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Assessing Cellular and Humoral Immunoreactivity to Lanolin: A Retrospective Cohort Study in Atopic and Contact Dermatitis Patients

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Authors' contributions

This work was carried out in collaboration among all authors. The author CEO is responsible for the conceptualization, data curation, formal analysis, literature review, and writing the original draft. Authors DGP, APMT, CSM, JLSS and RPSL performed laboratory procedures. Author RAPGS performed cutaneous tests. All authors read and approved the final manuscript.

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ABSTRACT

Background: Several publications report lanolin as responsible for hypersensitivity reactions in patients with atopic dermatitis and/or contact dermatitis, as diagnosed by *in vivo* provocation tests. There is no standardized lab exam that can endotype the mechanisms responsible for these phenotypes.
Aim: To evaluate the potential of the Tube Titration of Precipitins (TTP) and the Leukocyte Adherence Inhibition Test (LAIT) to discriminate and endotype immunoreactivity against lanolin in patients with atopic dermatitis and/or contact dermatitis.
Methods: We retrospectively examined the medical charts of two cohorts of patients diagnosed with atopic dermatitis and/or contact dermatitis with clinical suspicion of lanolin hypersensitivity, who were investigated with the help of TTP or *ex vivo* challenge tests monitored by LAIT against lanolin. The registered results were distributed in ranges through cascade distribution charts. The statistical characteristics of these cohorts were calculated.
Results: The TTP results spread a distribution concentrated over the more diluted titrations (Fig. 1). There was no negative result. The mean was estimated at 1:343; the median was 1:512; the standard deviation was estimated at 1:187; the mode was 1:512 (appeared 53 times). The LAI ranged from 0% to 95%. The mean was 41.5%; the median was 41.5%; the standard deviation was 27.3%; the mode was 0% (appeared sixteen times). The cascade distribution demonstrates a widespread distribution of LAI results.
Conclusion: TTP and LAIT performed with lanolin solution were able to discriminate diverse degrees of humoral and cellular immunoreactivity in patients suffering from atopic and/or contact dermatitis. It is worthwhile conducting more in-depth studies to evaluate the usefulness of TTP and LAIT in endotyping Non–IgE-mediated hypersensitivity to lanolin.

Keywords: Atopic dermatitis; contact dermatitis; endotype; hypersensitivity; lanolin; leukocyte adherence inhibition test; precipitins; precision medicine.

ABBREVIATIONS

LAI : Leukocyte Adherence Inhibition
LAIT : Leukocyte Adherence Inhibition Test
TTP : Tube Titration of Precipitins

1. INTRODUCTION

In the past, when synthetic garments were not yet produced, natural wools were dominant allergens in cold months, associated with atopic dermatitis, eczema, or textile contact dermatitis, especially in infants [1]. Wool allergy has been traditionally diagnosed by scratch, patch, and intracutaneous tests with wool extracts [2]. Wool allergy has been successfully treated by desensitization since the 1930s [3]. Concomitantly, the cause of wool allergy was attributed to the wool fat: lanolin [4]. Lanolin is a complex mixture of free fatty acids, fatty acid esters, cholesterols, and other hydrocarbons extracted from sheep's wool [5]. Lanolin is produced from the secretion of the sebaceous glands of sheep to serve as a wool's protective coating, which is a composition that varies according to the breed of sheep, geographic location, method of extraction, and level of purification [6]. The first extraction of this "wool wax" is attributed to the ancient Greeks, who documented, in 700 BC, boiling wool in water produced a top layer of greasy froth that could be skimmed [7]. In 1882, the Germans Otto Braun and Oscar Liebreice applied a patent describing a sequential centrifugation of the wool froth along with water to incorporate both elements, resulting in a suspension which, after refrigeration, boiling, and alkalinization became what they coined "lanolin" (US Letters Patent Nº. 271,192 dated January 23, 1883) [8]. Nowadays, several more sophisticated modified techniques are employed to produce several varieties of lanolin-based products and derivatives through physical and chemical modifications (hydrolysis. hydrogenation, acetylation, ethoxylation, transesterification, and so forth) [9]. Very soon, the industrial production of lanolin was widespread. It began to be incorporated into skin-cream products as an emulsifier, stabilizer, emollient, and skin moisturizer, such as toilet articles, shaving creams, toilet soaps, hair lotions, shampoos, hair conditioners (to prevent hair drying, scaling and brittleness), cosmetic creams, lipsticks, nail polish removers, eye make-up (for more uniformly dispersion of the pigment), hair sprays (as a plasticizer), hair bleaching agents, and used by pharmacists as

an excipient for topical medications [10]. Studies done by freeze-fracture and transmission electron microscopy of stratum corneum found that most applied lanolin occupied intercellular spaces. Some penetrated corneocytes and had a special affinity for the cell junction [11].

Allergic contact dermatitis to lanolin was first described by Ramirez and Eller in 1929 [12]. Very soon, several case reports of hypersensitivity to lanolin were published worldwide [13-15]. The 1950s saw the beginning of studies on the allergenic components of lanolin, as well as on the differences in immunoreactivity between the different versions, demonstrating, through patch tests, that the main allergenic components could be into the hydroalcoholic or the fatty lanolin components [16,17].

Allergy to lanolin is more common in children (4.5%) than in adults (3.2%) and patients with a previous history of eczema and hay fever [18]. Although lanolin is considered a weak sensitizer over undamaged skin, there is a higher risk of sensitization when applied over skin-damaged conditions such as contact dermatitis, atopic dermatitis, psoriasis, dermatitis herpetiformis, seborrheic dermatitis, stasis dermatitis, leg ulcers, perineal dermatitis, and so forth [19].

In the eighties, the widespread use of this moisturizer exposed a lanolin allergic "crisis", which was also described as a "myth", and a "comedy", when several pharmaceutical ointments began to declare on their packages to be "lanolin free" [20, 21].

The presence of lanolin is unanimous among the diverse batteries historically recommended for making diagnostic contact test kits (patch tests) [22]. The biggest obstacle to diagnosing hypersensitivity to lanolin is its multiple varieties, components, allergens, versions, contaminants, and additives, such as preservatives and antioxidants [14]. The standard patch test agent for diagnosing lanolin contact allergy is lanolin alcohol 30% in petrolatum [23, 24].

However, this method alone has a very low sensitivity to diagnosis of lanolin hypersensitivity, a fact that had been contributing to the "lanolin paradox", leading the physicians to use for tests the suspected materials brought in by the patients [25]. Several papers report discrepancies among cutaneous tests performed with lanolin derivatives such as lanolin alcohols and Amerchol L101 (a mixture of 10% lanolin alcohols and mineral oil) [26, 27].

Atopic Dermatitis and Contact Dermatitis are interrelated phenotypes with several associated endotypes [28]. While the Atopic Dermatitis phenotypes usually develop in patients presenting hypersensitivity to food allergens or House Dust Mites, the typical Contact Dermatitis phenotype develops in patients presenting hypersensitivity to organic and inorganic contactants [29]. Some patients presenting predominantly the Atopic Dermatitis phenotypes may also present less evident Contact Dermatitis phenotypes and vice versa [30].

There is not yet a satisfactory laboratory exam to diagnose the non-IgE-mediated Atopic Dermatitis or Contact Dermatitis endotypes. Several trial evaluations were conducted on the relationship between leukocytes and allergy tests. However, the results did not significantly yield definitive conclusions [31].

The better way to diagnose lanolin hypersensitivity is the exclusion/provocation test when the patient excludes the use of the suspected allergen(s) until the symptoms disappear, and then the allergen is re-introduced to observe reactions. However, this is particularly difficult when polysensitization dominates the clinical picture. In order to shorter the list of suspected allergens, we performed in our facilities the Leukocyte Adherence Inhibition Test (LAIT) and the Tube Titration of Precipitins (TTP) as triage tests to elect the allergens that will be emphasized in the exhaustive *in vivo* exclusion/provocation tests [32-37].

The present study hypothesizes that the LAIT and the TTP may help differentiate diverse endotypes and degrees of immunoreactivity against lanolin among patients suffering from atopic dermatitis and/or contact dermatitis. To evaluate the potential of the LAIT and the TTP to endotyping Non–IgE-mediated immunoreactivity against lanolin, we retrospectively compiled the electronic medical charts of patients with these conditions who were investigated with these procedures.

2. MATERIALS AND METHODS

2.1 Subjects

After receiving Institutional Review Board approval from the Instituto Alergoimuno de

Americana (Brazil; 10/2024), we proceeded with the electronic chart review of 9,700 outpatients who attended our facility from January 2018 to November 2024.

A cohort of 100 outside patients had been submitted to TTP with lanolin solution for presenting non–IgE-mediated atopic dermatitis and/or contact dermatitis. This cohort counted 23 males; mean age 38.9 years; SD 19.9 years; range 7 to 91 years; median 37.5 years; modes: 16; 23; 37; and 70 years (each appeared 4 times); geometric mean = 32.8 years.

A cohort of 100 outside patients had been submitted to an *ex vivo* allergen challenge test with lanolin solution monitored with LAIT for presenting non– IgE-mediated atopic and/or contact dermatitis. This cohort counted 25 males; mean age 40.9 years; SD 18,5 years; range 3 to 86 years; median 40.5 years; mode = 50 (appeared Five times); geometric mean = 35.0 years.

This study did not include patients under biological and/or systemic anti-inflammatory therapy. These procedures were offered to patients with clinical suspicion of lanolin hypersensitivity who demonstrated a non-reactive or inconclusive skin test against lanolin solution [38].

2.2 Lanolin Solution

In a Becker flask, 10 mL of lanolin (Farma Norte™) and 10 mL of glycerin [Glycerin P.A. – ACS, $C_3H_5(OH)_3$, Dinâmica™] were homogenized and kept under refrigeration (4 °C) to perform the allergic skin tests, TTP, and LAIT.

2.3 *Ex vivo* Investigation: Leukocyte Adherence Inhibition Test

2.3.1 Procedure for allergen *ex vivo* challenging

We performed the LAIT as previously described [39-49]. Shortly, each donor's fresh plasma was divided into two parts and used in paralleled *ex vivo* challenging tests with lanolin solution and the unchallenged plasma assay. We collected plasma with high leukocyte content (buffy coat) from the heparinized tube after one hour of sedimentation at 37 °C. Then, we distributed aliquots of 100 µL into Eppendorf tubes kept under agitation for 30 minutes (200 rpm at 37 °C) with lanolin solution (10µL) or without lanolin solution (when used as control).

2.3.2 Procedure for adherence assay

After incubation, the plasma was allocated into a standard Neubauer hemocytometer counting chamber with a plain, non-metallic glass surface and left to stand for 2 hours at 37 °C in the humidified atmosphere of the covered water bath to allow leukocytes to adhere to the glass. Next, we counted the leukocytes, removed the coverslip, and washed the chamber by immersion in a beaker with PBS (phosphate-buffered saline) at 37 °C. Then, we added a drop of PBS to the hemocytometer's chamber and allocated a clean coverslip over it. The remaining cells were counted in the same squares as previously examined.

2.3.3 Procedure for calculation

The percentage of Leukocyte Adherence (LA) of each assay was estimated as: (the number of leukocytes observed on the hemocytometry chamber after washing divided by the number of leukocytes observed on the hemocytometry chamber before washing) and multiplied by 100 (%). The Leukocyte Adherence Ratio (LAR) was estimated based on the ratio between the LA from the antigen-specific challenged plasma and the LA from the unchallenged control plasma: LAR = LA of the challenged sample divided by LA of unchallenged control plasma multiplied by 100 (%). To further calculate the Leukocyte Adherence Inhibition (LAI), we subtracted the LAR from 100 (%). We employed the LAI results for the cascade distribution chart and the statistics calculations, both performed with the help of the Microsoft Excel® statistical package.

2.4 *In vitro* Investigation: Tube Titration of Precipitins (TTP)

As previously reported, a transparent vitreous tube array performed the semi-quantitative TTP against the lanolin solution [50-54]. Shortly, the patient's blood was collected in a clot-activator collecting tube. After separation, the serum was centrifugated at 2,000 rpm for 10 minutes. The allergen extracts were allocated in sets of eleven glass tubes at progressive duplicated serum dilutions. The progressive dilutions were combined with the 15 µL of the antigen solution with 250 µL of the patient's serum, progressively diluted into physiological saline solution (NaCl 0,9%) in the dilution ratios of 1:1; 1:2; 1:4; 1:8;

1:16; 1:32; 1:64; 1:128; 1:256; and 1:512. One tube was a blank control done with the water and serum to observe occasional spontaneous precipitation (Sia Test). After 24 hours, the tubes were examined, and the titers (the highest dilution factor that yields a positive reading) were recorded [55].

3. RESULTS

As a retrospective survey, there was no research protocol; therefore, we report the incidental immune investigation as registered in the digital medical charts.

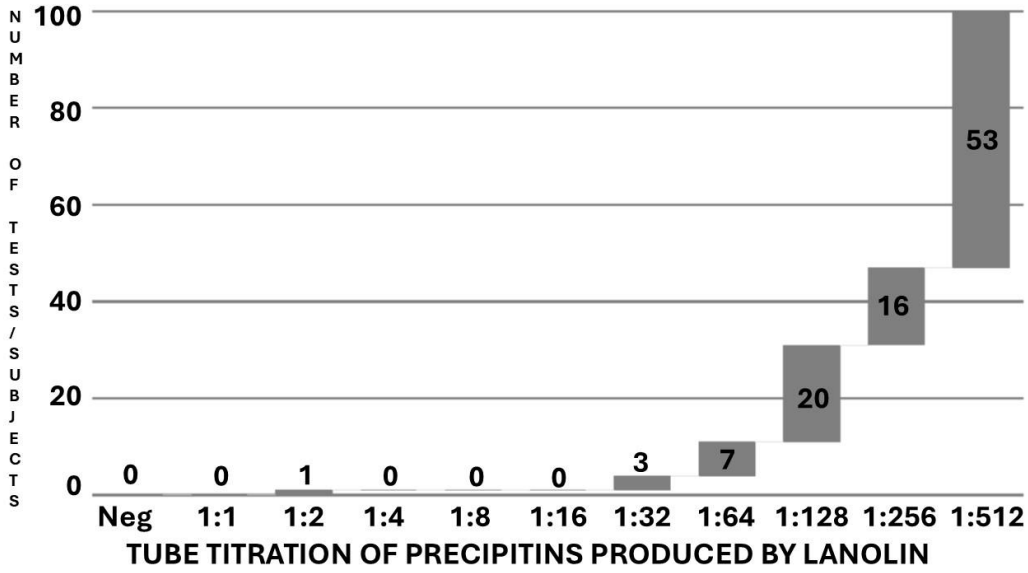

Fig. 1. Cascade distribution chart of the tube titration of precipitins (x-axis %) resulting from the lanolin solution against the serum of a cohort of 100 tests/subjects (y-axis)

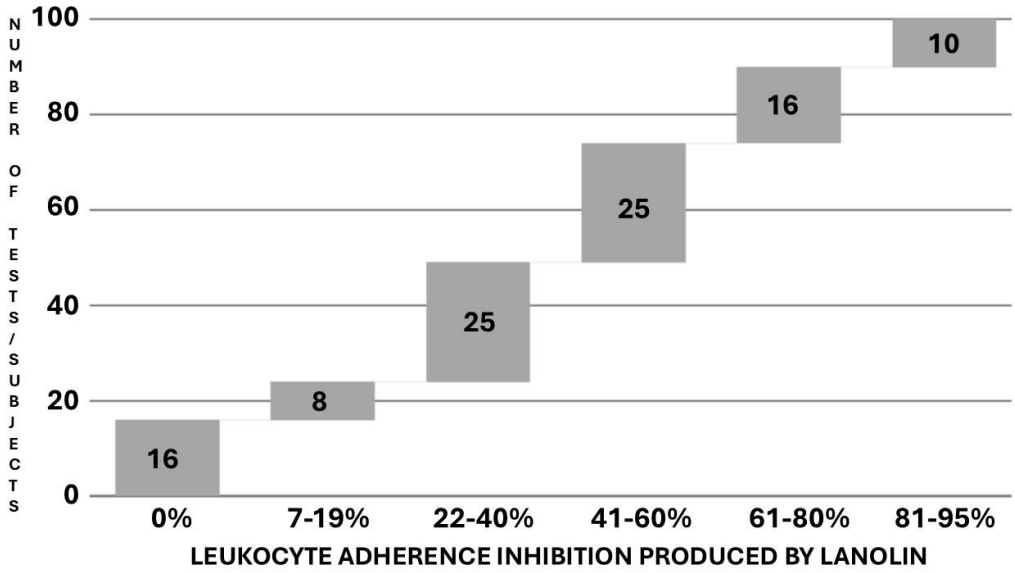

Fig. 2. Cascade distribution chart of the range groups of Leukocyte Adherence Inhibition (LAI) results (x-axis %) of *ex vivo* lanolin solution monitored by the Leukocyte Adherence Inhibition Test (LAIT), according to the respective number of outcomes over a cohort with 100 tests/subjects (y-axis)

The TTP showed a distribution concentrated over the more diluted titrations (Fig. 1). There was no negative result. The mean was estimated at 1:343; the median was 1:512; the standard deviation was estimated at 1:187; the mode was 1:512 (appeared 53 times). All Sia tests were negative.

The LAIT showed a wide distribution range of results. The LAI ranged from 0% to 95%. The mean was 41.5%; the median was 41.5%; the standard deviation was 27.3%; the mode was 0% (appeared sixteen times). The cascade distribution demonstrates a wide range spread of LAI results (Fig. 2). Half of the patients presented moderate immunoreactivity during the ex vivo challenge test (LAI = 22 to 60%). At the same time, one quarter displayed strong immunoreactivity, while the other quarter displayed low or no immunoreactivity.

4. DISCUSSION

Lanolin-based creams are frequently prescribed for patients with atopic and/or contact dermatitis due to their emollient properties [54].

The American Contact Dermatitis Society elected lanolin as the "Allergen of the Year 2023" [55].

Despite the emphasis borrowed by this title, there is a total lack of scientific studies about the physiopathology of the hypersensitivity (or hypersensitivities) against lanolin. The only tools to verify hypersensitivity against lanolin are the cutaneous tests.

There is no record in the literature of any standardized lab examination (such as specific IgE, associated cytokines, or any serologic technique) to diagnose lanolin hypersensitivity or suggest lanolin immunoreactivity. Endotyping the mechanisms responsible for allergic phenotypes is crucial, not only for diagnosis but also for supervising treatments under the perspective of personalized Medicine and recognizing differential diagnosis among phenotypes [56].

As a proof of concept, we submitted lanolin to an ex vivo challenge monitored by the LAIT to testify to cellular immunoreactivity. In the same proof-of-concept mentality, we research precipitins against lanolin to testify to humoral immunoreactivity through the TTP. Despite non-reactive or inconclusive skin tests, we propose these procedures to patients with atopic dermatitis and/or contact dermatitis with a strong clinical suspicion of hypersensitivity against lanolin. The clinical reasoning to indicate these tests is in the assumption that they may function as triage tests to reinforce the need for a more exhaustive exclusion-provocative test (when the patients exclude the suspected allergen until the symptoms disappear and then re-introduces the allergen to observe the reactions).

There was no prospective plan. We spreadsheeted the results of a retrospective compilation of data produced by TTP and TIAL, exploring humoral and cellular immunoreactivity against lanolin. These assays provide clues about humoral and cellular immunoreactivity, and the results distribute themselves in an extensive spectral range between immune tolerance and symptomatic hypersensitivity. Results provided by LAIT and TTP were interpreted as markers of the immune response after contact with the specific antigen, configuring themselves as techniques to identify exposition to the antigen, as proposed by the exposome-wide association study [57].

This retrospective survey demonstrated significative cellular and humoral immunoreactivity demonstrated by the TTP and the *ex vivo* challenge test monitored by LAIT against lanolin in two cohorts of patients with atopic and/or contact dermatitis. All patients evaluated with TTP demonstrated some degree of humoral immunoreactivity (there was no negative result), and most presented positivity by the more diluted titrations, demonstrating that lanolin allergens are widespread among patients with dermatitis and are highly immunogenic. Sixteen patients did not present cellular immunoreactivity against lanolin (LAI = zero%). In contrast, others presented an extensive range of inhibition of the leukocyte adherence after the *ex vivo* provocation test, suggesting that cellular immunoreactivity must be a better parameter to differentiate hypersensitivity reactions among patients.

None of our patients presented an exclusive reaction to lanolin. We assessed every patient simultaneously with several chemical and biological allergens, demonstrating positive results for some of them, according to the clinical suspicions. The most vital suggestion driven by the results is that allergic patients may impair their symptoms by using creams or cosmetics produced with lanolin.

In our practice, we have observed immediate cutaneous reactions (obtained by the skin scrape

test) and delayed reactions obtained by a forty-eight-hour contact test or a photosensitized ninety-six-hour contact test (patch test). Based on this clinical experience, we can hypothesize that at least three endotypes are associated with lanolin hypersensitivity. The results presented by this work demonstrated that there is yet a lot unknown about the endotypes responsible for lanolin hypersensitivity, which may be produced by at least three mechanisms: a predominantly humoral, a predominantly cellular, and a compound of both.

5. LIMITATIONS

This study is a retrospective analysis of data collected over six years. There was no protocol research, and the subject's data was limited to the essentials available on our electronic sheets. Therefore, we could not establish a cross-comparison between positive and negative controls to validate the results. The number of subjects is appropriate for a preliminary study; however, future studies must be more comprehensive. The lack of a research protocol implies the possibility of a bias produced by the physician's point of view, who suggested the exam barely on clinical suspicion led purely by the anamnesis and physical examination. The study lost many of these patients to follow-up, so assuring the relationship between the immunoassays' results and the patient's clinical outcome is impossible.

6. CONCLUSION

Our preliminary results show that the LAIT and TTP may differentiate diverse cellular and humoral immunoreactivity degrees against lanolin in patients clinically diagnosed with Non–IgE-mediated allergies. This methodology can provide a socioeconomic impact since the technologies to perform TIAL and TTP are inexpensive and can be performed in a single lab room attached to the facilities with minimum laboratory equipment. However, the propaedeutic meaning of these results and the possibility of interferents must be better established [58]. More studies focused on the quality-by-design approach with prospective larger double-blind cohorts need to evaluate the potential contribution of LAIT and TTP for endotyping immunoreactivity of patients suspected of symptomatic hypersensitivity against lanolin and other similar food processing additives [59]. We are planning future work with control groups to draw more substantiated conclusions.

7. FUTURE DIRECTIONS AND RECOMMENDATIONS FOR CLINICAL PRACTICE

The primary intended use of *in vitro* or *ex vivo* allergen challenge tests is to spare the patients from being submitted to unnecessary, exhaustive, and dangerous *in vivo* challenge tests. Exploring the humoral and the cellular arms of immune systems, the TTP and TIAL alone or combined may represent, in the near future, a tool for allergists to construct an etiologic diagnosis from their patients, as well as determine the endotypes (mechanisms) of hypersensitivity, in order to choose more convenient and personalized therapies for them.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

ETHICAL APPROVAL

As a retrospective survey of results recorded *in cognito*, consent was given collectively by the institution's ethics committee following the principles of the Declaration of Helsinki [60].

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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