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Interaction of Resistin and Systolic Blood Pressure in Psoriasis Severity

Journal of Investigative Dermatology (2020) **140,** 1279–1282; doi:10.1016/j.jid.2019.07.727

TO THE EDITOR

In a prospective cohort study, Snekvik et al. (2017) observed that obesity doubles the incidence risk for psoriasis. This finding may be attributable to the inflammatory role of adipokines: adipose-tissue associated hormones, including resistin, leptin, and adiponectin. Resistin induces inflammatory markers, including tumor necrosis factor-alpha and IL-6 (Johnston et al., 2008). Independent associations have been reported between psoriasis, elevated serum resistin levels, and cardiovascular disease (CVD) (Huang et al., 2015; Muse et al., 2015; Pina et al., 2015; Takahashi et al., 2013). Furthermore, resistin levels are elevated in hypertensive patients (Papadopoulos et al. 2007; Zhang et al. 2017) and are positively correlated with systolic blood pressure (SBP) (Makni et al., 2013; Norata et al., 2007), suggesting that resistin may be a risk factor for hypertension, or vice versa. Hypertension, adipocyte activation, resistin recruitment of tumor necrosis factor and/or IL-6 and subsequent skin inflammation may lead to psoriasis intensification in susceptible cohorts. Therefore, resistin is a possible link between psoriasis and increased cardiovascular risk.

We initially examined the correlation between resistin levels and psoriasis severity (expressed as the Psoriasis Area and Severity Index [PASI] score) in a primary patient cohort identified through the Murdough Family Center for Psoriasis. Resistin, leptin, high-density lipid, and low-density lipid levels in the serum of these patients were measured. We included only those participants with quantified resistin levels (n = 100). In Figure 1, the correlation between PASI and resistin levels are shown, with outliers winsorized to the 5th and 95th percentiles (Ghosh and Vogt, 2012). Although outliers were found, the assessment of all other measures of these patients was within the standard levels for our cohort. Therefore, we presented all the resistin and PASI data and probed for whether or not this relationship may be modified by covariates, including sex, race, smoking, atherosclerosis status, age, body mass index, low-density lipid/ high-density lipid ratio, and SBP (transformed from continuous to a binary variable based on the median SBP [normal: < 131 mmHg, high: > 131 mmHg]). We depicted this data and correlation analysis between PASI and resistin stratified by SBP category. Supplementary Figure S1 depicts the resistin-PASI relationship for those with (i) Low SBP < 131 mmHg (n = 50), (ii) High SBP > 131 mmHg (n = 50), and combined, with scatter representing observed data, and solid colored lines representing unadjusted trend lines.

Table 1 (column 1) summarizes patient characteristics. The median PASI score was 7.95 (3.6–15.5). The median resistin was 6,362.6 (2,883–12,079) pg/L. The mean SBP was 128.1 + 16.8 mmHg/ml. The median SBP was 131 mmHg/ml. The median resistin in the non-hypertensive group was 6,012.8 pg/L compared to a median resistin of 6,750.7 pg/L in the hypertensive group ($P = 0.39$, Wilcoxon test).

A multivariable analysis revealed a positive relationship between the resistin and PASI score ($P < 0.0001$) after adjusting for age, sex, and SBP (Table 1, adjusted model 1), supporting the evidence of an association between resistin and psoriasis severity.

Because previous findings demonstrated that patients with psoriasis are more likely to develop hypertension and that hypertensive patients have elevated resistin levels, we were also interested in exploring whether SBP influenced the resistin-PASI relationship (Armstrong et al. 2013; Papadopoulos et al. 2007; Qureshi et al. 2009; Zhang et al. 2017). To determine if the PASI-resistin relationship varied between patients

Abbreviations: CVD, cardiovascular disease; PASI, Psoriasis Area and Severity Index; SBP, systolic blood pressure

Accepted manuscript published online 15 November 2019; corrected proof published online 16 December 2019

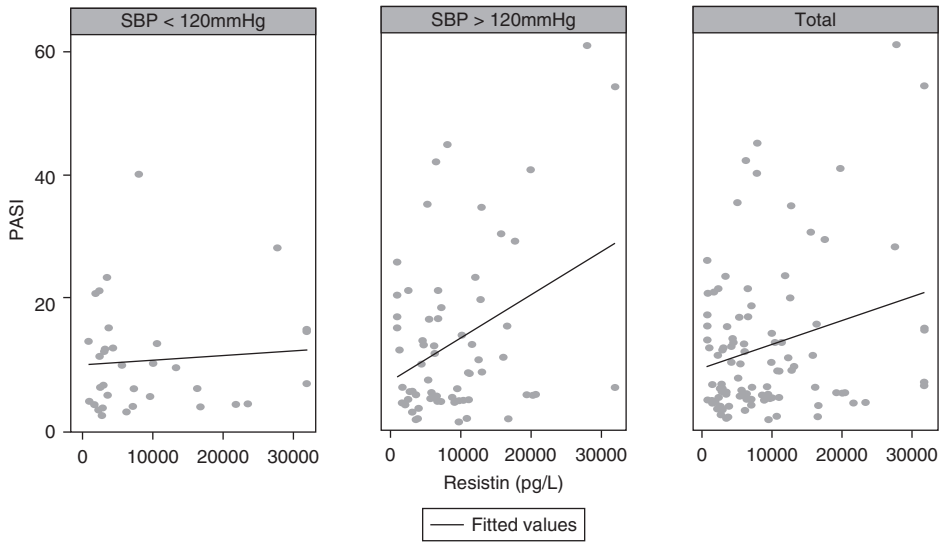

Figure 1. PASI-resistin relationship stratified by SBP category. Graphs depict resistin-PASI relationship for those with (i) Low SBP < 120 mmHg (n = 34), (ii) High SBP > 120 mmHg (n = 66), and (iii) all patients (n = 100), with scatter representing observed data and solid lines representing unadjusted trend lines. Outliers were winsorized to the 5th and 95th percentiles (Ghosh and Vogt, 2012). PASI, Psoriasis Area and Severity Index; SBP, systolic blood pressure

with hypertension and those without it, we included an interaction term to test for the effect of modification by SBP in our multivariable model:

Covariates that remained statistically significant at the $\alpha = 0.10$ level were sex and the interactive variable of resistin and binary SBP (Table 1, adjusted model 2). These findings suggest that SBP is an effect modifier on the relationship between PASI and resistin in our cohort. The model indicates that among those with low and/or normal SBP, every 10,000 pg/L increase in resistin is associated with a 0.9-point increase in the PASI score (covariates held constant). In contrast, among those with high SBP, a 10,000 pg/L increase in resistin is associated with a 5.4-point increase in the PASI score (covariates held constant), a six-fold difference.

These findings suggest that resistin is positively associated with PASI in our cohort and that this relationship is augmented by SBP. Conversely, in patients with high blood pressure,

Table 1. Multivariable Analyses of PASI-Resistin Association

	Descriptive	Adjusted Model 1[2]		Adjusted Model 2[3]	
Characteristic (n = 100)	**Median (IQR) or N%**	**Coefficient (95% CI)**	***P* value**	**Coefficient (95% CI)**	***P* value**
PASI	7.95 (3.6–15.5)				
Resistin (pg/L)	6,362.62 (2,883–12,079)	**0.0004 (0.0002–0.0006)**	**<0.0001**	0.00009 (0.0002–0.0004)	0.562
Age (Years)	46.2 (33.4–58.1)	-0.12 (-0.27 to 0.03)	0.117	-0.12 (-0.26 to 0.03)	0.114
Female	48.0%	4.12 (-0.41 to 8.67)	0.057	4.19 (-0.24 to 8.62)	0.064
Caucasian	87.0%	–	–	–	–
Smoking	38.0%	–	–	–	–
Current use of ACE inhibitors	14.0%	–	–	–	–
BMI (kg/m^2)	28.8 (24.3–34.4)	–	–	–	–
Atherosclerosis[1]	60.7%	–	–	–	–
Psoriatic Arthritis	14%	–	–	–	–
SBP (mmHg)	131 (115.5–139)	–	–	–	–
High SBP (> 131 mmHg)	50%	5.41 (0.53–10.30)	0.030	1.02 (-5.09 to 7.12)	0.741
Resistin * SBP category (> 131 mmHg vs. < 131 mmHg)	–	–	–	**0.00045 (0.00007–0.0008)**	**0.024**
LDL/HDL Ratio	2.3 (1.8–3.0)	–	–	–	–

Abbreviations: ACE, angiotensin converting enzyme; BMI, body mass index; CI, confidence interval; IQR, interquartile; LDL, low-density lipid; HDL, high-density lipid; PASI, Psoriasis Area and Severity Index; SBP, systolic blood pressure.

Boldface represents statistically significant associations.

[1]Data regarding atherosclerosis status was available in 89% of the patients.

[2]Model 1 was determined based on the backward selection of covariates and adjusts for sex (male vs. female), systolic blood pressure category (>131 mmHg vs. < 131 mmHg), and age.

[3]Model 2 was determined based on the backward selection of covariates and adjusts for sex (male vs. female), systolic blood pressure category (> 131 mmHg vs. < 131 mmHg), age, and interaction term of resistin*SBP category.

increasing PASI severity leads to elevated resistin levels (results not shown), which may mark a population that needs additional cardiovascular attention. This demonstrates the importance of exploring interaction terms to assess whether the effect of an exposure varies across different groups (Corraini et al., 2017; Gail and Simon, 1985). Effect modification assesses heterogeneity across cohorts, which may be used to inform treatments and research (Wang et al., 2007). For example, pravastatin's efficacy in reducing coronary events was greater in patients with an elevated baseline low-density lipid (Sacks et al., 1996; Wang et al., 2007). It is particularly important for relationships involving overlapping pathways, such as that between psoriasis and cardiovascular risk (Makni et al., 2013; Norata et al., 2007). In the search for cardiovascular risk biomarkers, interaction term analyses may indicate that psoriasis patients cannot be treated as one group, revealing endotypes with different risks and/or needs.

Thus, in the psoriasis subset with hypertension, resistin elevation appears to associate with more intense psoriasis expression and may biomark a higher CVD risk population via adipocytokine-mediated inflammation. One limitation of our study is its cross-sectional nature; therefore, the association of the interaction term of resistin and SBP with psoriasis disease severity warrants further research into the biomarkers of CVD in psoriasis. Furthermore, these findings are purely correlative, not causative, and merit further study. The findings presented here build on prior work on CVD-psoriasis biomarkers that demonstrated that myeloperoxidase, a pro-inflammatory hemeprotein associated with CVD events, is elevated 2.5-fold in psoriasis patients (Cao et al., 2013; Dilek et al., 2016). We contend that resistin and SBP are additional biomarkers to consider for cardiovascular risk among psoriasis patients.

The data came from a psoriasis prevalence data set from University Hospitals Cleveland Medical Center and the Murdough Family Center for Psoriasis, Cleveland, Ohio with data on 276 individuals with skin disorders. Study participants completed a detailed questionnaire, including socio-demographics, smoking history, current medications and treatments, psoriatic arthritis, and cardiovascular disease. Resistin, leptin, high-density lipid, and low-density lipid levels in serum were measured. We included only those participants with quantified resistin levels (n = 100).

Participant characteristics were reported as medians with interquartile ranges for non-parametric variables and as means with standard deviations for parametric variables. Proportions were reported for binary variables. Univariate regression was performed using independent t-tests to test each covariate against the PASI score at a significance level of $\alpha = 0.10$. Potential covariates were selected based on the existing literature and backward selection using Akaike's information criteria to reduce overfitting. The model diagnostics included independence of residuals, heteroscedasticity, multicollinearity, and influential outliers. Based on the existing literature, we were interested in the potential effect modification of SBP on the relationship between PASI score and resistin. For clinical interpretability, we transformed SBP from a continuous to a binary variable.

As the study is exploratory in nature, *P*-values are reported without correction for multiple testing. All the analyses were performed in Stata 14 (College Station, TX).

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available owing to privacy concerns of research participants.

ETHICS STATEMENT

This study was approved by the University Hospitals Human Research Committee (IRB 03-07-10).

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CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Ming Li for her statistical support. This work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Numbers T32AR007569 and P50AR070590. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This study was supported through funding from the Murdough Family Center for Psoriasis and Skin Diseases Research Center.

AUTHOR CONTRIBUTIONS

Conceptualization: DS, KDC, TSM, MC; Data Curation: DS, JBG, ANE, GD; Formal Analysis: DS, GD, JBG, ANE; Funding Acquisition: KDC, TSM, MC; Investigation: DS, JBG, ANE; Methodology: GD, JBG, ANE; Resources: KDC, TSM, MC; Software: DS, JBG; Supervision: KDC, TSM; Validation: GD, ANE, MC, Visualization: DS, JBG, GD; Writing – Original Draft: DS, GD, KDC, TSM, MC; Writing – Review & Editing: DS, ANE, JBG, GD, MC, KDC, TSM

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2019.07.727.

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The Utility of T-Cell Clonality in Differential Diagnostics of Acute Graft-versus-Host Disease from Drug Hypersensitivity Reaction

Journal of Investigative Dermatology (2020) **140,** 1282–1285; doi:10.1016/j.jid.2019.11.009

TO THE EDITOR

Graft-versus-host disease (GVHD) is a severe complication of hematopoietic stem cell transplantation. The skin involvement often appears before the involvement of other organs. Cutaneous manifestations of acute GVHD have features that are similar both clinically and histologically to other morbilliform eruptions, such as drug hypersensitivity reaction (DHR) and viral or bacterial exanthem, thus creating a diagnostic pitfall. The correct diagnosis of DHR versus GVHD is crucial because the therapy for those two conditions has a different direction: discontinuation of the offending agent in DHR and early administration of a high dose of systemic steroids in GVHD.

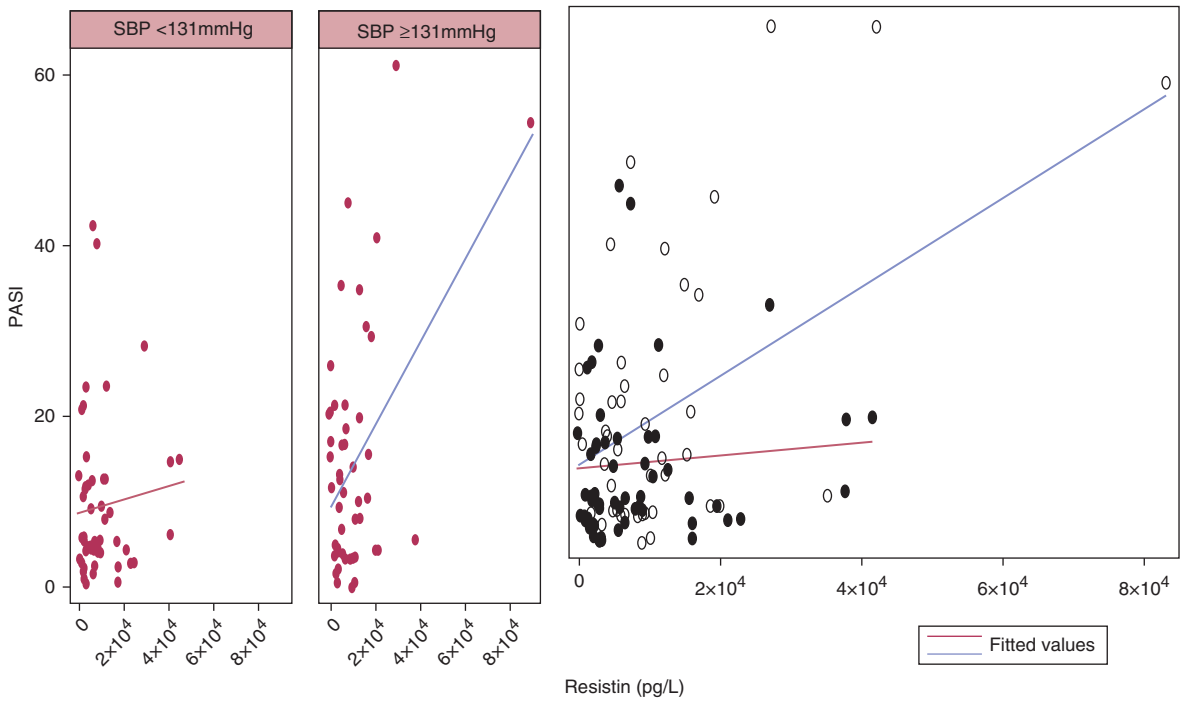
Previous investigations have shown that GVHD has a lower T-cell receptor (TCR) repertoire diversity and is characterized by expansion of certain T-cell clones (Yew et al., 2015), suggesting that GVHD is mediated by clonal amplification of T cells. As opposed to GVHD, the T-cell response in hapten-induced delayed-type DHR can be nonspecific and polyclonal, reacting to multiple antigens affected by one small molecule (Illing et al., 2012; Schrijvers et al., 2015). Because the clonal diversity of GVHD and DHR is different, we hypothesize that GVHD may be distinguished from DHR based on the presence of dominant TCR clones.

To test this hypothesis, we performed immunosequencing of the TCR β chain on formalin-fixed, paraffin-embedded skin samples obtained from 17 patients, including seven patients with DHR and 10 patients with acute GVHD (Tables 1 and 2). Skin biopsies were obtained from a biobank repository (University of Pittsburgh Institutional Review Board protocol PRO15090247). None of those patients had been treated with systemic steroids before the procedure. None of those patients used topical steroids at the site of future skin biopsy. Of the seven patients with DHR, antibiotics were the inciting drugs for six patients; allopurinol or hydroxyurea was for one patient. The rash started up to three weeks after the initiation of the inciting drugs. All seven patients had exanthematous morbilliform drug eruption on their trunk and extremities; one patient also had facial involvement. No patient presented with diarrhea or an abnormal liver function test. Rash resolved upon cessation of the inciting drugs (two patients) or initiation of topical (two patients) or systemic steroids (three patients). Of the 10 patients with GVHD, all had morbilliform exanthem on their trunk and extremities; four had facial involvement. Four patients presented with diarrhea; three presented with transaminitis.

We sequenced the CDR3 region of the TCR β chain using the high-throughput immunoSEQ Assay (Adaptive Biotechnologies, Seattle, WA) (Robins et al., 2009, 2012; Carlson et al., 2013). The CDR3 region of the TCRβ loci was amplified from genomic DNA using PCR primers specific for all Vβ and Jβ genes, barcoded, and sequenced. Individual sequence reads were mapped to TCR genes and

Abbreviations: DHR, drug hypersensitivity reaction; GVHD, graft-versus-host disease; SN, sensitivity; SP, specificity; TCR, T-cell receptor

Accepted manuscript published online 2 December 2019; corrected proof published online 16 December 2019



Supplementary Figure S1. PASI-resistin relationship stratified by SBP category. The graphs depict resistin-PASI relationship for those with (i) Low SBP < 131mmHg (n = 50), (ii) High SBP > 131mmHg (n = 50), and combined, with scatter representing observed data and solid colored lines representing unadjusted trend lines. PASI, Psoriasis Area and Severity Index; SBP, systolic blood pressure