IRRITANT OCCUPATIONAL DERMATITIS: HIGHLIGHTING THE ROLE OF THE SKIN'S PH

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Summary

Occupational contact dermatitises have a chronical evolution, due to absence of an early diagnosis and curative treatment. Identifying the skin's pH has many practical applications in screening methods, but also in the prevention area, being demonstrated that a normal ranged pH is involved in protecting the skin from external aggresion. Therefore, changes in skin's pH level will lead to an altered skin barrier. In this sense, the risk awareness at workplace along with protective measures (protective creams, work protective equipment) will reduce the incidence of irritant contact dermatitis.

Key words: *irritant dermatitis, occupational dermatitises, skin's pH.*

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Introduction

In 1895 Josef Jadassohn described for the first time the contact dermatitis in subjects exposed to mercury. The contact dermatitises (CD) represent 4–7% of the total cases that requier dermatologist's attention, represent > 50 % of the overall occupational diseases and represent the forms most commonly seen in terms of occupational dermatitises. [1, 2]

Discussions

Contact dermatitis develops after a cutaneous inflammatory reaction produced by the cutaneous cells (keratinocytes, Langerhans cells, fibroblasts, mastocytes, macrophages, endothelial cells) or leucocytes that adhere to tissue injury and secrete proinflammatory mediators such as cytokines and chemokines. The cutaneous inflammatory reaction is triggered by physical, chemical or biological factors. [3]

Contact dermatitises have a chronical evolution, due to the absence of a curative medical treatment and an early diagnosis.

Based on the underlying mechanism (allergic, immediate reaction, late reaction or non-allergic), etiology and clinical, histologic and molecular aspects, there are three types of contact dermatitises: irritant contact dermatitis, allergic contact dermatitis and contact urticarial. [4]

Irritant contact dermatitises represent 80% of contact dermatitises and they are mostly occupational dermatitises. Despite there are many different occupational triggers depending

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on the different workplaces that are known to be an etiological factor, the irritant contact dermatitises share the same pathogenic mechanism, characterized by the activation of the inflammatory innate immune response with hyperproduction of cytokines, chemokines and cellular polymorph infiltrate. The inflammatory reaction appears after physical, chemical and biological environmental factors that had altered the skin barrier. [5]

Therefore, three main phases are identified in the evolution of the irritant contact dermatitis physiopathologic process: the alteration of the skin barrier, the innate immune system activation and the formation of the inflammatory infiltrate at the affected site.

The alteration of the skin barrier, **first phase** of the physiopathologic process, involves changes in one or multiple components of the stratum corneum.

The mechanical skin barrier is made of corneocyes, protein rich cells and an "inter-corneocyte adhesion" layer consisting of lipids with a bilamellar disposition. The physio-pathological processes can produce the dysfunction of the proteins of the skin barrier (keratin, involucrin, filaggrin and loricrin), lipid solubilization and the disruption of the lipid layer consisting of ceramides (sphingosine), cholesterol, fatty acids(ensure water retention and electrolytes) leading therefore to the increase of the skin permeability and subsequently the transepidermal water loss (TEWL = trans-epidermal water loss). [6]

The **second phase** of the process is re-presented by keratinocytes activation which synthetizes IL1α and IL1β, IL8, TNFα, GM-CSF and chemokines. The production and secretion of the proinflammatory mediators in the extra-cellular matrix will lead to the third phase of the process: the "actual cell infiltration" due to the migration of the Langerhans and local dendritic cells in the epidermis, and the recruitment of the systemic inflammatory cells (macrophages, neutrophils, lymphocytes and mastocytes) at the affected site that will amplify the inflammatory cascade. [6]

Recent studies have shown that the highest incidence of irritant occupational dermatitis is not only determined by direct exposure to irritants, but can also be determined by cases where the skin is constantly traumatized or the skin is exposed to wet environment under skin occlusion conditions, producing tegumentary hyperhydration and transepidermal water loss. [7]

For example, traumas secondary to repetitive professional gestures performed with a certain force on hard surfaces cause friction or abrasion injuries; microtraumas due to glass fibers handling, mechanically destroy the stratum corneum, producing excoriation and leading to pruritus due to nerve fibers irritation.

Taking in consideration the importance of the physical factors that are associated with the workplace in the alteration of the skin barrier and the initiation of the pathological processes leading to contact dermatitis, this article will present the role of the skin's pH in the occurrence of the irritant contact dermatitis.

Therefore, we are bringing physio-pathological arguments regarding the influence of the changes in pH as a trigger or an adjuvant factor in the initiation of the inflammatory process, in order to demonstrate that by correcting the skin's pH (often ignored) we can prevent or improve the evolution of occupational irritant contact dermatitis.

At the skin level the pH is neutral at birth and becomes acid during the first weeks of life. Under normal circumstances, the skin's acid pH remains relatively constant with aging (above 70 years old), with the exception of the axillary, inguinal, submammary and interdigital regions, where the degree of moisture is higher. The value of the skin pH varies with sex and race: men tend to have a superficial skin pH lower than females and a higher level of hydration. Studies have shown that in black population, the skin pH is even lower than in white population, due to a higher number of sweat glands and a hypersecretion of acidic sweat fluid. [8]

The value of pH decreases from depth to surface leading to a value of 7 under the stratum corneum and decreases to 5 at the stratum corneum's surface. [9]

Factors that influence the cutaneous pH

The bicarbonate ion concentration in sweat plays an important role in the production and maintenance of an acidic skin pH. The sweat initially formed in the secretory coil has a concentration of Na^+ ~ 145 mmol/L and the concentration of CL^- ~ 115 mmol/L. However, during the ionic reabsorption processes the sweat that reaches the skin surface has approximately 70 mmol/L Na^+ and 80 mmol/L CL^- . [10] If the sweat production and passage through the re-absorptive area (glandular duct) are increased, the ionic reabsorption activity is lower, therefore the bicarbonate level tends to increase. Instead, in a low flow, the bicarbonate becomes practically nonexistent in the sweat and the pH decreases. In conclusion, sweat is more alkaline at higher rates and more acidic at lower elimination rates. [11]

We could thus formulate the hypothesis, that in workplaces which involve physical effort and an increased rate of production and elimination of sweat, the sweat's acidity is decreased, leading to an environment where saprophytic bacteria can become pathogenic. This hypothesis provides theoretical arguments, however will necessitate an experimental validation.

The maintenance of skin pH is conditioned by exogenous and endogenous mechanisms acting on the skin. The exogenous mechanisms are represented by free fatty acid produced by skin microbial flora lipases and pilosebaceous glands and by lactic acid production in eccrine sweat gland. [12, 13]

There are three endogenous pathways identified that are involved in establishing an acidic pH in the stratum corneum**: the urocanic acid production** (trans-urocanic acid converts to cis isomer, under UVB) from L-histidine through the action of histidinase and **pyrrolidone carboxylic acid**, derived from glutamic acid, **free fatty acids synthesis** from phospholipids under secretory phospholipase A2 (sPLA2) and **an antiporter mechanism** (ions exchange) for sodium-proton (Na^+/H^+) with a central role in the cellular pH regulation. [9, 14, 15, 16, 17]

The role of the antiporter at the level of the stratum corneum is the same as in other human cells in maintaining the intracellular pH by transporting the H^+ ions in the extracellular environment. [17, 18]

Other factors that influence the skin's and sweat's pH are: serum pH, urea and ammonium concentration and also carbonic anhydrase activity and vacuolar-type H^+ ATPase located in the secretory part of the sweat gland. Increased activity of carbonic anhydrase associated with a decreased activity of the extracellular pH has been associated with rapidly skin healing. [19]

The sebum fatty acids are also responsible for maintaining an acidic pH, therefore changes in the epidermal lipid layer increase the pH. [20] Other contributors to the final composition of sweat and pH are: epidermal ionic channels and sebaceous and eccrine glands, amiloride-sensitive sodium epithelial channels (ENaC) and cystic fibrosis transmembrane conductance regulator (CTRF) from sebaceous glands along with the CI-/HCO3 antiporter and vacuolar type-H+ATPase. ENaC, the main Na^+ re-absorption channel, is highly represented in the skin, especially in the eccrine glands; a functional deficit of this channel leads not only to a transepidermal water loss but also to a cutaneous hyperkeratosis and inflammatory processes activation. [21-24]

CFTR (Cystic fibrosis transmembrane conductance regulator) functional alteration caused by mutations in the cystic fibrosis genes, conducts not only to a loss of Na^+, but also bicarbonate, which is associated with an increase of skin's pH. [25]

Another major factor that may increase the skin's pH is the peripheral vascular stasis (PVD), responsible for the alteration of the oxygenation, cellular metabolism and the plasma extravasated content. During stasis the elimination of the catabolism waste products (lactic acid, CO2) is reduced. [26]

The influence of cutaneous pH in irritant contact dermatitis

An acidic pH of stratum corneum is essential in maintaining the skin barrier intact, necessary for antimicrobial defense, leading to development of commensal flora (saprophytic flora) and fighting against multiplication of pathogenic germs. It also provides control of enzymatic activities at the lipidic structure of stratum corneum and skin regeneration. [9, 18]

An effective skin barrier and acidic pH ensures a normal lipid metabolism at this level and optimal functionality of some key enzymes: beta-glucocerebrosidase and acid sphingomyelinase. At an alkaline pH, the degradation of this enzymes by serine proteases is accelerated and the lipid components of the barrier are altered. [20] At the same time the production and also release of interleukins by keratinocytes is increased. The synthesis of interleukins in inflammasome is activated through the caspase 1 and the release of IL1α and IL1β by keratinocytes is due to the activation of the serine proteases. All these stages lead to an amplified inflammatory reaction by recruiting local dendritic and systemic cells.

The importance of the skin's pH in irritant contact dermatitis has been substantially debated in relation to the "loss of function" mutations of filaggrin gene, these type of mutations are associated with an increased skin pH. Filaggrin is normally produced as profilaggrin (400 Kda) by the keratinocytes from the granular layer. Profilaggrin (400 Kda) is a macromolecule which contains 1–12 filaggrin monomers and is deposited in keratohyalin granules. During the evolution of the keratinocytes to corneocytes, by profilaggrin dephosphorylation processes the following are released: filaggrin monomers (37Kda) and the N-terminal fragment. [27, 28]

Filaggrin mutations are associated with a decrease in the number of filaggrin molecules produced by keratinocytes resulting in decreased levels of histidine and glutamine, amino acids whose cutaneous origin is mainly from filaggrin. [29] A decreased level of these amino acids leads to a decreased production of the urocanic and pyrrolidone carboxylic acids (natural moisturizing factors) and therefore to an increase of stratum corneum pH. A decreased level of natural moisturizing factors produces changes in skin integrity. An alkaline pH leads to an increased release of proinflammatory cytokines and a decreased level of skin ceramides. [30]

The connection between alkaline pH and irritant contact dermatitis is also sustained by clinical data, not only by experimental research; the subject with a more alkaline pH are more susceptible of developing irritant dermatitis. [9] An alkaline pH developed after exposing to organic solvents which destroy the skin lipid barrier will determine important changes in: lipid metabolism and its enzymes (decreases the activity of beta-glucocerebrosidase, acid lipases, sphingomyelinase acid, phospholipases and increases the activity of serine proteases).

In addition a skin pH inclined towards alkaline increases the susceptibility of metal sensitivity (Co, Ni). In construction workers, lime solution and cement slurry, strongly alkaline products, determine irritant lesions and significantly increase the incidence of contact dermatitis in this industry. [31]

On a skin with preexistent lesions produced by alkaline components and microabrasions, exposure to chrome (Cr) and cobalt (Co) from cement slurry can induce metal sensitivity ten times faster than on a healthy and normal skin. [32, 33]

Recent studies have shown that the highest incidence of occupational irritant dermatitis is found at wet-workers using occlusive protective gloves. Depending on the skin's pH, the release of the components from the gloves' chemical structure is different: for example, the gloves containing small amounts of chrome, will release more Cr^{+6} (with highly allergic potential) at a higher pH, and Cr^{+3} at an acidic pH. [34]

It has been proven that an exogenous acidification of stratum corneum stimulates epithelialization, therefore, the skin altered by acetone products, for example, recovers faster in an environment where strongly acidic buffers are being used. [35, 36]

Cumulative toxic contact dermatitis is a clinical entity described after repeated contact at workplace with aqueous substances, such as solvents, detergents, soaps, low acidic or alkaline pH substances or on the contrary, with drying skin factors (low air humidity, particles, etc.). [37] Chronical development of the lesions is the result of simultaneous action of several factors on skin barrier alteration, which allow the exogenous environment substances, especially liposoluble, to penetrate the epidermis and initiate the inflammatory process. In developing cumulative toxic contact dermatitis, the cleaning products used to clean the skin after being exposed are those that generate an increased alkalinity which overlaps the irritant effect of the substances that

the worker was initially exposed to; therefore, instead of cleansing the skin, and preventing the irritant effect these cleansing skin products will exacerbate the negative effects of exposure. In general the lack of information and lack of awareness at the work place, results in the use of detergents along with industrial solvents to remove the chemical skin contaminants, favoring their penetration through the skin and amplifying the risk of lesions appearance. [38]

How could this data impact the practice of occupational medicine?

Identifying the role of pH in the balance of cutaneous bacterial flora, in maintaining the skin barrier intact, in the maturation and structural integrity of the stratum corneum, has many practical applications.

First of all, measuring the skin's pH could represent a way of evaluating the workers risk, particularly the ones with an eczema history. Until now, this investigation is rarely used as a screening method, although there is an international consensus, regarding skin's pH measuring at the workplace. [39] Measuring the skin's pH before and after exposure or at the end of the work shift, could bring useful information regarding the risk and the efficiency of the preventing methods.

Another important direction of pH applicability is the prevention area in occupational medicine, in choosing the right cleansing products and skin barrier creams. Most of the cleansing products are alkaline. The alkalinizing effect of the skin's pH, after using alkaline products, appears rapidly and the pH will go back to normal after many hours (6-8 hours). Subsequently, after cleansing hands with soap (for example, during lunchbreak), the exposed person will gain a lower resistance to cutaneous aggression for the whole worktime. Therefore, whenever it is needed, a neutral or non-alkaline soap will be chosen. [40]

As a general measure, the use of industrial degreasing and cleaning products for working tools should be forbidden for the cleansing of the skin (degreasing or removing traces of the substances on the skin).

In addition, if the risk of irritant contact dermatitis occurrence is identified or if there are people whose professional activity involves frequent handwashing (leading to an increased skin pH), it is advisable to use protective creams. Employers and employees risk awareness along with the correct use of protective creams have shown effective prevention, that have significantly reduced the incidence of irritant contact dermatitis. [41, 42]

Conclusions

In conclusion, there are multiple fundamental and clinical evidences, attesting that a normal skin pH represents a protective factor against skin's contact with aggressive chemical substances. Especially in the occupational environment, where the contact with chemical substances is prolonged and repetitive, maintaining the pH in a normal range is crucial.

In this sense, a preventive attitude along with the education of the exposed persons, as well as the choice of individual protective measures, represent the key factors for the effectiveness of a multidisciplinary team in reducing the contact dermatitis incidence.

Bibliography

1. Bourke J., Coulson I., English J., Guidelines for the management of contact dermatitis: an update, *Br J Dermatol*., 2009 May; 160 (5): 946-54.
2. Coenraads P.J., Diepgen T., Uter W. et al., Epidemiology. In: Frosch P.J., Menne T., Lepoittevin J.P., eds. Contact Dermatitis, 4th edn. Berlin: Springer, 2006; 135-63.
3. Nosbauma A, Nicolasa J.F., Vocansonc M et. al. Archives des Maladies Professionnelles et de l'Environnement 2010; 71:394-397 Allergic and irritant contact dermatitis. Pathophysiology and immunological diagnosis.
4. Kasemsarn P, Bosco J, Nixon RL. The Role of the Skin Barrier in Occupational Skin Diseases. *Curr Probl Dermatol*. 2016; 49:135-43. doi: 10.1159/000441589. Epub 2016 Feb 4.
5. Jürgen Harder et Ehrhardt Proksch Les protéines antimicrobiennes: les effecteurs innés de la défense cutanée, *Keratin* 2009 Nr.15:18-27.

6. Lee HY, Stieger M, Yawalkar N. et. al. Cytokines and Chemokines in Irritant Contact Dermatits, Mediators Inflamm. 2013; 2013:916497. doi: 10.1155/2013/916497. Epub 2013 Nov 25.
7. Friis UF, Menné T, Schwensen JF et al. Occupational irritant contact dermatitis diagnosed by analysis of contact irritants and allergens in the work environment, *Contact Dermatitis,* 9 OCT 2014 DOI: 10.1111/cod.12290.
8. Warrier AG, Kligman AM, Harper RA et al. A comparison of black and white skin using noninvasive methods. *J Soc Cosmet Chem,* 1996, 47, 229-240.
9. Schmid-Wendtner MH, Korting HC. The pH of the skin surface and its impact on the barrier function *Skin Pharmacol Physiol*. 2006;19(6):296-302. Epub 2006 Jul 19.
10. Bovell D. The human eccrine sweat gland: structure, function and disorders. *J Local Global Health Sci* 2015: 5:1-16
11. Saint-Criq V, Gray MA. Role of CFTR in epithelial physiology. Cellular and Molecular Life Sciences. 2017; 74(1): 93-115. doi:10.1007/s00018-016-2391-y.
12. Puhvel SM, Reisner RM, Sakamoto M. Analysis of lipid composition of isolated human sebaceous gland homogenates after incubation with cutaneous bacteria. Thin-layer chromatography, *J Invest Dermatol* 1975; 64: 406-11.
13. Ament W, Huizenga JR, Mook GA et al Lactate and ammonia concentration inblood and sweat during incremental cycleergometer exercise. *Int J Sports Med* 1997;18: 35-9.
14. Fluhr JW, Kao J, Jain M et. al. Generation of free fatty acids from phospholipids regulates stratum corneum acidification and integrity. *J Invest Dermatol* 2001; 117: 44-51.
15. Krien PM, Kermici M. Evidence for the existence of a self-regulated enzymatic process within the human stratum corneum-an unexpected role for urocanic acid. *J Invest Dermatol* 2000; 115: 414-20.
16. Behne MJ, Meyer JW, Hanson KM et al. NHE1 regulates the stratum corneum permeability barrier homeostasis. Microenvironment acidification assessed with fluorescence lifetime imaging. *J Biol Chem* 2002; 277: 47399-406.
17. Sarangarajan R, Shumaker H, Soleimani M et al, Molecular and functional characterization of sodium–hydrogen exchanger in skin as well as cultured keratinocytes and melanocytes, In *Biochim Biophys Acta* (BBA) 2001: 1511(1): 181-192.
18. Rippke F, Schreiner V, Schwanitz HJ. The acidic milieu of the horny layer: new findings on the physiology and pathophysiology of skin pH. *Am J Clin Dermatol*. 2002;3(4):261-72.
19. Barker H, Aaltonen M, Pan P, et al. Role of carbonic anhydrases in skin wound healing. Experimental & Molecular Medicine. 2017;49(5): e334-. doi:10.1038/emm.2017.60.
20. Joachim W. Fluhr. KERATIN Actualites en recherche dermatologique Nr. 15-2009 Le point sur la barrière épidermique 5-12.
21. Hanukoglu I, Boggula VR, Vaknine H et al Expression of epithelial sodium channel (ENaC) and CFTR in the human epidermis and epidermal appendages. Histochem Cell Biol, 2017: 147: 733-748).
22. Marunaka Y, Marunaka R, Sun H et alNa+ homeostasis by epithelial Na+ channel (ENaC) and Nax channel (Nax): cooperation of ENaC and Nax. *Ann Transl Med* 2016; 4 (Suppl 1): S11).
23. Frateschi S, Charles RP, Hummler E. The Epithelial Sodium Channel ENaC and its Regulators in the Epidermal Permeability Barrier Function. *Open Dermatol J*, 2010, 4: 27-35.
24. Xu W, Hong SJ, Zeitchek M et. al. Hydration Status Regulates Sodium Flux and Inflammatory Pathways through Epithelial Sodium Channel (ENaC) in the Skin, *J Investig Dermatol,* 2015: 135 (3): 796-806, ISSN 0022-202X.
25. Saint-Criq V, Gray MA. Role of CFTR in epithelial physiology. Cell Molec Life Sci. 2017;74(1):93-115. doi:10.1007/s00018-016-2391-y.
26. Wilhelm KP, Cua AB, Maibach HI Skin aging. Effect on transepidermal water loss, stratum corneum hydration, skin surface pH, and casual sebum content. *Arch Dermatol.* 1991 Dec; 127(12): 1806-9
27. Sandilands A, Sutherland C, Irvin A.D. et al. Filaggrin in the frontline: role in skin barrier function and disease. *Journal of Cell Science.* 2009 May 1; 122(9): 1285–1294.).
28. Yamamoto Y.A., Takahashi H, Presland RB et al. Translocation of profilaggrin N-terminal domain into keratinocyte nuclei with fragmented DNA in normal human skin and loricrin keratoderma. Laboratory investigation; a journal of technical methods and pathology. 1998 Oct; 78 (10): 1245-53.
29. Tan SP, Brown SB, Griffiths CE et al. Feeding filaggrin: effects of l-histidine supplementation in atopic dermatitis. *Clin Cosmet Investig Dermatol*. 2017; 10:403-411. doi: 10.2147/CCID.S146760.
30. Kezic S, O'Regan GM, Lutter R et al. Fillagrin loss-of-function mutations are associated with enhanced expression of IL-1 cytokines in the stratum corneum of patients with atopic dermatitis and in a murine model of filaggrin deficiency *J Allergy Clin Immunol.* 2012 Apr; 129 (4): 1031-9 e1. doi: 10.1016/j.jaci.2011.12.989. Epub 2012 Feb 8.
31. Shah KR, Tiwari RR. Occupational skin problems in construction workers. *Indian J Dermatol.* 2010; 55 (4): 348-351.

32. Avnstorp C, Cement eczema - An epidemiological intervention study Acta.Derm Venereol Supplementum, Stockholm, 1992,179, pp.1-22.
33. Fregert S, Gruvberger B, Correlation between alkalisulphate and water-soluble chromate in cement, *Acta Derm Venereol*., 1973, 53 (3): 225- 228.
34. Mathiason F, Lidén C, Hedberg YS, Chromium released from leather – II: the importance of environmental parameters. *Contact Dermatitis.* 2015; 72 (5): 275-285.
35. Fluhr JW, Mao-Qiang M, Brown BE et al. Functional Consequences of a Neutral pH in Neonatal Rat Stratum Corneum, *J Invest Dermatol* 2004; 123: 140-51.
36. Mauro T, Hollerian WN, Grayson S et. al. Barrier recovery is impeded at neutral pH, independent of ionic effects: implications for extracellular lipid processing. *Arch Dermatol* res 1998:290(40:215-22.
37. English J. Current concepts in contact dermatitis. *Br J Dermatol*. 2001 Oct; 145 (4): 527–529.
38. Rushton L, Williams HC, English JSC. Intervention development in occupational research: an example from the printing industry. *Occup Environ Med.* 2006; 63 (4): 261-266.
39. Stefaniak A, Plessis J, Eloff F. (2013), International guidelines for the in vivo assessment of skin properties in non-clinical settings: part 1. pH. *Skin Res Technol,* 19: 59–68. doi:10.1111/srt.1 2016.
40. Kampf G, Löffler H., Prevention of Irritant Contact Dermatitis among Health Care Workers by Using Evidence-Based Hand Hygiene Practices: *A Review, Ind Health,* 2007:45(5):645-52.
41. Kampf G, Ennen J. Regular use of a hand cream can attenuate skin dryness and roughness caused by frequent hand washing. BMC *Dermatology.* 2006; 6:1. doi:10.1186/1471-5945-6-1.
42. Mauro M, De Giusti V, Bovenzi M. et al 2017, Effectiveness of a secondary prevention protocol for occupational contact dermatitis. *J Eur Acad Dermatol Venereol* 2017, 31: 656–663. doi:10.1111/jdv.13947.

Conflict of interest
NONE DECLARED

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