-
ture and function [28–30].

Leprosy is caused by Mycobacterium leprae, a bacte-
rium that attacks both the skin and the peripheral ner-
vous system. Both residual hyperpigmentation or hy-
popigmentation and reduction or loss of cutaneous sen-
sory function (anesthetic lesions) can remain in treated 
leprosy patients [31–34]. Moreover, xerosis is a prominent 
feature of treated leprosy, a feature that can become ich-
thyosiform in some subjects [35–37]. A reduction in epider-
mal proliferative activity, as measured by thymidine 
incorporation, has been observed in lepromatous leprosy, 
and a decreased SC sphingolipid content has been found 
in leprosy lesions, which further points to potential 
changes in epidermal function in leprosy [38, 39]. How-
ever, epidermal function has not yet been assessed in ei-
ther active or microbially cured leprosy lesions.

Clinical cure in leprosy means only that subjects are 
free of the causative pathogen. Yet, in most subjects who 
have recovered from leprosy, some structural and func-
tional alterations, such as deformities, localized anesthesia 
and dyspigmentation remain, and even worsen [40–43]. 
Even bone lesions have been reported to progress for years 
after termination of treatment, and lepromatous granulo-
as can persist in cured leprosy subjects [44, 45]. Clni-
cally, the skin tends to be drier in cured leprosy than in 
normal subjects. Moreover, cured leprosy subjects may 
have persistent ulcers [46, 47]. In addition, leprosy patients 
generally experience increased psychological stress [48], 
which in turn could compromise epidermal function [29], 
especially in regions where subjects are restricted to re-
 mote rural areas and deprived from social activities. All 
these problems suggest that persistent alterations in SC 
function could occur in microbially cured leprosy sub-
jects, which would predispose these patients to ongoing 
and diverse clinical complications. Accordingly, we mea-
sured epidermal functions, including basal transepider-
mal water loss (TEWL), barrier recovery rates, SC hydra-
tion and skin surface pH in cured leprosy patients. We 
identified multiple alterations in SC function in cured lep-
rosy subjects, which could both complicate rehabilitation.

Table 1. Characteristics of the study subjects

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>LL</th>
<th>BL</th>
<th>BB</th>
<th>BT</th>
<th>TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Females</td>
<td>19</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>76.14 + 1.2</td>
<td>66.74 ± 1.69</td>
<td>67.3 ± 2.13</td>
<td>65.2 ± 2.38</td>
<td>66.58 ± 1.47</td>
<td>70.8 ± 2.27</td>
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**Subjects and Methods**

**Experimental Subjects**

A total of 29 normal control subjects, aged 66–88 years (10 males, 19 females), and 43 subjects, whose forearms had previ-
ously been involved in leprosy and who had recovered from lep-
rosy, aged 49–86 years (31 males, 12 females), were enrolled in this 
study (table 1). The leprosy cases included multiple lepromatous 
(LL), borderline lepromatous (BL), borderline (BB), borderline tu-
berculoid (BT) and tuberculoid (TT) types (table 1), which were 
determined by both histology and clinical symptoms when pa-
tients were first admitted to the leprosy control center located in 
a remote rural area. Control subjects had no skin disorders nor 
systemic diseases such as diabetes and renal disease, which could 
influence epidermal function. In addition, skin care products 
were not applied to measurement sites for at least 24 h, and no 
soap wash, which could affect SC pH, hydration and barrier func-
tion, for at least 4 h prior to skin measurements. All human 
research procedures were conducted according to a protocol ap-
proved by the local human ethnical research committee (Dalian 
Skin Disease Hospital, Liaoning, PR China).

**Functional Studies**

Skin surface pH, TEWL, and SC hydration were measured on 
the forearm (flexor side, about 10 cm above wrist) with a Courage-
Khazaka MPA5 (CK Electronic GmbH, Germany), as described 
previously [48, 49]. In addition to baseline readings, TEWL was 
measured at 0 and 3 h after acute barrier disruption by repeated 
tape-stripping to assess barrier recovery. Before all measurements 
were taken, subjects rested for 30 min in a temperature-controlled 
room (22–24°C), with a relative humidity of 45–55%. These stud-
ies were performed in early December.
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Statistics
A two-tailed Student’s t test was used to determine the significance between 2 groups, and a one-way ANOVA was used to determine the significance when 3 or more groups were compared. Data are expressed as means ± SEM.

Results

Competent or Supernormal Barrier Function in Subjects Who Had Recovered from Leprosy
To determine whether epidermal permeability barrier function is abnormal in cured leprosy, we first measured basal TEWL. Basal TEWL was significantly lower in the cured leprosy group as a whole than in normal controls (fig. 1a; \( p < 0.0001 \)), but basal barrier function did not differ significantly from normal controls in BT and TT cases (fig. 1b). However, the TEWL in BL, BB and LL types was significantly lower than in normal controls (fig. 1b; \( p < 0.01 \)), and basal TEWL was also significantly lower in BL and BB types than in TT type subjects (fig. 1b; \( p < 0.05 \)). These results show that basal permeability barrier function varies according to the prior type of leprosy. Although cured leprosy subjects showed competent or superior basal permeability barrier function, we next determined whether barrier recovery kinetics differed among cured leprosy and normal subjects. In contrast to basal barrier function, there were no significant differences in barrier recovery kinetics among cured leprosy and normal subjects (fig. 2).

Reduced SC Hydration in Subjects Who Had Recovered from Leprosy
Clinical observations suggest that the skin of cured leprosy subjects is drier than normal. Hence, we next...
measured skin capacitance, an indicator of SC hydration. In contrast to basal permeability barrier function, which was supernormal in some cured leprosy subjects, SC hydration was significantly subnormal in cured leprosy as a whole compared to normal subjects (fig. 3a; p < 0.0001). Moreover, BL, BB and LL types, which showed the best basal barrier function among the 5 subtypes, displayed the lowest SC hydration (fig. 3b; p < 0.01 vs. normal), but SC hydration did not differ significantly among the 5 leprosy subtypes. Finally, SC hydration in BT type leprosy did not differ significantly from normal subjects (fig. 3b). These results suggest that SC hydration is impaired in most cured leprosy subjects.

**Increased Skin Surface pH in Subjects Who Had Recovered from Leprosy**

We next assessed skin surface pH in cured leprosy subjects. Skin surface pH was significantly elevated in the cured leprosy group as a whole (fig. 4a) and in all subtypes of leprosy (fig. 4b; p < 0.01). Yet, in contrast to permeability barrier function and SC hydration, there were no significant differences in skin surface pH among the 5 subtypes of cured leprosy.

**Discussion**

The importance of epidermal protective functions is well appreciated [49], and measurements of SC function can be an indicator of the clinical status of skin disease [50], but little is known about SC function in leprosy subjects. Here, we examined epidermal permeability barrier function, skin surface pH and SC hydration in 5 different subtypes of microbially cured leprosy subjects. Our results demonstrated that the SC hydration was significantly lower in cured leprosy subjects although their barrier function was competent. Interestingly, BT and TT cases showed better SC hydration in comparison with LL, BL and BB subjects.
Regarding the mechanism by which SC hydration was reduced, defective sweat gland function is likely to be a key contributor. It has been demonstrated that the sweat gland response to stimulation was altered in active leprosy lesions [51–54]. In addition, a reduced content of water-soluble, osmotically active components has been found in the SC of active leprosy patients [55]. But whether these alterations persist in microbially cured leprosy subjects is not known. Furthermore, SC lipids, especially sphingolipids, are important regulators for SC hydration [56]. It has been shown that the SC sphingolipid content declines in leprosy patients [39]. Decreased SC hydration could have a significant impact on cutaneous function. It has been demonstrated that lower SC hydration alone can increase epidermal DNA synthesis and amplify epidermal proliferation induced by repeated barrier abrogation [11, 57]. Conversely, topical moisturizers reduce epidermal proliferation and decrease epidermal thickness in both photodamaged skin and psoriasis [12, 58]. Moreover, decreased SC hydration could increase cytokine release [59, 60], which in turn could exacerbate cutaneous inflammation, thereby complicating rehabilitation in leprosy. Thus, increased epidermal proliferative activity and epidermal thickness in leprosy might result from the decreased SC hydration. Hence, improving SC hydration could be a valuable treatment option for patients with microbially cured leprosy.

Acknowledgements

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References

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