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Effect of Systemic Treatment with Cholesterol-lowering Drugs on the Skin Barrier Function in Humans

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The intercellular lipids of stratum corneum are predominantly formed by cholesterol, ceramides and free fatty acids. Cholesterol synthesis is inhibited by statins, cholesterol-lowering drugs (lovastatin, pravastatin, simvastatin). The present study was undertaken to examine the effect of these drugs on skin barrier function. Knowledge about the effect on epidermis of systemic inhibition of cholesterol synthesis may improve our understanding of the skin barrier function. Seventeen statin-treated subjects were compared to controls. All were patch-tested with sodium lauryl sulphate (SLS), and the skin was evaluated after 24 h and after 7 days by measurement of transepidermal water loss (TEWL), erythema and visual scoring. After 24 h as well as after one week erythema was significantly less pronounced in the statin-treated group than in controls ($p<0.001$). No significant differences in TEWL were found between the groups at any time. The results imply a decreased bioavailability of SLS in the statin-treated group, while no evidence for an altered permeability barrier to water was found. ***Key words: cholesterol synthesis; SLS; TEWL; erythema.***

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The water permeability barrier of the skin is regulated primarily by the lamellar arrangement of lipid bilayers (1, 2). This intercellular lipid membrane bilayer system is derived from lamellar bodies, synthesized within spinous and granular cells. The lipids are predominantly formed by ceramides, free fatty acids and cholesterol, and an imbalance in the stratum corneum lipid composition may cause abnormal barrier function (3).

The synthesis of epidermal lipids is modulated by the skin barrier function, and, normally, disruption of the barrier will result in an increased synthesis (2, 4). The synthesis of cholesterol may, however, be inhibited pharmacologically. The rate-limiting enzyme in the cholesterol synthesis is hydroxy-methyl-glutaryl CoA-reductase (HMG CoA-reductase), which is inhibited by the group of cholesterol-lowering drugs called statins (lovastatin, pravastatin, simvastatin). Local application of lovastatin on naked mice was earlier reported to delay barrier repair (3). The present study was undertaken to examine the skin barrier function in humans treated with statins. Examination of the effects on the skin barrier of a systemic, pharmacological inhibition of cholesterol synthesis will improve our understanding of stratum corneum lipids and barrier function. To our knowledge there are no studies available on the effect of these drugs on the composition of the stratum corneum lipids.

The observation that side effects to hypercholesterolaemic drug therapy include dry and scaly skin dates back more than 25 years (5). Nicotinic acid and azacosterol, both drugs used in the past to lower serum cholesterol, caused generalized dry skin and palmoplantar keratoderma, respectively. Today, statins are the most commonly used hypercholesterolaemic therapeutic agents, and in spite of their widespread use, only a few reports on side-effects on the skin are available (6).

MATERIAL AND METHODS

Participants

Seventeen patients with hypercholesterolaemia treated with cholesterol-lowering agents (lovastatin 20–80 mg daily or simvastatin 10–40 mg daily) for more than 3 months participated in the study. Subjective evaluation of dry skin was noted. Age and sex distribution as well as smoking habits are shown in Table I. Patients were consecutively recruited from the Department of Internal Medicine, Elsinore Hospital, and referred from a consulting cardiologist. Nine patients received other medications: 5 were treated with calcium antagonists, 3 with β-blocking agents, 1 with an ACE inhibitor and 1 with clonidine. One patient had type 2 diabetes mellitus. Patients with psoriasis, atopic dermatitis or ichthyosis were excluded from the study.

Seventeen healthy volunteers served as controls (Table I). Informed consent was obtained from all participants, and the study was approved by the local ethical committee.

Methods

Basal values of transepidermal water loss (TEWL), electrical capacitance and erythema were obtained by measurement on the flexor aspect of the left lower forearm, using the following non-invasive methods:

TEWL was measured using an Evaporimeter (Servo Med, EP1, Stockholm, Sweden) (7). The sensors of the Evaporimeter determine the water vapour pressure gradient of the boundary layer between the skin surface and ambient air in order to quantify the diffusion of water through the skin as the TEWL. The probe was hand-held using an insulating glove to avoid heating of the probe. Values were displayed on a pen recorder, and the mean value during the period 30–60 s after application of the probe to the skin was read. A probe protection cover (no. 2107, supplied with the Evaporimeter) was used, and all measurements were performed inside an incubator to avoid convection of air, according to the guidelines of the Standardization Group of the European Society of Contact Dermatitis (8).

Table I. *The distribution of sex, age, smoking habits and subjective registration of skin dryness is given for 34 participants, 17 statin-treated patients and 17 controls. Age is given as medians and 25/75 percentiles.*

	Sex ratio ♀/♂	Age (range)	Smoking yes/no	Skin dryness
Statin-treated	7/10	52 (34–67)	11/6	11/6
Controls	7/10	45 (31–65)	7/10	2/15

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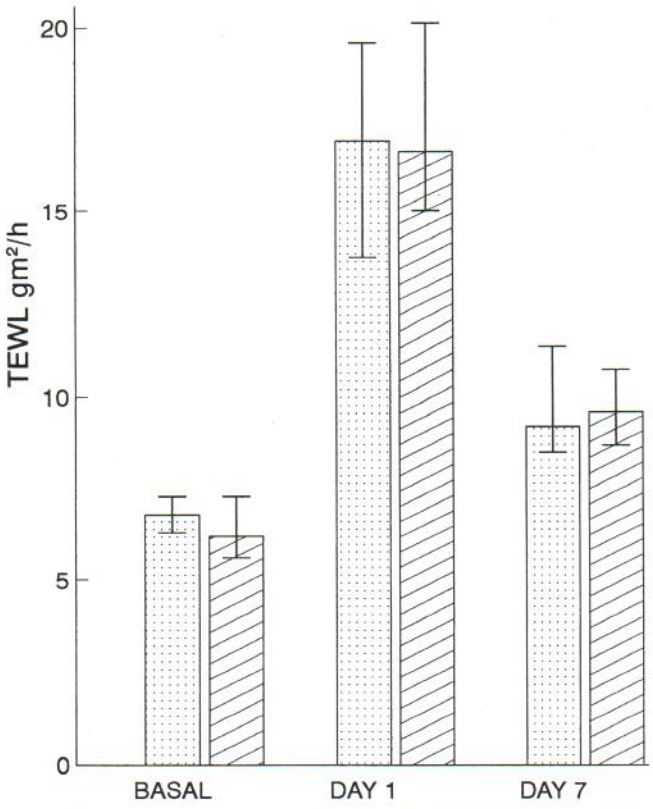

Fig. 1. TEWL in statin-treated patients and controls before SLS exposure, after 24 h and after 7 days. No significant difference between patients and controls was found. Values are given as medians and 25/75 percentiles. ▨ Patients, ▨ Controls.

Variation in quantification of irritant patch test reactions by non-invasive measuring methods and comparison between methods have been presented elsewhere (9, 10).

Electrical capacitance was measured by a Corneometer CM 420® (GMBH, Köln, Germany) (9). The corneometer measures the electrical capacitance of the outer epidermis. The probe of this instrument is a plastic foil-covered brass grid, which functions as one electrode, while the skin functions as the other, and registers hydration down to a depth of about 0.1 mm (11). In an earlier study, considerable variations of electrical capacitance were found when quantifying irritant patch test reactions, and for this reason measurements in this study were restricted to basal values (12).

Erythema index was measured using a Derma Spectrometer (Cortex Technology, Hadsund, Denmark). This method is based on the amount of reflected red and green light from the skin (13). The spectrometer was placed in contact with the site to be measured, with minimal pressure on the skin.

Visual scoring of erythema was performed according to the following scale: 0 = no reaction; ½ = very weak erythema; 1 = weak erythema; 2 = marked erythema, 3 = severe erythema.

Irritant trauma

Closed patch tests with 60 μl of aqueous solution of 0.5% sodium lauryl sulphate (SLS, Sigma, 99% purity) on filter discs were applied on the flexor aspect of the left forearm, using large Finn chambers (diameter 12 mm) on Scanpore tape, and left on for 24 h. Skin reactions were evaluated 1 h after removal of the Finn chambers, and again after 1 week, by measurement of TEWL and erythema index and by visual scoring.

The study was carried out in the period May 1993–January 1994. Each patient and their sex- and age-matched control were examined within 4 weeks of each other. The relative humidity varied between 26–46%, and the room temperature was kept at 20–22°C. Measurements were expressed as the mean values of 2 recordings for evaporimetry and of 3 recordings for electrical capacitance and erythema index.

Statistics

The Mann-Whitney test for unpaired samples was used for statistical analysis. The chosen level of significance was $p < 0.05$.

RESULTS

None of the participants had any ichthyosiform skin changes. After information of the intention of the study, 11 patients complained of slight or severe skin dryness, versus 2 of the controls.

The results of the study are shown in Figs. 1–2.

Basal values: No significant differences were found between statin-treated subjects and controls considering basal electrical capacitance (statin-treated 73 a.u. (70–78), controls 77 a.u. (73–86)), basal TEWL or basal erythema index.

After SLS exposure (24 h): No significant differences in TEWL after SLS exposure were found between statin-treated subjects and controls (Fig. 1). After SLS exposure erythema index was significantly increased in controls as compared to the statin-treated group ($p < 0.001$) (Fig. 2). The increase in erythema index was also significantly lower in the statin-treated group than in controls ($p < 0.01$). Visual grading of erythema

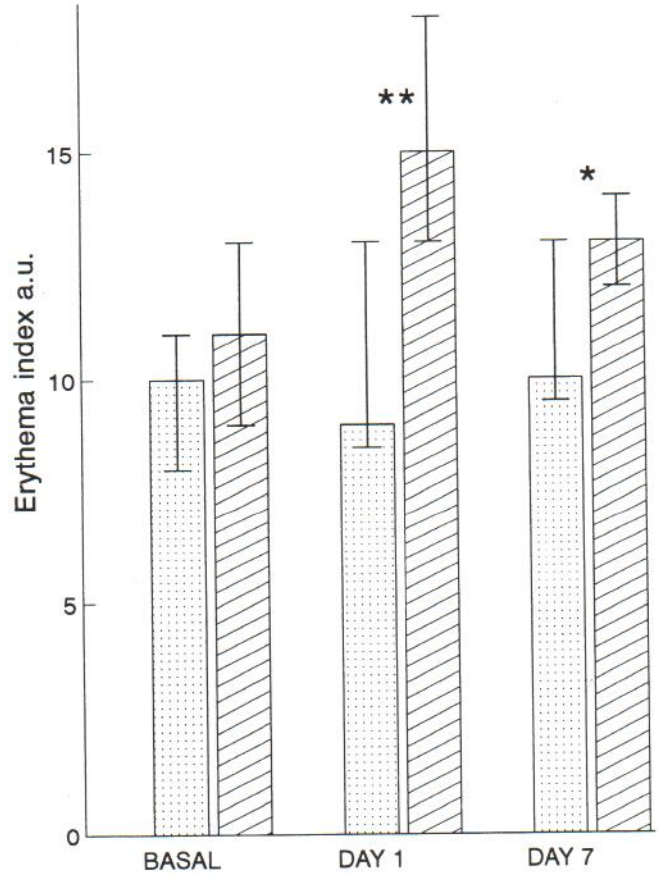

Fig. 2. Erythema index in statin-treated patients and controls before SLS exposure, after 24 h and after 7 days. Erythema values were significantly higher in controls than in patients after 24 h as well as after 7 days (* = $p < 0.01$, ** = $p < 0.001$). No significant difference was found before SLS exposure. Values are given as medians and 25/75 percentiles. ▨ Patients, ▨ Controls.

showed significantly more pronounced erythema in the control than in the statin-treated group ($p < 0.05$).

After SLS exposure (1 week): No significant differences in TEWL one week after SLS exposure were found between statin-treated subjects and controls (Fig. 1). Erythema index was still significantly increased in controls as compared to the statin-treated group after one week ($p < 0.01$) (Fig. 2). No statistically significant difference in visual grading of erythema between the groups was found.

DISCUSSION

No objective skin changes due to hypercholesterolaemic drug therapy were found. No differences in basal TEWL, basal erythema index or basal electrical capacitance were found between statin-treated subjects and controls. The response to SLS was found to be decreased in statin-treated subjects when evaluated by measurement of erythema, but not when evaluated by measurement of TEWL. The difference in erythema observed was not found to be related to smoking or to medication other than statins.

The normal level of basal TEWL found in the statin-treated group indicates that the permeability barrier to water was not affected by cholesterol-lowering drug medication (statins). Basal values of electrical capacitance were without significant differences between the groups, and no evidence was found for decreased hydration of stratum corneum in the statin-treated group.

When studying the barrier function by patch-testing with SLS, we found no difference in skin response when evaluated by measurement of TEWL. Increase in TEWL after SLS exposure is generally accepted to reflect the degree of barrier disruption caused by the irritant (14), although it may also reflect an increased water-binding capacity of stratum corneum (15). The erythema response to SLS was, however, found to be significantly reduced in the statin-treated group as compared to controls, when evaluated objectively by measurement of erythema index, as well as by visual scoring of erythema. The impaired erythema response in the statin-treated group, reflecting a lack of vascular response, could be due to a decreased penetration of SLS in the statin-treated group. Since erythema after one week was still more pronounced in controls than in statin-treated subjects, the difference cannot be explained as a delayed penetration of SLS. Even if the permeability barrier for water seems undisturbed, it is possible that the barrier permeability for other substances may be affected by hypercholesterolaemic drug therapy, depending on the structure and penetration route of the substance. The impaired erythema response could also be interpreted to reflect a decreased skin reactivity. Statins are, however, not known to have any such pharmacological effects, and the difference observed was not found to be related to smoking habits or to medication other than statins. Decreased skin reactivity in old as compared to young persons has been reported (16), but no statistically significant difference in age between the groups was found in the present study (Table I). Decreased skin reactivity has also been reported in severe chronic illness (17). All participants in the present study had a normal daily life with social activities, and most were fully employed.

In a recent study by our group (18), the skin barrier function in patients with recessive X-linked ichthyosis was studied. In this disease the cholesterol/cholesterolsulphate-ratio in stratum corneum is disturbed, leading to disorder of cornification. An impaired erythema response to SLS was also found in patients with ichthyosis, probably due to decreased bioavailability of SLS, but in these patients the TEWL response to SLS was also decreased. Whether a common mechanism for the impaired erythema response in ichthyosis patients and in statin-treated subjects exists is not known.

Under normal conditions, not influenced by cholesterol-lowering agents, epidermal cholesterol may be supplied from systemic sources and delivered to peripheral tissues as serum LDL cholesterol, or it may be synthesized de novo in the epidermal cells. In most cell types cholesterol is delivered from systemic sources, but epidermal sterol metabolism seems to deviate from this model. Epidermal HMG CoA-reductase activity is probably not regulated by serum LDL, but more likely by the current function of the permeability barrier (3, 4). Today, very little information is available on the effect on epidermis of the inhibition of cholesterol synthesis by drug therapy, and this is the first study on skin barrier function in subjects treated with cholesterol-lowering drugs (statins). Functional studies of skin barrier function after pharmacological inhibition of cholesterol synthesis may contribute to our understanding of stratum corneum lipids and barrier function. To further improve this understanding, future studies should include more direct measurements of skin penetration.

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