

Possible Correlation between Self-Reported Sensitive Skin and Physical and Chemical Biomarkers

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Abstract

We conducted a study to evaluate the urogenital skin environment of pre-menopausal and post-menopausal women. Differences in biomolecular and physical measures of urogenital skin sites are reported in a separate publication, however, compelling observations on self-perceived sensitive skin, in light of the differences observed in the measured biomarker and physical parameters, prompted this brief communication. Women enrolled in the study included; 15 pre-menopausal (Pre-M), 15 post-menopausal receiving no form of hormone replacement therapy (Post-M Non-HRT), and 15 post-menopausal receiving HRT (Post-M HRT). Notable trends among post-menopausal women who claimed sensitive genital skin compared to those whose skin was not sensitive were: higher histidine/histamine ratios at the introitus and labia majora; higher levels of NMF and its components at the introitus, and; higher levels of IL1- at the introitus, labia minora and labia majora. Differences in these parameters were not observed in the pre-menopausal women when those with sensitive were compared to those whose skin was not sensitive. In pre- and post-menopausal women individuals claiming sensitive genital skin had a directionally higher pH vaginally, and at the introitus. Not all observed differences were statistically significant. In fact, the relatively small number of participants resulted in a low likelihood of differences achieving significance. However, understanding the associations between sensitive skin and physiological parameters is an important step in peeling back the basis of sensitive skin. These interesting trends provide directions for further investigation.

Introduction

Sensitive subjects experiencing this condition report exaggerated reactions when their skin is in contact with cosmetics, soaps and sunscreens, and often report worsening condition after exposure to dry and cold climate [1]. In the industrialized world sensitive skin is reported by a large portion of the general population, with various surveys reporting 38-90% [1-3]. Objective signs are typically absent, but occasionally erythema [4], dryness or rash are described, as well as more intense inflammatory responses such as wheal [5]. No single cause for 'sensitive skin' has been identified, however, several factors contribute to this condition, including: genetics (e.g., gender and skin type), physiology (e.g., age, hormonal status and structural aspects of the stratum

corneum), and environmental (e.g., weather and exposures to products and irritants) [6].

We previously reported no significant gender-related or age-related differences in the perception of sensitive skin in general or sensitive skin of the face or body. However, the percentage of women who perceived that they have sensitive genital skin increased with age. A significantly ($p = 0.03$) higher percentage of women perceived their genital skin as sensitive to some degree (58.1% for all women and 44.2% for all men) [7]. Older women were significantly ($p=0.01$) more likely to claim sensitive genital skin than younger women [7].

As a manufacturer of feminine care products, we were inter-

ested in evaluating the urogenital skin environment of pre-menopausal and post-menopausal women. We conducted a clinical study to evaluate potential differences in biomolecular and physical measures of the urogenital skin, and reported the majority of our findings in a prior publication [8]. In this current, brief communication we report observations on self-perceived sensitive skin among the test subjects in light of the differences observed in the measured biomarker and physical parameters. Although the relatively small number of participants resulted in a low likelihood of statistical significance, interesting trends were observed that provide directions for further investigation.

Table 1. Subject-proclaimed skin type in the genital area.

			Self-proclaimed genital skin type	
			Not sensitive	Sensitive to some degree ^a
Group	Description	N	N	N
Pre-M	Pre-menopausal	15	10	5
Post-M Non-HRT ^b	Post-menopausal, taking no HRT	15	11	4
Post-M HRT ^b	Post-menopausal with HRT	15	10	5
All subjects	All groups combined	45	31	14

^a Includes individuals that responded their skin was very sensitive, moderately sensitive, or slightly sensitive.

^b HRT= Hormone Replacement Therapy

Methods

A detailed description of the study subjects and methods is provided in a separate publication [8]. Briefly, 45 female subjects, age 21-70, meeting all entrance criteria was enrolled. There were three groups with 15 subjects in each group; pre-menopausal females (Pre-M), post-menopausal females showing signs of urogenital atrophy (Post-M Non-HRT), and post-menopausal females receiving hormone replacement therapy and showing no signs of urogenital atrophy (Post-M HRT). Physical measurements (skin temperature and pH) and cytokine levels (via tape strip samples, CuDerm DSquame discs) were obtained from three genital sites (labia majora, labia minora and introitus) as described separately [8]. Methods of analyses are detailed in this separate publication [8]. Self-assessed subject-reported symptoms were recorded including: genital and vaginal dryness, genital and vaginal itch, and difficulty having intercourse. In addition, participants also responded to a questionnaire on self-perceived sensitive skin that has been used in previous studies [7,9,10].

Within each study group (Pre-M, Post-M, Non-HRT, and Post-M HRT), differences between the sensitive skin and normal skin types were analyzed using an ANOVA model for each of the chemical biomarkers at three different sites (introitus, labia minora and labia majora). For pH an additional analysis was conducted for measurements taken in the vagina.

Results and Discussion

Table 1 presents number of subjects claiming some degree of sensitivity of genital skin (slightly sensitive, moderately sensitive or very sensitive). Approximately one third of each group responded that they perceived sensitivity. This is a lower percentage compared to a previously published result among a population including 869 women from the same geographic area in which 58% reported some degree of sensitivity of genital skin using the identical questionnaire [7, 11]. It is unclear why the difference exists but the small sample size used in the current study may have contributed.

We compared quantitative measures of histamine and histidine from those individuals claiming sensitive genital skin to those who responded that their genital skin was not sensitive (Table 2a). In the Post-M HRT group, histidine/histamine ratio was significantly higher at the introitus and the labia majora ($p < 0.0001$) in the individuals who claimed sensitive skin compared to those who responded that their genital skin was not sensitive. In the Post-M Non-HRT group, this ratio at the introitus was also considerably higher in individuals with sensitive skin, but the difference was not statistically significant ($p = 0.08$). Histamine is derived from the decarboxylation of the amino acid histidine [12]. An altered ratio of histamine to histidine may indicate a change in the induction of histidine decarboxylase or a shift in the equilibrium between these two materials.

Significantly ($p < 0.05$) higher levels of NMF and its components (i.e., proline, 2-pyrrolidone-5-acid, and trans-urocanic acid) were recovered from the introitus in the sensitive skin individuals in the Post-M Non-HRT group compared to the non-sensitive individuals (Table 2b).

No such pattern was observed at the other anatomic sites (labia minora and labia majora). In both the Post-M groups, IL-1 α was consistently higher among individuals claiming sensitive genital skin at all three body sites (introitus, labia minora and labia majora) compared to individuals who responded that their skin was not sensitive (Table 2c). This difference was statistically significant in both groups at the

Table 2. Chemical biomarkers detected from individuals based on perceived sensitivity of genital skin.

Study group Skin type	Pre-M			Post-M Non-HRT			Post-M HRT		
	Non-Sensitive (N=10)	Sensitive (N=5)	P-value	Non-Sensitive (N=11)	Sensitive (N=4)	P-value	Non-Sensitive (N=10)	Sensitive (N=5)	P-value
	Mean ± SE	Mean ± SE		Mean ± SE	Mean ± SE		Mean ± SE	Mean ± SE	
a. Histamine and histidine content *									
Introitus									
Histamine	0.58 ± 0.25	0.17 ± 0.41	0.41	0.02 ± 0.01	0 ± 0.02	0.34	0.12 ± 0.06	0.01 ± 0.05	0.20
Histidine	10.62 ± 6.73	28.75 ± 9.52	0.15	6.64 ± 4.57	14.32 ± 6.86	0.37	8.96 ± 29.03	39.7 ± 25.14	0.46
Histidine/Histamine	757 ± 469	362 ± 765	0.67	1918 ± 1303	6476 ± 1955	0.08	5228 ± 4926	8044 ± 4926	<.0001
Labia minora									
Histamine	0.78 ± 0.48	1.23 ± 0.67	0.60	0.09 ± 0.06	0 ± 0.1	0.45	0.05 ± 0.03	0.05 ± 0.04	0.94
Histidine	24.1 ± 7.99	29.94 ± 11.3	0.68	14.8 ± 7.24	38.33 ± 11.45	0.11	14.04 ± 3.53	9.94 ± 5	0.52
Histidine/Histamine	1011 ± 530	135 ± 749	0.36	4536 ± 3099	12322 ± 4899	0.20	4463 ± 1947	1889 ± 2754	0.46
Labia Majora									
Histamine	0.16 ± 0.09	0.15 ± 0.13	0.93	0.07 ± 0.03	0 ± 0.05	0.31	0.12 ± 0.09	0.01 ± 0.13	0.51
Histidine	51.07 ± 15.9	53.66 ± 22.48	0.93	24.49 ± 4.91	19.23 ± 8.14	0.59	40.27 ± 15.02	79.4 ± 23.75	0.19
Histidine/Histamine	3934 ± 1827	963 ± 2583	0.36	3409 ± 1575	8593 ± 2613	0.11	8852 ± 4368	18342 ± 4368	<.0001
b. NMF and components *									
Introitus									
NMF+Histamine	53.17 ± 26.92	92.29 ± 38.08	0.42	26.07 ± 17.81	106.79 ± 28.16	0.03	47.94 ± 149	216.51 ± 129	0.43
Proline	7.62 ± 2.51	11.52 ± 3.55	0.39	4.64 ± 1.72	15.03 ± 2.72	0.007	6.17 ± 8.47	18.51 ± 7.33	0.32
2-Pyrrolidone-5-Acid	22.45 ± 10.64	33.65 ± 15.05	0.56	10.51 ± 8.15	50.06 ± 12.89	0.02	20.29 ± 77.21	109.66 ± 66.86	0.42
Trans-Urocanic Acid	11.89 ± 7.82	18.25 ± 11.06	0.65	4.92 ± 4.44	27.37 ± 7.03	0.02	18.61 ± 47.55	48.62 ± 33.62	0.63
Labia minora									
NMF+Histamine	107.7 ± 42.81	173.83 ± 60.55	0.39	89.75 ± 22.89	168.02 ± 37.95	0.10	60.97 ± 12.09	53.82 ± 17.1	0.74
Proline	10.28 ± 2.8	14.08 ± 3.96	0.45	8.99 ± 1.29	13.92 ± 2.14	0.07	5.3 ± 0.9	6.68 ± 1.27	0.39
2-Pyrrolidone-5-Acid	49.32 ± 22.19	86.88 ± 31.38	0.35	42.19 ± 11.42	79.18 ± 18.93	0.12	28.16 ± 5.84	25.08 ± 8.26	0.77
Trans-Urocanic Acid	22.7 ± 13.1	41.7 ± 18.53	0.42	25.02 ± 5.58	36.19 ± 9.25	0.32	15.33 ± 3.22	12.06 ± 4.27	0.56
Labia Majora									
NMF+Histamine	347.53 ± 79.27	423.42 ± 112.11	0.59	253.15 ± 25.02	201.99 ± 41.49	0.31	281.39 ± 67.14	303.5 ± 94.95	0.85
Proline	24.82 ± 3.81	26.13 ± 5.39	0.85	17.92 ± 1.82	11.69 ± 3.03	0.10	15.45 ± 3.58	16.65 ± 5.07	0.85
2-Pyrrolidone-5-Acid	179.54 ± 44.15	227.2 ± 62.43	0.54	128.94 ± 13.64	109 ± 22.61	0.46	149.02 ± 33.77	156.53 ± 47.75	0.90
Trans-Urocanic Acid	79.61 ± 15.77	116.09 ± 22.31	0.20	81.59 ± 11.8	62.06 ± 19.58	0.41	76.03 ± 20.82	66.79 ± 29.44	0.80
c. IL1a and IL-1ra ^b									
Introitus									
IL-1a	1.9 ± 0.38	1.54 ± 0.54	0.59	1.86 ± 0.69	6.97 ± 1.14	0.002	2.25 ± 0.49	5.29 ± 0.7	0.004
IL-1ra	90.08 ± 24.37	65.23 ± 34.46	0.57	55.22 ± 11.58	32.94 ± 19.21	0.34	68.64 ± 15.56	63.09 ± 22	0.84
IL-1a/IL-1ra	67.15 ± 21.18	51.6 ± 29.95	0.68	61.58 ± 22.08	6.53 ± 36.62	0.22	42.02 ± 11.88	14.75 ± 16.8	0.21
Labia minora									
IL-1a	1.86 ± 0.42	1.77 ± 0.59	0.90	3.09 ± 0.52	6.14 ± 0.87	0.01	2.08 ± 0.56	3.22 ± 0.79	0.26
IL-1ra	77.13 ± 15.52	59.58 ± 21.95	0.53	78.95 ± 17.55	71.02 ± 29.11	0.82	106.43 ± 29.18	141.61 ± 41.26	0.50
IL-1a/IL-1ra	65.26 ± 11.64	35.55 ± 16.46	0.16	42.51 ± 11.33	9.82 ± 18.79	0.16	63.61 ± 22.9	83.72 ± 32.38	0.62
Labia Majora									
IL-1a	11.39 ± 1.99	8.81 ± 2.81	0.47	15.45 ± 3.27	28.17 ± 5.42	0.07	18.06 ± 2.33	23.02 ± 3.3	0.24
IL-1ra	9.83 ± 9.77	31.94 ± 13.81	0.21	11.99 ± 4.34	6.26 ± 6.85	0.49	4.88 ± 1.22	3.29 ± 2.23	0.54
IL-1a/IL-1ra	5.62 ± 4.14	3.15 ± 5.85	0.74	2.68 ± 1.6	0.25 ± 2.53	0.43	0.41 ± 0.16	0.14 ± 0.29	0.43

Table 3. Measurement of surface pH from individuals with perceived sensitive genital skin.

Study group: Skin type:	Pre-M			Post-M Non-HRT			Post-M HRT		
	Non-Sensitive (N=10)	Sensitive (N=5)	P-value	Non-Sensitive (N=11)	Sensitive (N=4)	P-value	Non-Sensitive (N=10)	Sensitive (N=5)	P-value
	Mean ± SE	Mean ± SE		Mean ± SE	Mean ± SE		Mean ± SE	Mean ± SE	
pH Measurement									
Vaginal	4.70 ± 0.14	4.80 ± 0.19	0.68	6.82 ± 0.27	7.12 ± 0.45	0.57	4.45 ± 0.16	4.70 ± 0.23	0.40
Introitus	5.37 ± 0.14	5.47 ± 0.19	0.68	5.87 ± 0.12	5.99 ± 0.20	0.63	5.83 ± 0.17	5.90 ± 0.25	0.81
Labia Minora	5.49 ± 0.13	5.25 ± 0.18	0.30	5.85 ± 0.16	6.18 ± 0.26	0.31	5.55 ± 0.23	5.84 ± 0.33	0.49
Labia Majora	5.80 ± 0.11	5.76 ± 0.15	0.83	5.87 ± 0.13	6.01 ± 0.22	0.60	5.95 ± 0.17	5.90 ± 0.25	0.88

introitus, and in the Pre-M Non-HRT group at the labia minora. Interestingly, the Pre-M group did not show the same pattern.

Differences in pH were small, however, those individuals claiming sensitive genital skin had a directionally higher pH vaginally, and at the introitus (Table 3). There was no consistent pattern at the labia minora or labia majora.

Importantly, this study was not designed specifically to explore correlations between physical and biochemical parameters and self-perceived sensitive skin, but was designed to catalog a number of measurements among three test groups, i.e., pre-menopausal, and post-menopausal with and without HRT [8]. The observed trends are intriguing, but the small numbers of subjects, and the relatively small differences resulted in a lack of statistical power. Additional investigations

on a larger test population may help to illuminate potential differences in physical measures or biochemical markers.

Sensitive skin is now generally accepted as a real physiological disorder; however, identifying a single cause remains elusive. Factors have been identified as possible contributors to sensitive skin, as reviewed by Farage and Maibach [2]. In this preliminary study, we identified potential associations between a perception of sensitive skin in the genital area and the levels of several biomolecules and pH measures in the genital area. Understanding the associations between sensitive skin and physiological parameters is an important step in peeling back the basis of sensitive skin. These observations provide an intriguing starting point for future research.

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