

Epidermal hydration and skin surface lipids in patients with long-term complications of sulfur mustard poisoning

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Background: Despite almost the three decades passed since the chemical attacks of Iraqi's army against the Iranian troops, some veterans are still suffering from long-term complications of sulfur mustard (SM) poisoning, including certain skin complaints specially dryness, burning, and pruritus. We thus aimed to evaluate the skin's water and lipid content in patients with a disability of >25% due to complications of SM poisoning and compare them with a matched control group. **Materials and Methods:** Sixty-nine male participants were included in this study; 43 SM-exposed patients, and 26 normal controls from their close relatives. The water and lipid content was measured in four different locations: Extensor and flexor sides of forearms and lateral and medial sides of legs by the Corneometer CM 820/Sebumeter SM 810. Collected data was analyzed and $P \leq 0.05$ was considered as statistically significant. **Results:** The mean age of the patients and controls was 49.53 ± 11.34 (ranges: 40-71) and 29.08 ± 8.836 (ranges: 15-49 years), respectively. In the veterans group, the main cutaneous complaint was itching and skin dryness. Cherry angioma, dry skin, and pruritus were significantly more common in the SM-exposed cases than in the controls. ($P = 0.01, 0.05, \text{ and } 0.04$, respectively). The moisture and lipid content of all areas were lower in the SM-exposed group, but it was only significant in skin sebum of lateral sides of legs ($P = 0.02$). **Conclusion:** Exposure to SM could decrease the function of stratum corneum and lipid production as a barrier, even after several years of its exposure.

Key words: Epidermal hydration, skin lipid, sulfur mustard, xerosis

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INTRODUCTION

Sulfur mustard (SM) or (bis-[2-chloroethyl] sulfide) was the most widely used chemical warfare agent in the past century. It was first employed in a large scale during the world war one. It was then used sporadically until the Iraqi army employed it on a large scale against the Iranian combatants and even civilians in 1983-1988.^[1]

SM is called a blistering agent, as the skin blister is the main local toxic effect. SM is absorbed by inhalation, through the skin, or via the gastrointestinal tract following consumption of contaminated foods. After

absorption, SM undergoes intramolecular cyclization to form an ethylene episulfonium ion intermediate to react with and alkylates nucleic acids, particularly DNA and proteins. These reactions induce cell toxicity which may lead to cell death.^[2]

The skin, eyes, and respiratory system are the three major target organs of SM poisoning.^[1] The lipophilic nature of SM and the affinity of the skin for lipophilic substances make the skin a fairly efficient transporting system for this agent. Despite over two decades after SM-exposure, the veterans still have certain skin complaints, mainly dryness, burning, and pruritus. Delayed skin complications of SM-exposed Iranian veterans have

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previously been reported.^[2-6] Davoudi *et al.* investigated the transepidermal water loss (TEWL) following SM-exposure in humans and showed the alteration in the function of stratum corneum as a barrier to water loss and also skin sebum years after SM-exposure.^[7,8]

Epidermal dehydration and lack of skin surface lipid contents may be responsible for the skin complaints of the SM veterans, particularly dry skin and pruritus. It was thus aimed to evaluate the epidermal hydration and skin surface lipid content in patients with a disability of >25% due to complications of SM poisoning^[9] and compare them with a normal control group.

MATERIALS AND METHODS

Study design and participants

This case-control study was conducted on patients with moderate to severe (disability of >25%) complications of SM poisoning 23 years after exposure during the chemical warfare attacks of Iraqi army against the Iranian troops in 1983-1988.^[1] Following approval of the Medical Ethics Research Committee of the Mashhad University of Medical Sciences and coordination with the veteran foundation of Khorasan Razavi with project number 88767, written informed consents were obtained from all subjects. We reviewed the files and selected the patients who met the following criteria:

- Documented exposure to SM, as confirmed by toxicological analysis of their urine and vesicular fluid during the war.
- Significant clinical complications of SM poisoning in one or more of the major target organs (skin, eyes, and/or respiratory system) and obtained >25% disability due to complications of SM poisoning according to the Veteran's Medical Review Committee criteria.

Patients with a known skin disease before exposure to SM and those with a proven systemic illness were excluded.

Forty-five male subjects fulfilled the above criteria. Among these, 43 patients volunteered to participate in this study and signed the written informed consent. We invited the first or second degree relatives of these veterans who did not have any history of exposure to SM or any other chemical agent to participate in our study as the control group, in order to reduce the probability of genetic susceptibility for some skin conditions such as skin dryness, atopic dermatitis, or cherry angioma. Among them 26 healthy males had our criteria and accepted to participate. The patients were hospitalized in the Toxicology Ward of Imam Reza Hospital, Mashhad, Iran and underwent a thorough medical history interview and physical examinations by a medical toxicologist (corresponding author) and different

clinical specialists. Two experienced dermatologists were investigated the skin complications of SM poisoning based on a thorough history and physical examination and completed related questionnaire.

Considering the results of previous studies on SM veterans, the most common location of skin dryness and itching was reported to be on extremities, therefore, we chose four different locations as the extensor and flexor sides of the forearm and lateral and medial sides of the legs for further assessment, using the following noninvasive biophysical methods.

Skin sebum and hydration measurement methods

Measurement of biophysical characteristics of the skin that means skin surface lipids and epidermal hydration were performed under standardized conditions; that is, a room temperature of 20°C and a relative humidity level of 35-40%. Before the measurements, the patients were given time to adapt to room conditions without covering the measurement sites with clothes. The measurements were always performed by the same investigator. On the day of examination, the skin was not washed and nothing was applied to the skin surface. Patients were instructed not to apply any preparation to the site of examination from 1-week before the investigation. In all subjects, the measured positions were free of eczematous involvement. All measured values were expressed as the mean of three recordings of neighbored skin area to avoid measuring inaccuracies. To determine the epidermal hydration, the Corneometer CM 820 (Courage and Khazaka Electronic GmbH, Germany) was used, and the skin lipids were measured by the Sebumeter SM 810. The Sebumeter SM 810 (Courage and Khazaka Electronic GmbH, Germany) was used for quantitative measurements of skin surface lipids composed of sebum and corneal lipids. It consists of a fat-stain photometer that measured the level of light transmission of a plastic sheet coated with sebum. This method was independent of humidity. A probe was pressed on to the skin region under investigation for 30 s at a constant pressure. The light transmission represented the sebum content on the surface of the examination area. The variation of light transmission was proportional to the quantity of lipids absorbed. The Corneometer CM 820 determined the humidity level of the stratum corneum by measuring electrical capacitance. This measurement was based on the totally different dielectric constant of water and other substances. The probe was applied vertically on the skin for 1 s at a constant pressure. Alterations of epidermal skin hydration lead to a change in capacitance of the measuring condensator. The degree of epidermal skin humidity was indicated in system-specific units. One unit represented a water content of stratum corneum of 0.02 mg/cm².^[10-12]

For comparisons of skin's sebum and hydration between the veterans and healthy controls, three measurements were performed on clinically normal appearing skin on four different locations: Extensor and flexor sides of the forearms and lateral and medial sides of the legs.

Statistical analysis

All data were statistically analyzed by SPSS (version 11.5) for Windows TM Version Software Package (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics with the central tendency and distribution measures were used. Data related to moisture and lipid between the veterans and control groups were checked for normality by Kolmogorov-Smirnov test then independent *t*-test analysis for parametric data or Mann-Whitney test for nonparametric data were used. Furthermore, association between the qualitative variables was analyzed by χ^2 test. A two-sided $P \leq 0.05$ was considered as statistically significant.

RESULTS

Forty-three SM-exposed veterans and a control group consisting 26 of their relatives enrolled in this study. The mean age of the patients and controls were 49.53 ± 11.34 (range: 40-71) and 29.08 ± 8.836 (range: 15-49 years), respectively. In the veterans group, the main cutaneous symptoms reported were itching without a burning sensation in 14 patients (32.6%), skin dryness in 24 (55.8%), burning sensation in one (2.3%), and both an itching and burning sensation in two (4.7%) cases, and only three patients were symptom-free (7%). Twenty-nine (67.4%) complained from hyperhidrosis, especially in the flexor area. In 41.9% of the veterans regions of itching, burning and hyperhidrosis of skin were compatible with the area of blisters and erythema in their acute phase of exposure to SM. None of these patients showed abnormality in thyroid function test or any other systemic illnesses, which could cause dry skin or hyperhidrosis. The clinical findings of the skin and their frequencies in the two studied groups were summarized in Table 1.

It is important to note that most of the patients had a combination of two or three of these complications. Cherry angioma ($P=0.01$), dry skin ($P=0.05$), and pruritus ($P=0.04$) were significantly more common in the SM-exposed cases than in the controls. While hyper- and hypo-pigmentations, as well as atrophy, and hyperhidrosis were more common on the sites of healed skin blisters, other abnormal findings were observed on a more widespread distribution. Cherry angiomas in the veterans were multiple and large. As it is seen in Figure 1.

Table 2 represents the comparative results between the two groups. There were some differences in moisture and



Figure 1: Eruptive multiple and large cherry angioma on the trunk

Table 1: The clinical findings and their frequencies in the SM veterans and the control group

Clinical findings	SM veterans n (%)	Control n (%)	P
Cherry angiomas	25 (58.1)	3 (7)	0.001
Dry skin	24 (55.8)	8 (30.8)	0.051
Pruritus	14 (32.6)	3 (11.5)	0.044
Seborrheic keratosis	12 (27.95)	3 (7)	0.011
Seborrheic symptoms			
Dermatitis	1 (2.3)	11 (25.6)	0.001
Pityrosporum folliculitis	3 (7)	8 (18.6)	0.001
Scalp dandruff	7 (16.3)	4 (9.3)	0.60
Multiple melanocytic nevi	8 (18.6)	5 (11.6)	0.94
Dyspigmentation (poikilo derma)	7 (16.3)	1 (2.3)	0.24
Scar			
Atrophic	7 (16.3)	0 (0)	0.92*
Hypertrophic	1 (2.3)	1 (2.3)	
BCC	1 (2.3)	0 (0)	0.37

*This result has been calculated after summation of data related to items of atrophic and hypertrophic scar; SM = Sulfur mustard; BCC = Basal cell carcinoma

Table 2: Comparison of moisture and lipid content of stratum corneum between the SM exposed patients and the controls on four different locations: Extensor and flexor sides of forearms and lateral and medial sides of legs

Variable	Group		P
	Control	Patient	
Lipid ($\mu\text{g}/\text{cm}^2$)			
Flexor	2.53 \pm 3.58	1.16 \pm 1.91	0.16
Extensor	3.15 \pm 3.46	2.52 \pm 2.68	0.39
Medial	1.61 \pm 1.62	1.11 \pm 1.12	0.13
Latereral	1.80 \pm 1.78	0.95 \pm 1.14	0.02
Moisture (unit)			
Flexor	27.62 \pm 6.11	29.14 \pm 9.27	0.45
Extensor	31.50 \pm 9.03	31.12 \pm 12.92	0.99
Medial	26.93 \pm 10.29	27.81 \pm 10.11	0.72
Latereral	28.82 \pm 9.76	27.50 \pm 9.12	0.57

All of P values assessed by independent *t*-test; Significant values are in bold. SM = Sulfur mustard

lipid content of all areas between the two groups, but these differences were only statistically significant in lateral side of the legs for lipid content ($P = 0.02$). It means that lipid content in this particular area was lower in SM-exposed patients than the controls.

DISCUSSION

Over 100,000 Iranian combatants and civilians were exposed to SM during the Iran-Iraq war (1983-1988), and one-third of them are still suffering from the long-term complications.^[13]

SM is an oily lipophilic agent who easily penetrates the skin within 3-5 min of contact. The severity of skin lesions from exposure to mustard gas is dependent on the dose and duration of exposure, climates (temperature and humidity), and individual susceptibility.^[11]

Certain regions of the skin such as the genitalia, axilla, and buttocks are more vulnerable to SM. The skin of these sensitive areas is generally thinner and has more hair follicles which naturally facilitate SM penetration. Furthermore, because of the film of moisture in its surface, hot sweaty skin aggravates the damage from SM vapor.^[14]

Even after many years of SM-exposure one of the remarkable findings in this research which has also been noted in previous studies,^[1-4] the prevalence of the patients' major complaints of continuous itching or burning sensation in the primary exposed areas (55.8%). Moreover, in 41.9% of the cases, locations of chronic complaints were compatible with the area of blisters at the acute phase of SM poisoning. At present, the late cutaneous SM complications in our patients include hyper- and hypo-pigmentation, eczema, atrophy, and dry skin, which is consistent with previous reports.^[2,3,5]

Although atrophic scars were commonly found on the sites of healed SM-exposure, hypertrophic scars were considerably less frequent (16.3% vs. 2.3 %) in our study. Hyper-pigmentation, atrophy, and hypo-pigmentation were recorded in 55%, 27.5%, and 25%, respectively, in Hefazi *et al.* study.^[2] In our study, dyspigmentation and poikiloderma were more significant disorders than pure hyper- or hypo-pigmentation of the previously SM-exposed areas.

Similar to previous studies, multiple cherry angiomas were found to be more common in the veterans group which were also interestingly multiple and larger than their usual presentation.^[15-17]

Furthermore, some studies have been suggested the causal association between the acute exposure to SM and skin cancer.^[18-20] We found only one case of basal cell carcinoma with two lesions on the scalp, which has not been reported in previous studies. Thus, based on our results and those of Firooz *et al.*, although SM is a well-known carcinogenic substance but it could be concluded that cutaneous malignancies appear to be an uncommon consequence of SM-exposure.^[5] However, it may need a longer period of time for a malignancy to occur.

Skin dryness and itching have been reported as the most common delayed complaints of SM veterans in several studies. Moreover, the water content of the stratum corneum and the skin lipids act together as a barrier to the environment. If this balance is disrupted, a dermatologic condition known as "dry skin" ensues, a phenomenon which is observed, particularly in patients with atopic dermatitis, a chronic, relapsing, and pruritic form of dermatitis. To note, a defective barrier function, both in rough and in clinically healthy skin have been shown in atopic skin.^[21,22] Therefore, we decided to examine both the skin hydration and the skin surface lipids in SM-exposed patients to determine the extent of which these factors cause such a clinical features.

To date, there has been only one study by Davoudi *et al.* that investigated skin hydration and TEWL following SM-exposure in humans. They showed the alteration in the function of stratum corneum as a barrier to water loss and also skin sebum years after exposure. However, contrary to their expectations, trans-epidermal water loss was higher in the control group and lipid content was more in SM-exposed patients.^[7,8]

In our study, the skin surface lipids showed a decrease on all studied body locations in the veterans group in comparison to the controls. However, this difference was only significant in lateral side of the legs. The importance of sphingolipids and other neutral lipids for the water retention properties in the stratum corneum has well known for years. The physiological properties, relative composition, and the specialized intercellular physiological lipids within the intercellular lamellar lipid membrane serve to sustain stratum corneum water content, and modify the rate and magnitude of TEWL.^[23] The progression from normal skin to clinically evident xerosis and subsequent eczematous changes occur in a stepwise fashion so the epidermal abnormality is not just a secondary phenomenon but a critical trigger of inflammatory skin disease such as atopic dermatitis.^[24]

Based on our results and as well as Davoudi *et al.* it can be concluded that the clinical appearance of dry skin in patients with SM-exposure and their major symptoms, pruritus, could not simply explain by a change in hydro-lipid film of the stratum corneum. Perhaps similar to complex pathophysiology of pruritus in some other situations such as uremic pruritus, in which xerosis is common but pruritus does not necessarily correlate with xerosis. We could not simply explain the mechanism of itching and skin dryness in the SM-patients.

So far, the etiology of pruritus in the SM-exposed patients is poorly understood, thus, the possible role of causes other than xerosis such as neuropeptides, pro-inflammatory cytokines such as interleukins, pruritogen, mediators such

as substance P, or even nonimmunologic factors such as emotional stress must be considered. This idea is justifiable with references to several articles that examined the role of some anti-inflammatory oral or topical therapeutic agents on the inflammatory mediators of SM patients that in the majority of them were consistent with this hypothesis.^[25-30]

CONCLUSION

The clinical appearance of dry skin in patients with SM-exposure and their complaints of pruritus could not simply explain by a change in the hydro-lipid film of the stratum corneum. Perhaps similar to complex pathophysiology of pruritus in some other situations, such as uremic pruritus in which, xerosis is common but pruritus does not necessarily correlate with xerosis. We could not simply explain the mechanism of itching and skin dryness in the SM-patients. The etiology of pruritus in the SM-exposed patients is poorly understood, thus, the possible role of causes other than xerosis such as neuropeptides, pro-inflammatory cytokines such as interleukins, substance P, or even nonimmunologic factors such as emotional stress may be involved. However, our findings reveal that exposure to SM could decrease the function of stratum corneum and lipid production as a barrier, even after several years of its exposure.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

PL had substantial contributions to the conception or design of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MM had substantial contributions to the conception or design of the work, conducting the study, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. SRM contributed the conception or design of the work, drafting and revising the draft, and agreed for all aspects of the work. HYZ contributed in analysis, or interpretation of data for the work, and agreed for all aspects of the work. AMZ contributed in drafting the work and revising the draft and agreed for all aspects of the

work. SGM contributed the design of the work, drafting and revising the draft, and agreed for all aspects of the work. MBM had substantial contributions to the conception or design of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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