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OCCUPATIONAL CONTACT DERMATITIS: FROM PATHOPHYSIOLOGY, TO DIAGNOSIS AND PREVENTION

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ÍNDICE

1. ABSTRACT

Occupational Dermatitis is described as any alteration in the skin, mucosa or annexes that is directly or indirectly caused, conditioned, maintained or aggravated by agents present in the occupational activity/setting or work environment. Occupational Contact Dermatitis (OCD) is especially relevant in developed countries, as it is the cutaneous occupational disease with the greatest impact, constituting about 90 to 95% of cases. This prevalence is particularly relevant in some professional classes since it significantly affects the quality of life of patients and entails high costs for the national health system. In this sense, it is essential to clarify the cellular and molecular mechanisms that trigger the development of skin sensitisation, as well as to identify potential innovative preventive strategies for contact dermatitis.

This work reviews current general knowledge regarding contact dermatitis (CD) and its subtypes (allergic and irritative contact dermatitis). The cellular and molecular mechanisms are highlighted and it is also intended to identify the main allergens that cause these diseases in professionals related to the hairdressing and aesthetics sector. Furthermore, a comprehensive outline of several preventive strategies in the professionals under study is also provided.

Keywords: Contact Dermatitis; Occupational Allergens; Hairdressers; Prevention; Skin Irritation.

1. RESUMO

A dermatite ocupacional é descrita como qualquer modificação da pele, mucosa ou anexos cutâneos que seja direta ou indiretamente causada, condicionada, mantida ou agravada por compostos presentes na atividade / ambiente ocupacional ou ambiente de trabalho. A Dermatite de Contato Ocupacional (DCO) é especialmente significativa nos países desenvolvidos, sendo a doença ocupacional cutânea com maior impacto, constituindo cerca de 90 a 95% dos casos. Essa prevalência é particularmente relevante em algumas classes profissionais, uma vez que afeta significativamente a qualidade de vida dos pacientes e acarreta elevados custos para o sistema nacional de saúde. Nesse sentido, é fundamental esclarecer os mecanismos celulares e moleculares que despoletam o desenvolvimento da sensibilização da pele, bem como identificar potenciais estratégias preventivas inovadoras para a dermatite de contato.

Este trabalho representa uma revisão do conhecimento geral atual sobre a dermatite de contato (DC) e seus subtipos (dermatite de contato alérgica e irritativa). Os mecanismos celulares e moleculares subjacentes ao desenvolvimento da DC são destacados e pretende-se também identificar os principais alérgenos que causam estas doenças em profissionais relacionados com o setor de cabeleireiro e estética. Além disso, também é fornecido um esboço abrangente de várias estratégias preventivas nos profissionais em estudo.

Palavras-chave: Dermatite de Contacto; Alergéneos Ocupacionais; Cabeleireiros; Prevenção; Irritação da Pele.

ABBREVIATIONS USED:

ACD - Allergic contact dermatitis

ATP - Adenosine triphosphate

CD - Contact dermatitis

DAMPs - Damage-associated molecular patterns

DCs - Dendritic cells

ESCD - European Society of Contact Dermatitis

HMGB1 - High-mobility group box 1

ICD - Irritant contact dermatitis

ICDRG - International contact dermatitis group

LC - Langerhans cells

LMW - Low molecular weight

MSDS - Material Safety Data Sheets

NRL - Natural Rubber Latex

OCD - Occupational contact dermatitis

OSHA - Occupational Safety and Health Administration

PPD - p-phenylenediamine

PT - Patch Test

PTD - Toluene-2,5-diamine

PVC - Polyvinyl Chloride

TAAR - Open repeated application test

ROS - Reactive oxygen species

SCCS - Scientific Committee on Consumer Safety

2. BACKGROUND

As the body first line of defence, the skin is the largest human organ and forms an anatomical, chemical, and immunologic barrier to the outside world, being the organ most frequently exposed to chemicals present in professional health products, household products, or materials used in the work environment. In this context, skin disorders account for more than 40% of all occupational and work-related diseases, with contact dermatitis (CD) being the main occupational skin disease (1).

Two main types of contact dermatitis are described considering the pathophysiological mechanism involved: irritant contact dermatitis (ICD), and allergic contact dermatitis (ACD) (2).

Acute ICD occurs after a single exposure to an irritant or toxic substance (e.g. abrasives, cleaning, oxidizing, and reducing agents) and is characterized by skin damage resulting from a direct and local cytotoxic effect over the skin's cells. Clinical manifestations of ICD include burning, stinging, smarting, and usually start within seconds after exposure (3). Additionally, the lesions range from erythema to vesiculation and caustic burn with necrosis, itching, and pain as fissures develop (4). Chronic ICD is more frequent and results from multiple cumulative insults from minor irritants (surfactants, detergents, solvents, etc.). Lesions occur mostly as hand eczema with erythema, descamation, hyperkeratosis and fissures, with limited pruritus.

ACD is a skin inflammatory disease caused by reactive chemicals with low molecular weight termed haptens (5) that induce a T-cell mediated reaction. Impressively, there are currently more than 4000 substances identified as skin allergens, with some of them being present on a multitude of products in consumers' households such as cosmetics, cleaning products and fragrances (6).

The high risk of occupational skin disease among hairdressers is well known and remains a great concern. Major risk factors include skin exposure to irritants and sensitizers, particularly hair dye substances, preservatives, and fragrance substances (7). Oxidative hair dyes are still the most common causes of occupational contact allergy among hairdressers in Europe (8).

In a study focused on the incidence of hand eczema among hairdressers, it was concluded that many hairdressers develop hand eczema at an early age (9), reinforcing that deeper knowledge and understanding of the exposure scenario is needed to be able to develop efficient disease prevention strategies and reduce damage caused by exposure to risk agents (10). The Scientific Committee on Consumer Safety (SCCS) and its predecessors have assessed >110 hair dye substances and have found that half of them are skin

sensitizers mostly potent ones (11). The more frequent irritant exposure is wet work, including constant hand and hair washing, the use of gloves, and contact with irritating hair chemicals (12).

The high prevalence of this disease in the aforementioned professional group leads to a growing waning of the hairdressing profession, associated with the development of CD (13). Many workers with significant disease require prolonged absences from work, need to alter practices at work, or may even change to another line of work based on the severity of their disease (14).

Thus, it is also important to invest in an effective diagnosis and prevention. Several preventive measures are available to eliminate, avoid, or reduce skin-damaging factors in hairdressing but often the lack of knowledge and awareness leads to these measures not being applied. Preferably, strong allergens should be eliminated from hairdressing products. However, this is often not possible due to a lack of alternative substances with lower allergenic potential still providing similar cosmetic effects.

This work reviews current knowledge regarding the pathophysiology, epidemiology, symptoms and diagnosis of contact dermatitis and its subtypes (allergic and irritative contact dermatitis). In addition, it is intended to identify the main chemicals that cause these pathologies in professionals related to the hairdressing and aesthetics sector and also to highlight preventive measures aimed at preventing the development of these diseases in the these occupations.

3. METHODS

An online search was performed at Pubmed, using the keyword “contact dermatitis” in combination with “occupational”, “hairdressers”, “prevention” and “skin irritation” and in the Cochrane Library database using “contact dermatitis” as keyword, in the period between the 1990s and 2020.

The resulting review and original articles were analyzed, more recent articles were preferably chosen, but the rest were not excluded. Priority was also given to recent review articles, which addressed the various aspects of occupational contact dermatitis.

The bibliographic references of the selected articles were also analyzed considered relevant for this work.

4. OCCUPATIONAL CONTACT DERMATITIS

4.1. Pathophysiology

4.1.1. Irritant contact dermatitis

Irritant contact dermatitis (ICD) is the most common type of occupational skin disease (approximately 80% of cases) (15). It is caused by a nonspecific skin response to direct chemical skin damage with releasing of inflammatory mediators. In this way, the barrier function attributed to the skin plays a primordial role in the development of ICD (4,16). Skin damage is associated with disruption of skin barrier, cellular apoptosis of skin cells, transepidermal water loss and release of vasoactive peptides and proinflammatory cytokines and chemokines.

There are many substances related to irritant CD, mostly chemicals in solid, liquid, or gaseous phase, but also some mineral and vegetal molecules (e.g., chemical agents, physical agents, plants, phototoxic agents, airborne irritants, etc.). These substances can be classified as immediate or cumulative irritants. Immediate irritants are corrosive substances that produce chemical burns within a few minutes or hours after a single exposure (14). Cumulative irritants produce weaker effects and require a repeated application to produce some noxious effect. ICD is most commonly due to cumulative, chronic exposure to weak irritants (17). Irritant CD can therefore manifest in a form of acute and chronic lesions.

Irritation and damage of epidermal skin cells in ICD is more likely to lead to the release of stress-associated danger signals such as reactive oxygen species (ROS), adenosine triphosphate (ATP) and damage-associated molecular patterns (DAMPs). ROS, ATP, and DAMPs such as extracellular matrix components, high-mobility group box 1 (HMGB1), among others, activate innate immune cells resulting in the release of chemokines and cytokines (17). This generally produces a local pro-inflammatory micromilieu in the skin. There are no specific immune reactions, no prior exposure to any substance (sensitization) is required, neither the formation of specific T cells, and most individuals exposed to such (usually cytotoxic) substances manifest a similar reaction (4).

In ICD, innate immune responses are primarily triggered via the intrinsic cytotoxicity of the causative chemical or by physical/mechanical irritation of the skin (17).

Certain occupations confer unique risks and distinct distributions of ICD. For example, hairdressers and beauty professionals are continuously exposed to irritants, which might result in an altered skin pH. It is likely that an altered skin pH affects the skin microbiome and thereby this barrier. It has been shown that unprotected wet work for more than 2 h per day increases the risk for developing ICD in hairdressers (15).

However, this is a field that needs further investigations. Other common workplace irritants include (but are not limited to) cleaning agents, solvents, plastics, resins, degreasers, petroleum products and lubricants, metals, machine oils, coolants, inorganic and aliphatic acids, alkalis, heavy metal salts, aldehydes, alcohols, esters, proteins, hydrocarbons, and metallo-organic compounds (see Table 1). A detailed discussion of each is beyond the scope of this review.

4.1.2. Allergic contact dermatitis

ACD is a type IV delayed-type hypersensitivity reaction caused by activation of allergen-specific T cells towards low molecular weight (LMW) reactive chemicals and metal ions such as nickel NIi2+ and chromium Cr3+ (18). In contrast to ICD, ACD involves both innate and adaptive immunity.

In ACD, it is important to distinguish induction (also known as sensitization or primary) and effector (also known as elicitation or secondary) phases (19,20 and Figure 1) .

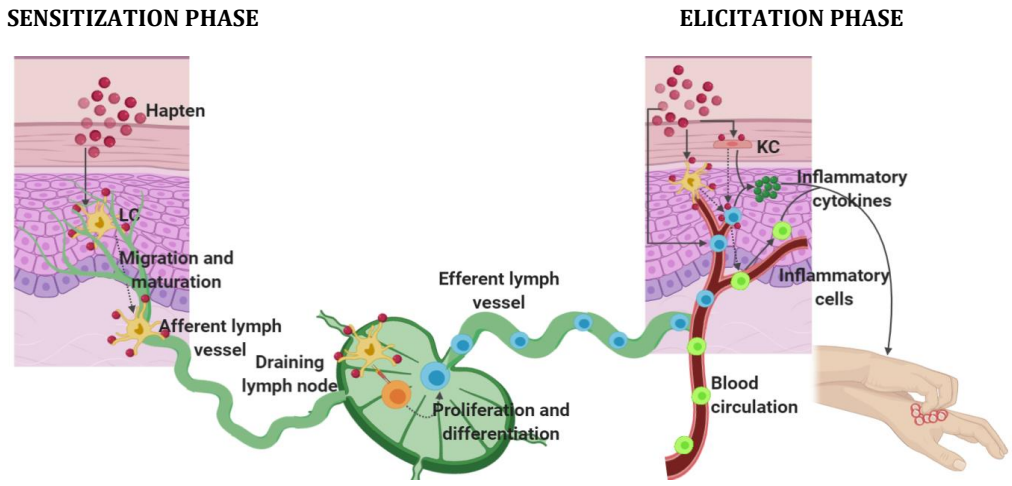

Figure 1. Graphical representation of sensitization and elicitation phases in ACD. The skin contact with a hapten triggers the formation of hapten-proteins complexes with subsequent induction of a pro-inflammatory environment. Hapten-protein complexes are then captured and processed by Langerhans cells (LC) and dermal dendritic cells that mature and migrate to the skin-draining lymph nodes, thus priming hapten-specific T-cells. During this phase (Sensitization phase), effector and memory T cells are formed, which subsequently expand and recirculate to the skin via blood vessels. Renewed allergen exposure triggers the elicitation phase. Due to their lowered activation threshold, hapten-specific effector T-cells are activated by various haptenized cells, including LC and keratinocytes (KC), to produce proinflammatory cytokines and chemokines, leading to a gradually developing eczematous reaction. Adapted from (19).

Its initial phase, sensitization, occurs after first contacts of the skin with the chemical and an important event of sensitization is the ability of sensitizers to penetrate the stratum corneum into the deeper layers of the epidermis (17,19). Due to their low molecular weight,

these chemicals, called haptens, are non-immunogenic *per se*, but become recognizable by the immune system due their ability to bind to epidermal proteins - a process called haptenization (21). Subsequently, there is activation of Langerhans cells (LCs), dermal dendritic cells (DCs), and endothelial cells. The LCs and dermal DCs take up and process the hapten-protein complex and migrate to regional lymph nodes where they prime hapten-specific T cells that proliferate and circulate in the blood stream and return to the location of the initial injury (17). The sensitization step lasts, as a minimum, 10–15 days in humans (17). With reexposure, the elicitation phase occurs and T cells specific for the allergen are recruited to, or activated at the site of contact, leading to an inflammatory cascade and resulting in cutaneous lesions and macroscopically detectable erythema, producing the clinical symptoms of ACD (5).

Clinically, the sensitization and elicitation phases are characterized by the latency that is often seen between exposure and the onset of symptoms. Often, with history, this can be helpful in distinguishing ACD from ICD, which is more often seen with early exposure. Additionally, lesions due to ACD also typically take longer to heal (4,5).

Some allergens are frequent triggers of ACD across professions. Often, environmental factors facilitate development and professions that involve wet work, temperature extremes, and repeated exposures, are more likely to lead to ACD. Nickel is the most common contact allergen worldwide, and nickel and p-phenylenediamine allergy is seen in hairdressers, cosmetologists, and barbers. Chromate and cobalt are other common occupational metal allergens (19,22).

4.2. Occupational epidemiology

Contact dermatitis (ICD and ACD) represents 90–95% of all cases with occupational skin disease in the Western countries (20), with a significant impact on healthcare costs and industry productivity due to absence to work. For instance, in some countries, it is estimated that the annual incidence registered of occupational contact dermatitis ranges from 0.5 to 1,9 cases per 1000 workers (23). However, true epidemiologic data regarding OCD are lacking.

The occupations most frequently diagnosed with diagnosed OCD are hairdressers and their apprentices, healthcare workers, cleaning staff and masons (24,25). A study in Germany demonstrated that the highest incidence of OCD was with hairdressers and that women were considerably more affected than men (23,26). In the hairdressing profession incidence rates from 56.1 to 97.4 cases per 10,000 workers per year (13) with the most prevalent age group between 15 and 24 years old. It appears that the risk of developing the disease decreases with age (24,27).

Until the present, there have not been available comparable data regarding the epidemiology of occupational skin diseases in the hairdressing trade in European countries, since the methods of analysis used are very diverse and there is general confusion in the diagnostic terminologies used (28) . According to Diepgen *et al.,* 2007 (29), the prevalence in studies has been estimated too low, and is actually 30-50 times higher than reported.

4.3. Occupational allergens

Hairdressers are especially at risk as they often work many hours a day in wet conditions (e.g., hair washing) and, in addition, are exposed to hairdressing chemicals endowed with strong irritant properties and/or skin sensitization ability (13,27 and Table 1). The high prevalence of this disease in an occupational setting has relevant negative repercussions, since a professional is, on average, only 8.4 years in this area of work before giving up (30). The most frequent irritant condition exposure is wet work, including frequent hand and hair washing, the use of gloves and contact with irritating hair chemicals (22) . Hairdressers perform different procedures throughout the working day, being exposed to several allergens depending on the stage they are performing. Therefore, it is important to distinguish the stages and the main allergens and irritants that act in each stage (8,13,32,33 and Table1).

The main causative allergens include oxidative hair dyes that are used for permanent hair dyeing (33). They contain reactive precursors, such as p-phenylenediamine (PPD), toluene-2,5-diamine (PTD), p-aminophenol and couplers (e.g., m- aminophenol, resorcinol, 1-naphthol, hydroquinone p-Phenylenediamine). Indeed, from a study of patch tests performed in hairdressers and matched controls, PPD, PTD, p-aminophenol and m-aminophenol were recognized as relevant sensitizers (33,34). Furthermore, contact allergy to thiurams from rubber gloves was also reported in hairdressers (22). Allergens present in products for permanent waves (thioglycolates) have been responsible for many cases of ACD. In order to substitute these well-known allergens, cysteamine hydrochloride and chloroacetamide have started to be used, due to their low sensitization rates; however, these chemicals present skin sensitization potential (35) being crucial their inclusion in future surveillance studies (36).

Another study demonstrated that in hairdressing/nail aesthetics professionals, methacrylates are the most frequently found allergens in allergic occupational contact dermatitis, especially in beauticians (37). This increase in allergy to methacrylates seems to go along with the greater demand and increased performance of certain aesthetic procedures, such as "gel nails". In addition, metracrylates are involved not only in the appearance of ACD in professionals but also in clients (38).

Table 1. Selected activity-related allergens and irritants in the hairdressing industry. Adapted from (28)

Activity	Products	Allergen substances	Irri-tation	Sensi-tization	Preventive strategies
coloring agents	Oxidation colors	p-phenylenediamine (PPD)	+	+	single use gloves nitrile gloves
		toluene-2,5-diamine (PTD), o-,m-toluylendiamine	-	-	
		m-toluylendiamine	-	-	
		o-aminophenol	-	-	
		p-, m-aminophenol	+	+	
		p-methylaminophenol	+	+	
		2-methyl-5-hydroxyethylaminophenol	+	+	
		m-phenylendiamine	-	+	
		1-naphtol	+	-	
		resorcinol	+	-	
	oxidation agents, bleaches	hydrogen peroxide	+	-	
		hydrochinone	+	+	
		kalium persulfate	+	+	
		sodium persulfate	+	+	
	blonding agents	ammonium persulfate	+	+	
perms	perming fluid	e.g. ammonium thioglycolate, glyceryl monothioglycolate (GMTG/GMT), cysteaminehydrochloride	+	+	single use gloves
hairwashing, hair care, hair styling	shampoo, cream rinse, conditioner, hair spray, hair gel, hair wax	tensides (such as cocamidopropyl betaine)	+	+	Long cuff single use gloves
		preservatives (such as methylchloroisothiazolinone MCI / methylisothiazolone MI)	+	+	
		perfumes (such as cinnamal, eugenol [phenylpropene], hydroxyisohexyl 3-cyclohexene carboxaldehyde [lyral, MPCC])	+	+	
		water	+	-	
		phenols	+	-	
		selenium disulfide	+	-	
		formaldehyde	+	+	
		parabens	+	+	
		dichloromethane (in hair lacquer)	+	-	

Hair straightening	brazilian straightening	Formaldehyde and/or methylene glycol	+	+	avoidance (airborne; carcinogenic) nitrile single use gloves
		sodium hydroxide	+	-	
		potassium hydroxide	+	-	
		lithium hydroxide	+	-	
cleaning	cleaning agents, disinfection agents	e.g. formaldehyde3 , glutaral, perfumes, tensides, preservatives	+	+	reusable gloves
contact with occupational tools	e.g. scissors	nickel	-	+	Nickel-free material
skin protection	protective gloves	latex, mercaptobenzothiazoles, thiurames, dithiocarbamates, phthalates, formaldehyde	-	+	gloves without latex, phtalates and accelerator free gloves
		Preservatives, lotion bases, perfumes	+	+	hypoallergenic products without color, fragrance, and preservatives
Hair cutting	hair		+	+	Arm protectors, closed shoes

4.4. Clinical Presentation of Contact Dermatitis in Hairdressers

The spectrum of the clinical condition varies from subjective symptoms as stinging, burning, and itching, to clinical signs as erythema, scaling, vesicles, rhagades, dermatitis, and frank eczema. The clinical picture is modified by duration of the disease and medical treatment. The hand is commonly involved in occupational contact dermatitis, sometimes extending to the wrists, forearms, and other exposed areas, such as the face and neck. The clinical presentation of contact dermatitis varies based on the causative allergen or irritant and the affected area of the skin (39–41 and Table 2).

Table 2. Distinguishing Features of Irritant and Allergic Contact Dermatitis. Adapted (41).

Feature	Irritant Contact Dermatitis	Allergic Contact Dermatitis
Pathogenesis	Direct cytotoxic effect	T cell-mediated immune reaction
Affected individuals	Almost everyone exposed	A minority of exposed individuals
Onset	Immediate (chemical burns) After repeated exposure to weak irritants	12-48 h in previously sensitized individuals
Signs	Subacute or chronic eczema with desquamation, fissures	Acute to subacute eczema with vesiculation
Symptoms	Pain or burning sensation	Pruritus
Concentration of contactant	High	Low
Investigation	None	Patch or prick tests

4.4.1. Irritant Contact Dermatitis

Irritant CD lesions occur mostly after repeated exposure to a substance (even in small concentrations) that induces a cumulative effect commonly leading to chronic skin damage and skin lesions (16). Irritant skin lesions are commonly localized mainly on the backs of the hands and fingers as well on exposed areas of the forearms, affecting the palms of the hands only later on (26,37). The disease is often asymmetric, with the dominant hand more affected.

Symptoms of acute irritant CD are burning, stinging, and soreness of the skin. Signs are erythema, edema, bullae, and possibly necrosis. These lesions are restricted to the area where the irritant or toxic damaged the tissue. Borders are mostly sharply demarcated (distant spread does not occur), and the asymmetrical pattern of the lesions hints at an exogenous cause. The prognosis of this type is good (20). On the other hand, chronic irritant CD is characterized by diffuse or localized lesions with typically poorly defined erythematous scaly patches and plaques, dryness of skin, lichenification and desquamation. As the disease persists, lichenification and fissures develop, with possible nail damage (paronychia with nail dystrophy, pitting, oil spots, etc.). Distant reactions usually do not occur and the disease is usually limited to the areas of repeated contact (16). In ICD pruritus generally is not as severe as in allergic contact dermatitis and with the development of the disease painful rhagades may arise.

It is important to mention that, throughout the profession, changes in the disease occur related to work exposure, for instance, gradual development with work, little

improvement over the weekend and the cure occurs only after long periods of absence. A “hardening skin effect” can also occur with prolonged work - the skin becomes adapted to the exposure and therefore tolerant to the regular aggression. In hairdressing apprentices, it was found that during the first months of work one of the first signs of skin damage was interdigital dermatitis. It has also been shown that exposure to cold seems to aggravate the skin damage (22), which associated with reactive edema and pain greatly hinders the mobility of the fingers and the ability of these professionals to carry out their work.

4.4.2 Allergic Contact Dermatitis

Allergic contact dermatitis may affect every part of the hands, with extension to wrists, underarm, neck, and face (5). The location depends on the area of exposure to the allergen, sometimes giving clues about which allergen the individual is dealing with. However, it can spread to surrounding areas (different from irritant hand dermatitis). For instance, ACD of the second and third fingers of the serving hand is often related to a hair color allergy, because these fingers grip the hair and present them to the scissors during cutting procedures after coloring (4,5). When cutting the hair with a knife, the thumb of the dominant hand has intensive contact with the hair. In nickel-sensitized hairdressers, handling a pair of nickel releasing scissors or a nickel releasing knife, the second and third fingers of the serving hand are exposed to the cutting parts of the scissors and a nickel-related dermatitis occurs on these fingers (4,5). When using a knife, the thumb of the cutting hand is exposed. Dermatitis on the back of the hands and around the wrists may indicate a latex allergy caused by a latex protective glove (42,43) or an allergy from accelerators in synthetic rubber gloves (20). In ACD, in contrast to irritant hand dermatitis, extension to surrounding areas occurs, which is one of the differences that helps in the diagnosis between the two types of CD. It is important to highlight that sensitization to airborne chemicals and airborne ACD is also possible (33), for instance ammonium persulfate sensitized hairdressers often complain of both skin and respiratory symptoms, because of the powdery and thereby volatile constitution of the product (33).

Regarding the morphology of the lesions in the ACD, they can be observed in different stages. In the acute stages it is possible to observe redness, vesicles, small blisters and severe itching, while in chronic stages hyperkeratosis and rhagades are more usual (4,26).

In occupational ACD a temporal relationship between exposure and disease is usual, with development and exacerbation at work, improvement on weekends, healing during vacation and recurrence within a few days of returning to work (4). Although there are differences in the clinic manifestations between the two types of dermatitis mentioned, it is

sometimes difficult to make the differential diagnosis, given that some manifestations of contact dermatitis can be both allergic and irritant (4). Therefore, patient history is crucial for the correct diagnosis and to disclose the causative substance in order to resolve the dermatitis and prevent further damage, but skin testing is mandatory to distinguish these two forms of occupational CD that have different prognosis.

4.5. Diagnosis

4.5.1. Clinical history

A detailed and complete history associated with a thorough physical examination is essential to perform the diagnosis. It is of utmost importance to obtain information on all types of agents involved in the patient's day, such as areas of the body involved, the time of exposure to a suspected allergen or irritant, to investigate previous problems and the respective response and evolution of the patient to these issues (44). In the case of occupational CD, it is crucial to focus on the nature of the work, on some aggravating factors, concomitantly taking advantage of the additional information that the location and distribution can confer to the diagnosis (45), such as the association between skin improvement during holidays or sick leave (41). Complementary tests will be required in most cases, and a visit to the workplace may occasionally be necessary, especially in the face of unexplained epidemics of contact dermatitis (39,46). Even so, sometimes it is difficult to assess what is actually causing CD, both for the patient and the clinic, as the reaction to the allergen is not always immediate and can last up to 72 hours. It has also been proven that there is an increased difficulty in identifying the causative agent in chronic cases of CD (41).

In order to better characterize and make more accurate diagnoses, Mathias developed seven objective criteria to identify occupational contact dermatitis (described in table 3) (47,48). The Mathias's criteria were recently validated and are currently accepted to do the diagnosis of OCD. The presence of four of the seven criteria confirmed the diagnosis.

However, even with a detailed medical history, a thorough physical examination and the help of the Mathia´s criteria, a patch test is often necessary.

Table 3. Diagnostic criteria for occupational contact dermatitis. Adapted from (47).

Citeria
1. Clinical appearance consistent with contact dermatitis.
2. Workplace exposure to potential cutaneous irritants or allergens.
3. Anatomical distribution consistent with cutaneous exposure related to the job.
4. Temporal relationship between exposure and onset consistent with contact dermatitis.
5. Non-occupational exposures excluded as likely causes.
6. Removal from exposure leads to improvement of dermatitis.
7. Patch or provocation tests implicate a specific workplace exposure.

4.5.2. Patch Test

Patch testing is a *in vivo* bioassay to test the allergic reaction to nonirritating concentrations of an allergen (46) and is the gold standard in the diagnosis of ACD. Antigen selection and test interpretation requires experience and expertise from the clinician. It is strongly emphasized that for the accurate diagnosis of ACD, it is essential to assess the exposure to the relevant allergen.

Therefore, patch testing including the patients' own products, as well as chemical analysis of the products from the workplace is required. Additionally, Material Safety Data Sheets (MSDS) are considered as important source of information concerning exposures in the workplace (46).

On the other hand, whereas MSDS are often useful in the workup of a patient with suspected OCD, they also have many deficiencies, since they provide incomplete information, but if the physician is confident that the affected worker has been exposed to irritants only, no further testing is necessary (49,50). The most common exemple of such, comes about when the substance is proprietary, which leads to specific chemical names being avoided in favor of general categorization, the unnecessary need to list irritants and sensitizers when the concentration levels are lower than 1%, and the MSDS's don't address prevention and sensitization and irritancy (50).

Close to 600 standardized allergens are currently available from different suppliers. They are grouped by allergens in series, such as the rubber, metals, and glues and adhesives series, or by profession, such as the hairdressers' series (41). The TRUE Test®, is the only FDA-approved patch test (51,52), with 35 allergens available, and is a prepackaged, ready to apply kit consisting of three adhesive panels in which the allergens of the standard series are embedded. With this easy to use, preimpregnated testing system, there was an

exponential increase in the number of patch tests performed (52), however, it is of relevance to notice that, often, it must be supplemented by additional allergens. Even the North American Baseline series, with 50 allergens, is insufficient to pick up all cases of occupational ACD. Indeed, studies have shown that almost 27% of allergens may still be missed using the European, North American or other Baseline series (46). In the case of OCD, particularly in hairdressing, it is essential not only to include baseline series but also to introduce supplementary series specific for hairdressers. Usually, additional testing to the rubber, preservatives and topical agents' series is necessary (13,53).

Commercial suppliers of patch test materials, except for the TRUE Test®, cater for this need by providing ready-to-order test series termed "hair cosmetics series" or "hairdresser series" (51). Information on suppliers of patch test materials is available at the European Society of Contact Dermatitis (ESCD) website (www.escd.org). Patients who may be tested with such a test series include consumers/self-users of hair cosmetics, clients of hairdressers, and hairdressers themselves. In a study performed by Uter *et al*. (53), the average age of patch testing for diagnosis of sensitization to hairdressing cosmetics was 26 years old for hairdressers, while it was 49 years old for hairdressing customers or self-users of hairdressing products.

The patch test procedures have been improved over the years keeping in mind the possibility of adding new allergens to the test series, thus improving the effectiveness of patch tests.

In hairdressers suffering from work-related contact urticaria, rhinitis, or asthma, prick tests with immediate readings should be performed with ammonium persulfate, hair dyes, and latex. However, some studies contraindicate the use of skin prick tests since they have high rates of false negatives (55,56).

In the case of detected nickel allergy, the dimethylglyoxime test could be helpful to assess nickel release from instruments, such as scissors, if a relevant occupational nickel exposure is expected in a nickel- sensitized hairdresser (54).

4.5.3. Patch testing

Patch tests should be applied to the upper back, ideally in areas without any skin lesions including CD, atopic dermatitis, psoriasis, or tinea corporosis. Oral corticosteroid use with prednisolone 10 mg daily, or an equivalent, is a relative contraindication to testing (57), because it may suppress positive reactions. Therefore, oral and topical corticosteroids must be discontinued four weeks and seven days, respectively, before the application of patch tests. In contrast, antihistamines do not interfere with their performance, but sun exposure should be avoided two weeks before it takes place and in pregnant women patch testing is proposed to be postponed if there is no need for an urgent result (58).

Testing materials are placed in a chamber, which can be aluminum (Finn chamber®) or plastic chambers (Curatest® or IQ chamber®), with no superiority of one system over the other yet proven (58), and then attached to an adhesive backing and applied to the patient´s back.

According to the international contact dermatitis group (ICDRG), the first reading is made 48 hours after the application of the patch test. The second reading is made 72 hours and / or 96 hours after the application of the patch test. The results should be evaluated approximately 30 minutes after the removal of the test materials to allow the irritant effect of the adhesive to decrease (44). Reading between 72h and 96h is very important clinically, since about 30% of negative readings at 48h become positive at 96h; therefore, most authors state that this is the ideal time for the second reading. Importantly, it helps to determine whether the reaction is irritating, which is a decreasing reaction, declining between the first and second reading, or allergic, which is an increasing reaction (59). According to the ICDRG, the interpretation of the patch test is carried out by a standardized scoring system, widely used, and shown in table 4.

Table 4. Scoring system for interpreting Patch Testing, according to the ICDRG (International Contact Dermatitis Research Group). Adapted from (58).

Score	Reaction
-	Negative reaction
?	Doubtful reaction - poorly defined mild erythema, without edema
+	Weak reaction - erythema plus edema, infiltration and rare papules
++	Strong positive reaction - erythema, infiltration, papules, isolated vesicles
+++	Very strong positive reaction - erythema, infiltration, papules, vesicles clustered
IR	Irritative reaction
NT	Not tested

When interpreting results, it is essential to be alert for possible false negatives and false positives. It is estimated that false-negative reactions occur in 30% of the tests. Causes include (58): (1) use of wrong vehicle; (2) low concentration of allergen in the extract; (3) poor patch test placement or loosening of patch tests; and (4) previous exposure to ultraviolet radiation or other concurrent immunosuppression capable of inhibiting the patch test response.

Potential reasons for false-positive reactions include: testing with allergens that are marginally irritant, (eg, metals, formaldehyde, and epoxy); testing beyond the irritancy

threshold; spill-over reaction from a nearby true-positive reaction; multiple simultaneous positive reactions; or testing patients with active dermatitis or otherwise sensitive or irritable skin (60).

In the presence of a positive patch test, it is necessary to assess their clinical relevance according with Table 5.

Table 5. Clinical revelation of a positive Patch Test (PT). Adapted from (58).

Recent exposure	**Definitive: PT is positive, dermatitis corresponds to the allergen's contact site. Dermatitis improves with eviction and increases with reexposure**
	Probable: The clinical presentation is consistent with the exposure, but there is no relative information on the improvement or worsening of the dermatitis.
	Possible: Contact with the material containing the allergen will have been possible.
Old exposure	PT is positive, but the exposure was in the past.

Serious adverse effects attributable to patch tests are uncommon. However, pruritus occurs more frequently, which may arise either through a positive patch test reaction, or as a result of tape irritation. Other reported adverse effects include anaphylaxis, angry back syndrome, active sensitization, infection, pigmentation changes, persistent patch test reaction, scarring and necrosis, although, as previously stated, they seldom occur (46).

4.5.4. Differential diagnosis

When carrying out the clinical history of a patient with suspected CD, it is always important to be aware of other potential diagnoses, therefore, it is essential to make a differential diagnosis with other diseases such as, Atopic dermatitis, Seborrheic dermatitis, Stasis dermatitis, Nummular dermatitis, Mycosis, Cutaneous T-cell lymphoma (notably parapsoriasis en plaques), Pityriasis rosea, Plaque psoriasis and pustular palmoplantar psoriasis, Lichen planus, Lupus erythematosus and Dermatomyositis (61,62).

4.6. Management and Prevention

OCD remains without a cure, mainly in ACD, since once sensitized the individual will always develop the clinical manifestations upon re-exposure to the same chemical. Therefore, the most important and effective approach is to cease causal exposure and no

form of symptomatic treatment can substitute this strategy (61,62). Unfortunately, this is not always possible pressing the need for developing preventive strategies such as educational activities, lifestyle changes as well as promoting the use of hand and body protection approaches. Indeed, the superior effectiveness of a multidisciplinary approach focused on prevention has been proven in several studies, with a dermatologist taking part in the special evaluation of the patient, training by a specialist nurse and the participation of an occupational physician (24,63).

Currently, it is possible to act at three different levels to reduce the burden of this disease in professionals (64). Primary prevention aims to avoid the onset of disease in individuals and to reduce the incidence of new cases at a population level. Secondary prevention aims to detect the disease at an early or pre-symptomatic stage (eg, by health surveillance) so that corrective interventions can be managed. Tertiary prevention aims to mitigate the effects of established disease (64).

The preferred approach to occupational exposure follows the OSHA stepwise strategy to hazard controls in the workplace, as demonstrated in Figure 2.

Primary prevention is the most effective approach, and it can be achieved by elimination, replacement, or reduction of the allergenic substances by substitution, namely by replacing the allergens with a less reactive chemicals (19). These include personal protective clothing (often primarily protective gloves in the case of hazardous activities), work-related precautionary measures (modifying work processes, avoiding wet/humid work conditions, using extraction systems), and consistent stage-related treatment (64).

In hairdressers, due to the high incidence and prevalence of OCD in professionals, it is imperative to adopt a different professional path (32), mainly focused on preventive procedures. As mentioned previously, it is possible to operate at different stages, and considering that about half of the cases of OCD occur in the first 2 years of work (29) it is crucial to act in the education of the hairdresser (14). Thus, ideally the apprentice's education should be done and assimilated before placement and resultant exposure to sensitizing and irritant chemicals.

Additionally, professionals should also receive periodic re-training. Education and training can begin at the time of hire and orientation and, where applicable, can be reinforced at the bedside (66). Accordingly, a controlled, prospective intervention study in hairdressing apprentices from Denmark demonstrated that the implementation of a training program in hairdressing schools increased the use of gloves and reduced the incidence of hand eczema in hairdressing apprentices (67).

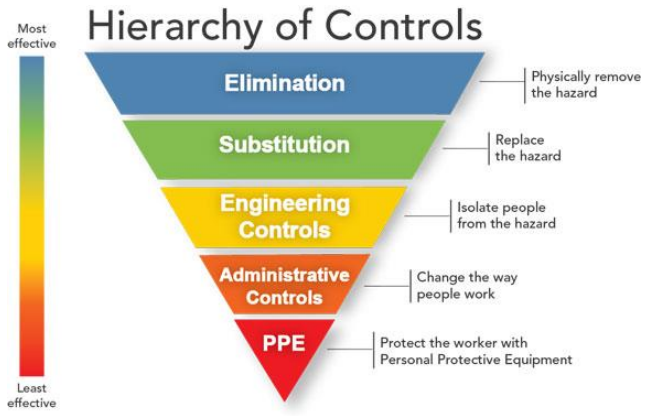

Figure 2. OSHA Hierarchy of Control to isolate and protect employees from hazards in the workplace. Adapted from (65).

Another study performed by Van der Walle and Brunsveld (68) corroborates the relevance of training programs, since a substantial improvement in the weight of OCD and the chance of a successful return to work for hairdressers with long-lasting sick leave due to hand eczema, increased after the introduction of safe hairdressing procedures in the salon.

Another way to minimize the weight of OCD in hairdressers may be to change the routine during the day, for example, distributing activities so that apprentices are not always doing wet work, equalizing the time between dry and wet activities and, thus, decreasing the weight that wet work has in the development of OCD (13). Importantly, personal protective equipment can additionally reduce exposure to skin hazards. Indeed, the use of protective gloves is highly recommended when preparing and applying hairdressing chemicals (hair dyes, bleaching, or permanent wave products), as well as during the contact with water, shampoo, or wet hair. However, the gloves are often used incorrectly due to lack of knowledge about their use (69), as it was found that a percentage of professionals use gloves more than once, which are often turned inside out after being rinsed with water and then reused. Indeed, Natural rubber latex gloves were often used for 2–3 months being only discarded after their damaged or torn. Under these conditions, gloves could indeed aggravate and potentiate the evolution of OCD, concomitantly being a source of contamination. Overall, proper glove use, including donning and removal techniques, frequency of glove replacement and glove storage are of utmost importance (70,71), given that the glove will only be efficient if used correctly. Moreover, in addition to their correct use, choosing the right gloves also has a high impact on the prognosis and well-being of these patients. Several studies have shown that single-use gloves made from nitrile rubber are more protective against permanent hair dyes than gloves made from other materials, even after 60 min of exposure to the hair dye (43). Additionally, besides nitrile rubber, gloves of polyvinylchloride (PVC) and natural rubber latex both give good protection against hair dye

exposure during hair dyeing. As the PVC gloves do not contain rubber allergens, they constitute a good option in order to minimize the risk of contact allergy resulting from hair dyeing (71,72). It is important to notice that several hairdressers refuse to wear protective gloves when cutting hair due to reduced fine motor skills (13). A description of the protection standards that can be defined to prevent OCD, by type of task, is available in Table 1.

Emollients and barrier creams also represent an important perspective in the prevention of OCD, increasing skin hydration, replacing depleted skin and providing a thin layer thus functioning as a physical barrier, helping to reduce the skin contact with contaminants (73). However, their real role in prevention remains controversial (64), as some studies have found them to be beneficial, while others have shown them to be ineffective or even to exacerbate skin irritation (74).

As for the barrier creams, water resistant barrier creams contain hydrophobic substances such as silicone, which protects against water soluble compounds like acids, alkali and dye. While on the other hand, oil or solvent resistant barrier creams protect against dust, oils, greases and solvents. Therefore, some pre-work creams may help to prevent the development of occupational contact dermatitis, even though pre-work creams are generally not effective as a protective measure (75).

Emollients and moisturizers improve hydration of stratum corneum through the use of humectants such as glycerine, urea, sorbitol, pyrrolidone carboxylic acid, and the emollients petrolatum, lanolin, mineral oil, silicone, and waxes. Studies regarding their use tend to be more consensual, demonstrating that a regular application of emollients improves the skin condition, helping to prevent the development of occupational contact dermatitis (75,76).

This way, moisturizers and emollients, used alone or alongside barrier creams, can result in a clinically significant protective effect for the primary prevention of the disease, both in the long and short-term. However, well-controlled, outcome-blinded studies still need to be performed in order to reach more accurate results and improve the impact that such creams can have in the prevention strategies of OCD (74).

5. CONCLUSIONS

Skin problems related to contact with chemicals is a continuous growing environmental and occupational health problem. Two main types of contact dermatitis are described considering the pathophysiological mechanism involved: irritant contact dermatitis (ICD), and allergic contact dermatitis (ACD). ICD is the most common occupational skin disease, accounting for 80% of all contact dermatitis cases. ACD accounts for 20% of the cases of contact dermatitis and represents the principal and most prevalent form of immunotoxicity found in humans. Indeed, about 20% of the general population has developed ACD to common allergens such as fragrances, preservatives, and metals, making this skin condition one of the most relevant occupational diseases. Overall, occupational contact dermatitis represents not only an economic burden but also affects different areas of lifestyle, health, and psychological wellbeing. Indeed, in severe cases it may interferes with the ability to perform household chores, may involve the need to take prolonged sick leave, to change occupation, and the necessity to pursue time-consuming treatments. In clinically relevant cases, the disease can be resolved by avoiding future skin exposure. Although, it can take months and, in some cases, due to professional reasons, it is not possible to fully eliminate or avoid the triggering chemical, such as with hairdressers. Indeed, hairdressers are especially at risk as they often work many hours a day in wet conditions and, in addition, are exposed to hairdressing chemicals endowed with strong irritant properties and/or skin sensitization ability. Therefore, and although most guidelines recommend ceasing exposure to the triggering chemical, there's a need to develop preventive strategies such as educational activities, lifestyle changes as well as promoting the use of hand and body protection approaches. This is of utmost importance in hairdressers, due to the high incidence and prevalence of OCD in professionals, being imperative to adopt preventive procedures. However, most of the current knowledge about preventive strategies are derived from studies undertaken in experimental settings, where outcomes were measured after only short intervention periods. Also, there is a need to extend the current studies to a broadened list of chemicals. Of relevance, preventive strategies depend largely on surveillance and must be complemented with clinical epidemiological data, which will allow the generation of important preventive regulations and legislation. Interestingly, there are currently a plethora of new tools for the identification and characterization of skin sensitizing chemicals as well as for conducting effective risk assessments and chemical testing for ACD and appropriate hazard labelling are currently required worldwide by regulatory authorities to minimize exposures. Furthermore, toxicologists have the responsibility to identify and characterize the skin sensitization potential of chemicals as well as to estimate human health risk. Finally, a great challenge will be the translation of the knowledge gathered in the pathophysiology of

contact dermatitis towards the development of new strategies able to effectively prevent the disease during a re-exposure.

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