Prevalence of contact allergy to corticosteroids in a Danish patient population

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Abstract

Background: Allergic contact dermatitis to corticosteroids can be a challenging diagnosis as corticosteroids are used in the treatment of dermatitis. The prevalence of contact allergy to corticosteroid varies between previous studies.

Objective: To study the prevalence of sensitization to budesonide, tixocortol-21-pivalate and hydrocortisone-17-butyrate in a Danish patient population from 2006-2020, cross-sensitization, risk factors and clinical relevance.

Methods: A retrospective analysis of patch test data and MOAHLFA index was performed among 6823 patients consecutively patch tested with TRUE test as part of the baseline series.

Results: A positive patch test for corticosteroids was found in 185 patients (1.2% budesonide, 1.6% tixocortol-21-pivalate, 1.0% hydrocortisone-17-butyrate) without gender difference. For women, the prevalence of tixocortol-21-pivalate sensitization increased significantly from 1.3% in 2006–2008 to 2.9% in 2018–2020. Tixocortol-21-pivalate sensitization had more frequently clinical relevance in women (61.3%) compared to men (34.5%). Age above 40 years was positively associated to corticosteroid sensitization. Budesonide and hydrocortisone-17-butyrate accounted for 67.7% of co-sensitizations.

Conclusions: The prevalence of corticosteroid sensitization was 2.7%. Age was the only risk factor for corticosteroid sensitization. The frequency of corticosteroid sensitization was stable over time except for tixocortol-21-pivalate sensitization for women. About one third of sensitized patients had co-sensitizations to other corticosteroid groups.

Keywords
allergic contact dermatitis, allergy, budesonide, contact allergy, corticosteroid, hydrocortisone-17-butyrate, hypersensitivity reactions, patch test, skin testing, tixocortol-21-pivalate
1 | INTRODUCTION

Corticosteroid creams and ointments are anti-inflammatory and immunosuppressive medications with a plethora of different indications of heterogeneous, often chronic, inflammatory dermatoses.

Adverse reactions to topical corticosteroids are various and depend on non-immunologic (e.g., atrophy, striae, acne) and immunologic reactions.\textsuperscript{1,2} Allergic adverse reactions to corticosteroids of delayed type is well described in patients using topical corticosteroids and the prevalence estimated to 1.5\%–4.1\%,\textsuperscript{3–5} whereas immediate-type systemic hypersensitivity after oral, parental or intra-articular steroids is more rare (0.3\%–0.5\%).\textsuperscript{6,7}

In 1989, Coopman et al.\textsuperscript{8} classified corticosteroids into four reactions groups (A, B, C, D) according to biochemical heterogeneity. Lepoittevin et al.\textsuperscript{9} described the importance of corticosteroid D-ring, and Matura et al.\textsuperscript{10} subdivided group D according to lability of esters. In 2011, Baeck et al. proposed the most recent classification of corticosteroid molecules into three groups according to the allergenic properties on the basis of patch test results and molecular modelling.\textsuperscript{11,12} Patients can be sensitized to one or multiple groups (cross-reactivity and/or co-reactivity).\textsuperscript{11–13}

Allergic contact dermatitis (ACD) to corticosteroids is challenging to distinguish from deterioration of the disease for which corticosteroids was prescribed due to the anti-inflammatory effect of the drug.\textsuperscript{2,14} The lesions may manifest as eczema, exanthema, purpura, urticaria.\textsuperscript{15} The inherent anti-inflammatory potency of corticosteroids influences the reading time; therefore, late readings on day D7, or even later is recommended.\textsuperscript{16,17}

From a dermatological perspective, increasing amount of corticosteroids applied to the skin increases the risk for delayed hypersensitivity, as the route of contact sensitization to topical corticosteroids is primarily cutaneous.\textsuperscript{16} Therefore, chronic dermatoses such as atopic dermatitis (AD) and stasis dermatitis of the lower extremities are specifically associated with development of ACD to corticosteroids.\textsuperscript{6,19}

In 2011, Vind-Kezungov et al.\textsuperscript{19} reported a prevalence of 2\% ACD to corticosteroids in a Danish patient population. To the best of our knowledge, there are no recent data on topical corticosteroids sensitization in Nordic patients.

The objective of this retrospective study was to investigate the prevalence and fluctuation of sensitization and ACD to corticosteroids among patients patch tested between 2006 and 2020 at Odense University Hospital, Denmark. The study further aimed to assess the co-reactivity of sensitizations to budesonide, tixocortol-21-pivalate and hydrocortisone-17-butyrate as well as the relation of the ACD to corticosteroids to eczema location, gender and age.

2 | METHODS

2.1 | Design and study population

This study was a retrospective study of all patients with suspected allergic contact dermatitis patch tested between January, 2006, and December, 2020, performed consecutively at the Department of Dermatology and Allergy Centre, Odense University Hospital, Denmark.

Data on patch test results, information about the relevance of the positive patch test reactions (current, past or unknown) and study population characteristics by the internationally accepted MOAHLFA index (acronym for: M = Male, O = Occupational dermatitis, A = Atopic dermatitis [current or previous], H = Hand dermatitis, L = Leg dermatitis, F = Facial dermatitis, A = Age > 40 years) method,\textsuperscript{20} were retrieved from the Allergen database, Odense University Hospital (journal no. 21/14482). The corticosteroid patch test data were stratified by test year, sex and age group. If patients were patch tested more than once in the test period, solely the last patch test result was included for further analysis.

2.2 | Patch testing

The patch testing was routinely performed with standard series of commercial allergens embodying the TRUE Test (SmartPractice A/S)\textsuperscript{21} with tixocortol-21-pivalate, budesonide and hydrocortisone-17-butyrate. The patch tests were applied on the upper backs of patients for 2 days and routinely read on D3 or D4, and D7.\textsuperscript{17} The reactions on the readings were categorized as: negative (−), irritant reaction (IR), doubtful (+?), positive (+++, ++ or ++++), by the clinician, according to the recommendations of the International Contact Dermatitis Research Group (ICDRG).\textsuperscript{22} Patch reactions categorized as −, IR and +? were registered as non-allergic responses.

Clinical relevance was subsequently assessed by a dermatologist according to exposure history and dermatitis pattern. The positive reactions were categorized into current, past or unknown relevance. Cases without registration of relevance were categorized as ‘unknown relevance’.

2.3 | Statistics

Comparison of frequency of patch test sensitizations and anamnestic relevance between males and females were performed by the chi-squared ($\chi^2$) test (Table 1). Comparison of the MOAHLFA characteristics frequencies between males and females as well as corticosteroid sensitized and non-sensitized subjects were performed by the $\chi^2$ test and the Fisher’s exact test ($n < 5$) (Table 2). A $\chi^2$ trend-test (Cochran–Mantel–Haenszel tests) tested for significant trends across the test years (Figure 2).

Logistic regression analyses with corticosteroid sensitization (budesonide, tixocortol-21-pivalate and/or hydrocortisone-17-butyrate) as the dependent variable and each specific MOAHLFA characteristics as independent variables and adjusted for the other confounding MOAHLFA characteristics were established (Table 2). Similar logistic regression models with test years (as continuous variable as well as 3-year intervals), age group and an interaction term between test years and age group as the explanatory variable, likewise
with sex and an interaction term between test years and sex as the independent variable were established.

Level of statistical significance for two-sided test was $p$ value <0.05 (set to 5% in all analyses); $p$ value = 0.05–0.10 was considered a trend. The results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The data analysis was performed with STATA version 12 (StataCorp.).

### 2.4 | Ethics

The Allergen database (journal no. 21/14482) and the present project (journal no. 21/27686) were approved by the Danish Data Protection Agency.

### 3 | RESULTS

A total of 6823 patients (65.2% females and 34.8% males) were patch tested between 2006 and 2020. The overall prevalence of corticosteroid sensitization was 2.7% ($n = 185$, 2.4% of men and 2.9% of women) across the test years (Table 1).

Of all corticosteroid sensitized ($n = 185$), 11.6% ($n = 21$), 47.6% ($n = 88$) and 7.6% ($n = 14$) were solely sensitized to budesonide, tixocortol-21-pivalate and hydrocortisone-17-butyrate, respectively. Concomitant sensitization was present for 22.7% ($n = 42$) to budesonide and hydrocortisone-17-butyrate, 3.2% ($n = 6$) for budesonide and tixocortol-21-pivalate and 1.1% ($n = 2$) for tixocortol-21-pivalate and hydrocortisone-17-butyrate. Twelve patients (6.5%) were sensitized to all three allergens (Figure 1).
The logistic regression models showed that the fluctuations in the prevalence of the sensitizations across the test years were not significantly dependent on age group ($p > 0.05$), but changes in the prevalence of budesonide sensitization ($p = 0.020$), tixocortol-21-pivalate sensitization ($p = 0.024$) and hydrocortisone-17-butyrate sensitization ($p = 0.024$) across the test years were significantly dependent on sex (data not shown). Thus, prevalence of corticosteroid sensitization across the test years is stratified by sex.

Figure 2 illustrates the change in corticosteroid sensitization among patch tested patients between 2006 and 2020. The overall prevalence of corticosteroid sensitization was 2.4% and 2.9% for men and women, respectively. The prevalence of tixocortol-21-pivalate sensitization increased significantly among female patients from 1.3% in 2006–2008 to 2.9% in 2018–2020 ($p = 0.043$). No other significant increase or decrease in the prevalence of corticosteroid in total or allergen-specific sensitization across the test years was found. However, Figure 2A shows that the prevalence of budesonide sensitization in men occurred approximately bell shaped.

Men more frequently than women experienced contact sensitization to budesonide and hydrocortisone-17-butyrate between 2012 and 2014, whereas women more frequently had sensitization to tixocortol-21-pivalate than men between 2018 and 2020. The differences were not consistent in the overall prevalence of corticosteroids (data not shown). The clinical relevance for tixocortol-21-pivalate was more frequent in women (61.3%) than in men (54.6%) ($p = 0.019$, Table 1).

The MOAHLFA index of the corticosteroid sensitization patients is presented in Table 2. The analyses showed no association between corticosteroid sensitization and sex, occupation, atopy or dermatitis of
face, hand or leg (Table 2). Significantly more patients with corticosteroid sensitization were above 40 years of age ($p < 0.001$). A trend towards a negative association between corticosteroid sensitization and occupational dermatitis was not observed in the adjusted logistic regression analysis (Table 2).

Facial dermatitis occurred significantly more often in women than in men with corticosteroid sensitization ($p = 0.016$), whereas leg ulcer/dermatitis was significantly more frequent in men than in women ($p = 0.034$), but rarely registered.

The $\chi^2$ test showed no association between budesonide sensitization and sex, occupation, atopic diseases or localization of eczema of face, hands or legs, which remained insignificant in the adjusted logistic models. However, significantly more patients with budesonide sensitization were older than 40 years of age ($p = 0.004$), which remained associated in the adjusted logistic regression model (data not shown). The $\chi^2$ test showed no association between tixocortol-21-pivalate sensitization and sex, age, atopy, dermatitis of hands or face. Significantly more patients with tixocortol-21-pivalate sensitization had leg dermatitis ($p = 0.043$) and age above 40 years old ($p \leq 0.001$), whereas the association only remained present for age ($p < 0.05$) in the adjusted logistic regression models. A trend towards negative association between male gender and tixocortol-21-pivalate sensitization was present in crude analysis as well as adjusted logistic regression analysis (data not shown). The $\chi^2$ test showed no association between hydrocortisone-17-butyrate sensitization and sex, occupation, atopy nor dermatitis of face, hands or legs. Significantly more patients were older than 40 years of age ($p = 0.003$), which remained associated in the adjusted logistic regression model (data not shown).

## DISCUSSION

The overall prevalence of contact sensitization to corticosteroid was 2.7% between 2006 and 2020 and in concordance with previously reported data from various European patch test populations,\textsuperscript{19,23,24} whereas recent data report decreasing trends of corticosteroid sensitizations with overall prevalence of 1.5%.\textsuperscript{3,4}

Budesonide sensitization of 1.2% was somewhat in concordance of expectations as various European multicentre studies before 2015 reported budesonide sensitization prevalence of 1.2%\textsuperscript{17} and 1.0%\textsuperscript{19} in Danish studies, supported by 1.8%,\textsuperscript{25,26} 1.6%\textsuperscript{24} and 1.4%\textsuperscript{27} in European populations. A Belgium study reported an overall budesonide sensitization of 1.9% between 1990 and 2014.\textsuperscript{23}

Recently, European multicentre studies reported decreased prevalence of 0.6%–0.7%,\textsuperscript{3,4,18} while the prevalence in our study was stable from 2006 to 2020.

The overall prevalence of tixocortol-21-pivalate sensitization was 1.6%, which was twice the only previous Danish report of 0.8% between 2005 and 2008\textsuperscript{19} and recent data by the European Surveillance System on Contact Allergies (ESSCA) which reported prevalence of 0.6%–0.8% depending on concentration between 2015 and 2018 (0.1% and 1% eth, respectively).\textsuperscript{4} The prevalence of sensitization in other reports have also been declining; 2.7% in 2003–2004,\textsuperscript{25} 1.4% in 2007–2011,\textsuperscript{27} 1.1% in 2008–2012,\textsuperscript{26} 0.3% in 2015,\textsuperscript{3} whereas overall prevalence between 1990 and 2014 was reported to be 1.6% in one study.\textsuperscript{23} However, most recently, Murphy et al.\textsuperscript{28} reported 1.9% tixocortol-21-pivalate sensitization prevalence between 2014 and 2019.

We report 1% hydrocortosone-17-butyrate sensitization in agreement with a previous Danish study from 2005 to 2008.\textsuperscript{19} Within the recent decade, studies report declining prevalence of hydrocortisone-17-butyrate sensitizations; 1.2% between 1990 and 2014,\textsuperscript{23} 0.3% in 2015,\textsuperscript{3} 0.2% between 2015 and 2016 in North America\textsuperscript{29} and 0.3% between 2015 and 2018 by the ESSCA ($n = 51,914$).\textsuperscript{4}

Age above 40 years was an only individual risk factor for development of corticosteroid sensitization, as previously reported.\textsuperscript{3,18} The time lived intuitively increase risk of corticosteroid skin contact, risk of chronic dermatosis and thereby cumulative dose of topical corticosteroids. The risk of inducing contact sensitization to corticosteroids is increased by cumulative exposure, simultaneous occlusion, potency of the allergen and the nature of the skin treated.\textsuperscript{30,31} Facial dermatitis was significantly more frequent in sensitized women than men, as expected,\textsuperscript{32} but facial dermatitis as risk factor was not associated with corticosteroid sensitization. Leg dermatitis was more frequent in men than in women ($p = 0.016$), but only few ($n = 5$) with registered leg dermatitis were sensitized to corticosteroids. Atopic dermatitis and hand eczema were not a risk factor for steroid sensitization.

The principal markers to detect most corticosteroid contact allergies are tixocortol-21-pivalate, budesonide and hydrocortisone-17-butyrate,\textsuperscript{2} which are surrogate markers for corticosteroid group 1.\textsuperscript{11,12} Tixocortol-21-pivalate and budesonide detect approximately 90% of patients with contact sensitization to corticosteroids.\textsuperscript{11,33} In Denmark, selected group 1 corticosteroids including hydrocortisone, which can be purchased over-the-counter. For males, the overall prevalence of corticosteroid sensitization was bell shaped, but the prevalence was primarily driven by budesonide sensitization. A significant linear increase of tixocortol-21-pivalate sensitization in women was observed throughout the test years. The tixocortol-21-pivalate sensitization was further trending towards more frequent in women and significantly more anamnestic relevant in women compared to men. These observations may be explained by the more frequent facial dermatitis in females, which primarily is treated with low-potency corticosteroids.\textsuperscript{32} Fear of high-potency corticosteroids and the easy over-the-counter access may cause women to increase usage of low-potency corticosteroids and thereby induce more cumulative exposure to group 1 corticosteroid.

Concomitant sensitization was frequent for budesonide and hydrocortisone-17-butyrate. The S-isomer of Budesonide is expected to cross-/co-react with hydrocortisone-17-butyrate due to molecular properties.\textsuperscript{12,34} The majority of patients sensitized to budesonide or hydrocortisone-17-butyrate additionally had positive patch test to other corticosteroid marker, but not as frequent as previously reported.\textsuperscript{34,35}

The study population is comprised to patients referred to a tertiary referral centre, thus potentially suffering from more severe dermatoses, which may indicate a referral bias, and thus a possible
over-estimation of corticosteroid sensitization. Our study report a relatively high prevalence of corticosteroid sensitization in the Danish population. The variability in prevalence of corticosteroid sensitization between studies may be due to diverse demographics, regional different prescribing habits of topical corticosteroids (potency, quantity), treatment traditions and the nature of the skin problems for which the CS were prescribed. The diagnostic procedures may differ in regard to awareness of corticosteroid allergy among medical professionals and patch testing methodologies as tested substances, vehicles and concentration of corticosteroid allergens. Interpreting relevance of steroid sensitization is an individual evaluation by the supervising clinician cause inter-individual variations. The patch test readings were performed on both D3/4 and D7, as early readings alone may underestimate sensitization by one-third.

In conclusion, this retrospective study encompassed 6823 consecutively tested dermatitis patients over a 15-year period with an estimated corticosteroid sensitization prevalence of 2.7% with an increasing trend for tixocortol-21-pivalate in female patients. Age above 40 years was identified as the only individual risk factor for development of corticosteroid sensitization.

CONFLICTS OF INTEREST
The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT
The data are not available due to ethical restrictions.

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