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Facial dermatosis associated with *Demodex*: a case-control study*

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Abstract: *Demodex* has been considered to be related with multiple skin disorders, but controversy persists. In this case-control study, a survey was conducted with 860 dermatosis patients aged 12 to 84 years in Xi'an, China to identify the association between facial dermatosis and *Demodex*. Amongst the patients, 539 suffered from facial dermatosis and 321 suffered from non-facial dermatosis. *Demodex* mites were sampled and examined using the skin pressurization method. Multivariate regression analysis was applied to analyze the association between facial dermatosis and *Demodex* infestation, and to identify the risk factors of *Demodex* infestation. The results showed that total detection rate of *Demodex* was 43.0%. Patients aged above 30 years had higher odds of *Demodex* infestation than those under 30 years. Compared to patients with neutral skin, patients with mixed, oily, or dry skin were more likely to be infested with *Demodex* (odds ratios (ORs) were 2.5, 2.4, and 1.6, respectively). Moreover, *Demodex* infestation was found to be statistically associated with rosacea (OR=8.1), steroid-induced dermatitis (OR=2.7), seborrheic dermatitis (OR=2.2), and primary irritation dermatitis (OR=2.1). In particular, ORs calculated from the severe infestation (≥5 mites/cm^2) rate were significantly higher than those of the total rate. Therefore, we concluded that *Demodex* is associated with rosacea, steroid-induced dermatitis, seborrheic dermatitis, and primary irritation dermatitis. The rate of severe infestation is found to be more correlated with various dermatosis than the total infestation rate. The risk factors of *Demodex* infestation, age, and skin types were identified. Our study also suggested that good hygiene practice might reduce the chances of demodicosis and *Demodex* infestation.

Key words: Facial dermatosis, *Demodex* infestation, Association, Case-control study, Age
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1 Introduction

The *Demodex* mites belong to the family Demodicidae (Acari: Cheyletoidea). *Demodex folliculorum* (*D.f.*) and *Demodex brevis* (*D.b.*) are two *Demodex* mites of permanent parasites found on humans (Desch and Nutting, 1972). *D.f.* occupies the hair follicles above the level of the sebaceous glands, while *D.b.* exists principally in depth of sebaceous and meibomian glands. These two *Demodex* species have been retrieved from almost every area of human skin but have a predilection for the face. The mites can be found in any age groups except newborns who are presumably infested soon after birth by direct contact (Bonnar *et al*., 1991). The mite population increases with host age, and in the adult population, these two *Demodex* species parasitize the normal skin with a prevalence of 100% and a usual density <5 mites/cm^2. *Demodex* mites are usually considered to play a pathogenic role when present in an excessive number or penetrating into the dermis (Ayres and

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Ayres, 1961; Ecker and Winkelmann, 1979; Bonnar *et al*., 1993; Forton and Seys, 1993; Erbagci and Ozgoztasi, 1998). They have been implicated in the occurrence of a wide range of clinical features, including pityriasis folliculorum (Ayres and Ayres, 1961), papulopustular and granulomatous rosacea (Bonnar *et al*., 1993; Forton and Seys, 1993), inflammatory papule (Seifert, 1978), folliculitis (Purcell *et al*., 1986), seborrheic dermatitis (Karincaoglu *et al*., 2009), perioral dermatitis (Dolenc-Voljc *et al*., 2005), and blepharitis (Post and Juhlin, 1963; Zhao *et al*., 2011a), although much controversy persists (Bonnar *et al*., 1993; Forton and Seys, 1993; Forton *et al*., 2005; Hsu *et al*., 2009). A definitive diagnosis of demodicosis requires a compatible clinical picture and the presence of more than 5 mites/cm^2 (Forton and Seys, 1993).

In order to confirm the association of various facial dermatosis with *Demodex* mites, we investigated 860 dermatosis patients in Xi'an, China by a case-control study and conducted multivariate logistic regression analysis.

2 Materials and methods

2.1 Study population

In the study, final diagnoses of the 860 outpatients aged 12 to 84 years were made by four dermatologists who had clinical experience for 10–35 years in Department of Dermatology at the Second Affiliated Hospital of Xi'an Jiaotong University College of Medicine between October 2008 and December 2009. There were 539 patients with facial dermatosis (patient group) and 321 with non-facial dermatosis (NFD, control group) included.

2.2 Diagnosis of dermatosis

Pathogenicity of *Demodex* has been under dispute for a long time and few demodicosis diagnoses have been made by a dermatologist at our clinic. In this study, we investigated the correlation between each of the following six kinds of facial dermatosis probably and *Demodex*.

Rosacea is a common skin condition of uncertain etiology, which usually affects the center of face among the middle-aged, causing transient or permanent facial erythema, telangiectasia, edema, papules and pustules, nodus and scar. Based on pathogenesis progress, erythematotelangiectatic rosacea, papulopustular rosacea, and phymatous rosacea appear subsequently. In this study, a total of 91 cases of rosacea were diagnosed, with 9 erythematotelangiectatic rosacea, 65 papulopustular rosacea, and 17 phymatous rosacea.

Steroid-induced dermatitis (SID), a dermatosis with obvious "anti-jump phenomenon", is caused by long-time inappropriate external use of hormone drugs (such as cortisone and prednisone). A total of 26 cases of SID were diagnosed.

Seborrheic dermatitis (Seb D) is a common condition with uncertain etiology that makes the skin greasy, scaly, and flaky. A total of 153 cases of Seb D were diagnosed.

Facial dermatitis is a facial dermatosis characterized by red, itchy, and blistering skin. It consists of two types: primary irritation dermatitis (PID) and sensitization dermatitis (SD). We identified 106 cases of PID and 34 cases of SD.

Acne vulgaris (AV) is a chronic inflammation of unknown etiology, predilecting young adults. It is characterized by skin with comedones, papules, pustules, nodules, cysts, etc., mostly affecting follicles and sebaceous glands. A total of 129 cases of AV were diagnosed.

2.3 Questionnaire and *Demodex* examination

The questionnaire covered information about age, gender, family address, telephone number, residence pattern, hygiene practices (sharing of sanitary ware, frequency of face-washing every day, and the use of facial cleanser), eating habits (alcohol, sweetmeat, spicy food (such as hot pepper, zingiber) consumptions), skin types (neutral, dry, oily, or mixed), and the dermatosis (rosacea, SID, Seb D, PID, AV, SD, and NFD) considered in this study. All the participants signed the written consent form. Ethical permission was not required for this study because the skin pressurization method was a non-invasive sampling technique routinely used in etiological agent.

Skin pressurization method was employed in the process of *Demodex* examination for all patients. It is convenient, quick, and is widely applied in the fast diagnosis of outpatients in Mainland China. It was conducted with the following steps. First, squeeze the left nasolabial fold and nasal ala (about 1 cm^2) with

the thumb to get some sebum. Second, place the sebum on the slide and add a drop of liquid paraffin. Finally, place the cover glass and examine the sample with a microscope (4×10). A positive diagnosis was made only after observing the *Demodex* mites (any of the developmental stages: egg, larva, nymph, adult of *D.f.* or *D.b.*) under microscopic magnification. Based on the limit value found by standardized skin surface biopsy (n<5 mites/cm^2) (Forton and Seys, 1993), we decided to apply the same limit value for our sampling method. The *Demodex* density was classified as severe (≥5 mites/cm^2) and mild (1–4 mites/cm^2).

2.4 Statistical analysis

The focus of the study was the occurrence of *Demodex* infestation. The *Demodex* infestation rate was calculated by sociodemographic characteristics of patients. χ^2 test was applied to compare the *Demodex* infestation rates of cases and controls. Seven independent variables (age, gender, residence, eating habits, hygienic practice, skin type, and dermatosis) were included in the logistic regression model to identify significant correlates of *Demodex* infestation and to calculate odds ratios (ORs) and P values, with a 0.05 significant level. Correlation between *Demodex* density and the age of patients was shown by a scatterplot. Associations between the rate of severe *Demodex* infestation and each of the six skin diseases (rosacea, SID, Seb D, PID, AV, SD) were estimated. We also estimated the correlation between the rate of severe *Demodex* infestation and age amongst the AV patients.

3 Results

3.1 General information

In this study, 860 dermatosis patients completed the questionnaire effectively. The total infestation rate of *Demodex* mites was 43.0% (370/860). Constituent ratio of *D.f.* infestation was the highest (52.4%, 194/370), followed by the infestation rate of *D.b.* (26.5%, 98/370), and the mixed infestation rate was the lowest (21.1%, 78/370). The three constituent ratios were significantly different (χ^2=93.5, P<0.01).

3.2 Multivariate logistic regression analysis

Results of multivariate logistic regression analysis revealed that after controlling for the covariates (Table 1), three variables (gender, residence pattern, eating habit) were found to be uncorrelated with *Demodex* infestation, whereas each of the other four variables (age, hygiene practice, skin type, and facial dermatosis) was still correlated with *Demodex* infestation. In particular, patients aged above 30 years had higher odds of *Demodex* infestation than those under 30 years. Compared to patients with neutral skin type, patients with mixed skin type were more prone to *Demodex* infestation (odds ratio (OR)=2.5), followed by those with oily skin (OR=2.4) and then dry skin (OR=1.6).

Table 1 also demonstrated that *Demodex* infestation was statistically associated with the developments of rosacea (OR=8.1), SID (OR=2.7), Seb D (OR=2.2), PID (OR=2.1), and AV (OR=1.5), whereas no significant statistical correlation was found between SD and *Demodex* infestation (OR=0.7).

3.3 Association between *Demodex* infestation and age of patients

Fig. 1 showed that *Demodex* infestation rates increased with age among the 12–30 years old patients and remained stable amongst the older patients.

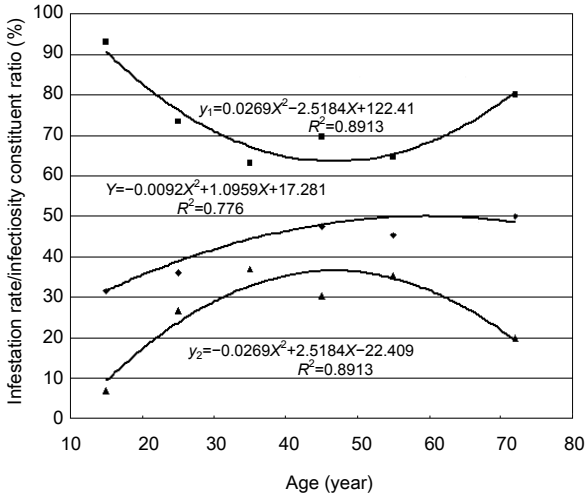

Fig. 1 Scatterplot of *Demodex* infestation and age of patients
X [age group (median) (year)]: 12–20 (15), 21–30 (25), 31–40 (35), 41–50 (45), 51–60 (55), 61–84 (72); Y [infestation rate (%), ♦]: 31.5 (29/92), 35.9 (94/262), 50.7 (114/225), 47.6 (79/166), 45.3 (34/75), 50.0 (20/40); y_1 [mild density constituent ratio (%), ■]: 93.1 (27/29), 73.4 (69/94), 63.2 (72/114), 69.6 (55/79), 64.7 (22/34), 80.0 (16/20); y_2 [severe density constituent ratio (%), ▲]: 6.9 (2/29), 26.6 (25/94), 36.8 (42/114), 30.4 (24/79), 35.3 (12/34), 20.0 (4/20)

Table 1 Results of logistic regression analysis of *Demodex* infestation (n=860)

Characteristics	Description		Frequency	Proportion (%)	Infestation rate (%)	OR (95% CI)	P-value
Age (year)	12–20		92	10.7	31.5		
	21–30		262	30.5	35.9	1.2 (0.7–2.0)	0.450
	31–40		225	26.2	50.7	2.2 (1.3–3.7)	0.002
	41–50		166	19.3	47.6	2.0 (1.2–3.4)	0.012
	51–60		75	8.7	45.3	1.8 (1.0–3.4)	0.067
	61–84		40	4.6	50.0	2.2 (1.0–4.6)	0.043
Gender	Male		236	27.4	44.5		
	Female		624	72.6	42.5	0.9 (0.7–1.2)	0.593
Residence	Urban		836	97.2	43.1		
	Rural		24	2.8	41.7	1.1 (0. 5–2.4)	0.892
Eating habit	Drinker	No	171	19.9	43.9		
		Yes	689	80.1	42.8	1.0 (0.7–1.5)	0.805
	Spicy diet	No	555	64.5	42.5		
		Yes	305	35.5	43.9	0.9 (0.7–1.3)	0.689
	Sweetmeat	No	416	48.4	44.2		
		Yes	444	51.6	41.9	1.1 (0.8–1.4)	0.489
Hygienic practice	With private sanitary ware		553	64.3	39.4		
	Without private sanitary ware		307	35.7	49.5	1.5 (1.1–2.0)	0.004
	Washing face once a day		73	8.5	56.2		
	Washing face twice a day		666	77.4	43.8	0.6 (0.4–1.0)	0.046
	Washing face three times a day		121	14.1	30.6	0.3 (0.2–0.6)	0.001
	Facial cleanser user		228	26.5	47.8		
	Otherwise		632	73.5	41.3	0.8 (0.6–1.0)	0.004
Skin type	Neutral		194	22.6	28.4		
	Dry		118	13.7	38.1	1.6 (1.0–2.5)	0.000
	Oily		254	29.5	48.8	2.4 (1.6–3.6)	0.000
	Mixed		294	34.2	49.7	2.5 (1.7–3.7)	0.000
Dermatosis	NFD		321	37.3	30.5		
	Rosacea		91	10.6	78.0	8.1 (4.7–14.0)	0.000
	SID		26	3.0	53.9	2.7 (1.2–6.0)	0.018
	Seb D		153	17.8	49.7	2.2 (1.5–3.3)	0.000
	PID		106	12.3	48.1	2.1 (1.3–3.3)	0.001
	AV		129	15.0	40.3	1.5 (1.0–2.3)	0.047
	SD		34	4.0	23.5	0.7 (0.3–1.6)	0.398

Although we found no significant differences between the four subgroups amongst the patients aged 31 to 84 years, the average infestation rates between the patients aged 12–30 years and 31–84 years were significantly different. Similarly, it was shown that *Demodex* density changed in the same direction as the infestation rates, except that the density decreased with age amongst patients older than 60 years.

3.4 Correlation between severe *Demodex* infestation and dermatosis

As shown in Table 2, the severe infestation ($\geq$5 mites/cm^2) was statistically correlated with rosacea, SID, Seb D, and PID, while not with SD and AV.

3.5 Relationship between *Demodex* infestation and age among acne patients

As shown in Table 3, both the total infestation rates and the severe infestation rates were higher amongst the 31–84 year-old acne patients than amongst the 12–30 year-old ones. Acne patients had a higher infestation rate than patients with non-facial dermatosis in both age groups. Regarding severe infestation, the rates were not significantly different between the acne patients and ones with non-facial dermatosis amongst those aged 12–30 years, whereas ORs of older (31–84 years old) acne patients and the control patients were statistically different.

Table 2 Relevance between severe *Demodex* infestation (≥5 mites/cm^2) and various dermatoses

Dermatosis	Frequency	Infestation rate (%)	χ^2	*P*	OR (95% CI)
NFD	321	5.0			
Rosacea	91	38.5	73.3	0.000	11.9 (6.2–23.0)
SID	26	19.2	6.1*	0.012	4.5 (1.5–13.6)
Seb D	153	16.3	16.9	0.000	3.7 (1.9–7.2)
PID	106	13.2	8.2	0.004	2.9 (1.4–6.2)
AV	129	9.3	2.9	0.086	2.0 (0.9–4.3)
SD	34	5.9	0.0*	1.000	1.2 (0.3–5.4)

Patients aged 12–84 years. * Continuity correction χ^2 value

Table 3 Relationship between *Demodex* density/infestation rate and age among acne patients

Demodex density	Age (year)	Dermatosis	Frequency	Infestation rate (%)	χ^2	*P*	OR (95% CI)
Total (≥1 mite/cm^2)	12–30	NFD	131	20.6			
		AV	110	35.5	6.6	0.010	2.1 (1.2–3.8)
	31–84	NFD	190	37.4			
		AV	19	68.4	6.9	0.008	3.6 (1.3–10.0)
Severe (≥5 mites/cm^2)	12–30	NFD	131	0.8			
		AV	110	5.5	3.2*	0.076	7.5 (0.9–63.3)
	31–84	NFD	190	7.9			
		AV	19	31.6	8.3*	0.004	5.4 (1.8–16.2)

* Continuity correction χ^2 value

4 Discussion

Demodex infestation can cause indistinguishable multiple skin disorders with white follicular scales, papules, and pustules as their frequent clinical picture (Ayres, 1930; Ayres and Ayres, 1961; Seifert, 1978). Yet it is still under debate whether *Demodex* is the cause of many kinds of skin diseases (Bonnar *et al*., 1993; Forton and Seys, 1993; Forton *et al*., 2005; Hsu *et al*., 2009). Based on the results of the present study, we conclude that rosacea, SID, Seb D, and PID are significantly associated with *Demodex* infestation, while SD is not. Until now, the dispute mainly focuses on the contradiction of high *Demodex* infestation rate in the population (few studies reported 100%) (Forton and Seys, 1993) and the low incidence of demodicosis. Some studies even showed that a few patients with excessive *Demodex* had no obvious clinical symptoms (Zhang *et al*., 2008). Three factors might explain the low incidence of demodicosis. First, the density of *Demodex* infestation is important. The mild cases, the majority of the infested, tend to ignore the symptoms and hence seldom seek medical advice. For instance, pityriasis folliculorum, the most frequent demodicosis (Forton *et al*., 2005), is rarely diagnosed in our hospital. The severe infestation could make great contribution to demodicosis. Although Forton and Seys (1993) proposed that the mite density of ≥5 mites/cm^2 can be a diagnostic criterion, Erbagci and Ozgoztasi (1998) suggested that a certain density might not be an appropriate criterion in the diagnosis of demodicosis. Nevertheless, in our study, the correlation between severe infestation (≥5 mites/cm^2) rate and various kinds of dermatosis was obviously higher than that between the total infestation (≥1 mite/cm^2) rate and the dermatosis (OR values were 11.9 and 8.1 in rosacea, 4.5 and 2.7 in SID, 3.7 and 2.2 in Seb D, 2.9 and 2.1 in PID, respectively). Second, due to the Chinese dermatologists' denial of *Demodex* pathogenicity, probably the demodicoses are often misdiagnosed or confused with other facial dermatoses in our clinical practice, thus leading to the nosological question of the demodicoses. One possible interpretation is that demodicosis is included in such related dermatosis as rosacea, SID, Seb D, PID, etc. The other one is that the same patient can have

two pathologies at the same time. Thirdly, the susceptibility of hosts could affect the effect of *Demodex* infestation. Akilov and Mumcuoglu (2003) have evidenced that people with the Cw2 and Cw4 haplotypes are more susceptible to demodicosis compared to people without the Cw2 and Cw4 haplotypes. In particular, the risk of developing clinical symptoms of demodicosis is 5.0 times higher for people with the Cw2 haplotype and 3.1 times higher for those with the Cw4 haplotype, whereas individuals who have the human leucocyte antigen (HLA) A2 phenotype are 2.9 times more resistant to demodicosis.

The role of *Demodex* mites as risk factors for rosacea has been confirmed recently (OR=7.6) (Zhao *et al*., 2010). The conclusion was drawn from 48 selected studies (9 in English and 39 in Chinese) conducted in 10 countries by meta synthetic quantitative study, which involved 28527 participants (4307 rosacea patients and 24220 controls). That finding was confirmed by the present study (OR=8.1). The hypothesis that SID and Seb D were associated with *Demodex* mites has not been confirmed at present, but our results were consistent with those of Dolenc-Voljc *et al*. (2005) and Karincaoglu *et al*. (2008; 2009).

It is worth clarifying that although English papers about the association between *Demodex* infestation and AV are very few and mostly give negative conclusions (Baysal *et al*., 1997; Okyay *et al*., 2006), a great number of Chinese papers have reported a positive association between *Demodex* infestation and the development of AV (Yang *et al*., 2006; Ma *et al*., 2009; Wang *et al*., 2010; Zhao *et al*., 2011b). Moreover, effective acaricidal treatments have also supplied indirect proof of a causal relationship between *Demodex* infestation and AV (Yang *et al*., 2006; Ma *et al*., 2009). In this study, a significant association between *Demodex* infestation and AV was established according to the total infestation rate (OR=1.5, 95% CI 1.0–2.3; $P<0.05$), whereas a weaker correlation was obtained according to the severe infestation rate (OR=2.0, 95% CI 0.9–4.3; $P>0.05$). The weaker correlation might be a result of statistical bias, because severe infestation of *Demodex* is rather rare amongst the 12–30 year-old patients in our study. For the younger age group (12–30 years old), we found no significant difference in the rate of severe infestation between the group with AV and the group with non-facial dermatosis (OR=7.5, 95% CI 0.9–63.3; $P>0.05$). After the 12–30 year-old patients with adolescent acne and non-facial dermatosis were excluded, the severe infestation rate of AV patients became significantly higher than that of non-facial dermatosis in the 31–84 years age group (OR=5.4, 95% CI 1.8–16.2; $P<0.05$). Therefore, any conclusions about the association between *Demodex* infestation and AV require further study.

In addition, we found that *Demodex* infestation could be affected by age, skin type, and hygienic practice. The infestation rate and the density of *Demodex* change with age. In our study, the *Demodex* detection rate increased along with age amongst the 12–30 year-old patients, which was in agreement with the study of 102 students aged 18–27 years reported by Okyay *et al*. (2006) and 2248 medical students aged 19–24 reported by Hu and Wang (2001). However, the high *Demodex* detection rate remained stable in the 31–84 year-old patients, which differed from the particularly big increase in the infestation rate of both *Demodex* species during the hosts' fifth and sixth decades reported by Aylesworth and Vance (1982). At the same time, the *Demodex* density kept a high level amongst the 30–60 year-old patients, significantly higher than that amongst the 12–30 year-old ones and those older than 60 (Fig. 1). This might be attributed to the development of sebum secretion, which is more mature at the age of 30–60 years than at 12–30 years, and less functional above 60 years.

Skin type is closely related with *Demodex* infestation. Our study revealed that the detection rate of mites in dermatosis patients with oily or mixed skin was higher than that in patients with neutral or dry skin. This corresponded to the conclusions of some previous studies (Cao *et al*., 2009; Peng *et al*., 2009). A possible reason is that *Demodex* mainly consumes living cells in follicles and sebaceous glands. The destruction of massive epithelial cells could lead to compensatory hyperplasia and secretion enhancement. To make it worse, the movement of chelae and claws of the mites in the pilosebaceous unit would stimulate sebaceous follicles and enhance the secretion. Conversely, the detection rate of mites in dermatosis patients with dry skin was found to be higher than that in patients with neutral skin in our study. The reason might be that the dry skin is only a false sensation (Forton *et al*., 2005), which is a result of the

opisthosomes of numerous *Demodex* protruding at the follicular orifices.

In addition to age and skin type, individual hygienic practice was also found to be statistically correlated with *Demodex* infestation, which coincided with Wang and Zhang (2006) and Cheng *et al.* (2008), but was not in accordance with Andrews (1982) and Xu and Zhang (2005). One possible explanation is that using private sanitary ware, increasing the frequency of face-washing every day, and the use of facial cleanser can help clean up the *Demodex* mites on skin-surface and reduce mite population and the chance of cross infestation, regardless of the parasites in the hair follicles and sebaceous glands. Therefore, to draw a definite conclusion about the effect of individual hygienic practice, we need to conduct further studies.

Regarding the influence of eating habits, Okyay *et al.* (2006) reported that *Demodex* infestation was associated with alcohol intake, but did not give a definite conclusion due to the small size of the alcohol-consuming group. It was also reported that spicy food (such as hot pepper) contributed to a higher infestation rate because spicy food might make epithelial hyperplasia of follicular and sebaceous glands, which could provide plenty of nutrition for *Demodex* reproduction (Wu *et al*., 2008; He *et al*., 2009; Tian, 2010). However, we have found no statistical correlation between eating habits (alcohol, spicy food, and sweetmeat consumptions) and *Demodex* infestation in the present study. The association between eating habits and *Demodex* infestation needs to be further investigated.

Gender and residence patterns were also not statistically correlated with *Demodex* infestation according to our results, which is in accordance with the conclusions of some previous studies (Andrews, 1982; Okyay *et al*., 2006).

In conclusion, *Demodex* infestation is significantly associated with the development of rosacea, SID, Seb D, and PID. Severe infestation ($\geq$5 mites/cm^2) is more frequently associated with varietas dermatosis compared with general infestation. The patients older than 30 years with oily or mixed skin are susceptible to *Demodex*, and demodicosis is more likely to be provoked in them. Good hygienic practice might reduce the chances of *Demodex* infestation and demodicosis.

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