SEXUAL MEDICINE REVIEWS REVIEWS

Male Sexual Health and Reproduction in Cutaneous Immune-Mediated Diseases: A Systematic Review

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ABSTRACT

Introduction: Information about the possible effects of cutaneous immune-mediated diseases (cIMDs) on male sexual function and reproduction is scarce. Factors known to impair sexual health and reproduction, such as inflammation, medication use, and hypogonadism, can be present in a significant proportion of male patients with cIMD.

Objectives: To systematically review the literature for the influence of paternal cIMD on many aspects of male sexual and reproductive health, such as sexual function, reproductive hormones, fertility, and pregnancy and offspring outcomes.

Methods: A systematic literature search was performed. The searches combined keywords regarding male sexual function and fertility, pregnancy outcomes, and offspring's health with a list of cIMDs.

Results: The majority of the identified studies included patients with psoriasis (22 of 27), and sexual function was the most common outcome of interest (20 of 27). For patients diagnosed with psoriasis, the prevalence of male sexual dysfunction reported in these studies ranged from 34 to 81%. Hypogonadism in patients with psoriasis was reported in 2 of 3 studies. Sperm analysis abnormalities in patients with psoriasis were reported in 3 of 4 studies. No information about the effect of paternal disease on pregnancy and offspring outcomes was identified.

Conclusions: Disease activity in psoriasis might play an important role in the development of sexual dysfunction, hypogonadism, and abnormal sperm quality. For the other cIMD included in this review, there is insufficient information regarding male sexual and reproductive health to draw firm conclusions. More research is needed to understand the association between cIMD and impaired male sexual and reproductive health. **Perez-Garcia LF, Dolhain R, te Winkel B, et al. Male Sexual Health and Reproduction in Cutaneous Immune-Mediated Diseases: A Systematic Review. Sex Med Rev 2020;XX:XXX–XXX.**

Key Words: Immune-Mediated Cutaneous Diseases; Sexual and Reproductive Health; Sexual Dysfunction; Male; Sexual Function; Inflammation

INTRODUCTION

Sexual and reproductive health (SRH) is defined as a state of complete physical, mental, and social well-being in all matters relating to the reproductive system, and every individual should have access to relevant information to make their own decisions about their SRH.[1]

In the general population, it is estimated that sexual dysfunction (SD) can affect up to 52% of men older than

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40 years of age[2] and that the fertility rate in men younger than 30 years of age is decreasing worldwide.[3] In addition, poor semen quality is now considered as a biomarker of poor general health and it has been associated with an increased mortality rate.[4]

Cardiovascular disease, obesity, smoking, depression, and anxiety are among the "classic" risk factors that are associated with this increased rate of SRH problems. In addition, an association between inflammation and SD has been described. Recently, a systematic review concluded that evidence suggests a role for the immune system in the generation of an inflammatory environment that contributes to vascular impairments and the development of erectile dysfunction (ED).[5] Inflammation of the reproductive tract is also considered as a significant cause of male factor infertility.[6]

Immune-mediated diseases (IMDs) are characterized by dysregulated immune responses leading to tissue-damaging inflammation and are also strongly associated with cardiovascular disease and comorbidities such as depression and anxiety.[7,8]

Altogether, this evidence led us to believe that systemic inflammation associated with IMD could also have a significant role in the development of SD and/or infertility. We began to test our hypothesis in the field of rheumatology, considered the hallmark field of autoimmunity. In rheumatic diseases such as rheumatoid arthritis or systemic lupus erythematosus, a link between inflammation and an impaired SRH seems plausible.[9]

The skin, a physical barrier that protects internal systems from foreign bodies, also participates actively as an immune organ. Dermatologic lesions of the external genitalia are common in men with psoriasis (30−40%) and can also be found in men diagnosed with other cutaneous IMDs (cIMDs). These lesions are associated with considerable physical symptoms and psychological distress that can directly impact male SRH.[10] Furthermore, SRH in men diagnosed with cIMD without genital lesions can also be impaired owing to other factors such as inflammation, medication, or associated comorbidities.

A review article published in 2009 concluded that "SD should be investigated and treated in patients with skin diseases."[11] A recent meta-analysis that included data from 9 studies and included 36,242 patients with psoriasis concluded that psoriasis was associated with an increased risk of ED.[12] Nonetheless, except for psoriasis, male SRH can still be considered as a neglected topic in dermatology.

Men diagnosed with a cIMD should receive proper SRH counseling. This information should not be limited to discussing the possible side effects from drugs on a future pregnancy (reproductive toxicology) but the impact that disease itself has on SRH should also be considered.

Our objective was to systematically review the literature for the influence of paternal cIMD on many aspects of SRH, such as sexual function, male fertility, pregnancy outcome, and on their offspring health outcome.

MATERIALS AND METHODS

This review is part of a larger systematic review (SR) that also included IMD from rheumatology and gastroenterology. The complete protocol was written in accordance with the PRISMA-P statement[9] and registered in PROSPERO and is available in https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=99845. The results from the rheumatology section have been published elsewhere.[9]

Search

A search strategy was developed by an experienced medical librarian (W.B.) using a structured methodology.[13] The searches combined keywords regarding male sexual function and fertility, pregnancy outcomes, and offspring's health with a list of cIMDs. Our full search strategy is provided in Supplement 1.

Information Sources

A systematic literature search was performed in the bibliographic databases: Embase (via Elsevier embase.com), MEDLINE via Ovid, Cochrane Central Register of Trials, and Web of Science Core Collection. In addition, Google Scholar and the clinical trial registries of Europe and the United States were searched. We also contacted authors for further information and included references from the primary search publications, in case these were missed in our search. The databases were searched from inception until February 28, 2019.

Eligibility Criteria

The literature search was limited to the English language and human subjects. Case-control studies, cohort studies, cross-sectional studies, case reports, and case series were included. Publications without original data, such as reviews, were excluded.

In the case of studies reporting pregnancy and offspring outcomes, publications were included if the diagnosis of the IMD took place before conception. In case of studies just reporting fertility parameters (ie, semen analysis, SD), we included publications were the diagnosis was taken into consideration. No restrictions were made regarding the comparison groups. The outcome data should include at least one of the following outcomes: sexual function, reproductive hormones, fertility, pregnancy outcomes, or offspring outcomes.

Study Selection

All articles were imported to EndNote X9. After removal of duplicates, 2 reviewers (L.P. and J.C.) independently and blindly screened titles, abstracts, and full text of the records for eligibility. Disagreements were resolved by consensus with the help of a third reviewer (R.D.).

Data Collection Process

One reviewer (L.P.) extracted relevant information for each studied outcome from the included studies.

Table 1. Description of characteristics and key findings of studies regarding sexual function

Article	Country	Number of participants	SD or ED prevalence	Association with psoriasis	Association with depression	Association with disease activity	Association with other factors
Psoriasis							
Tasliyurt et al[16]	Turkey	37	81.08% (ED)	NA	+ (Independent risk factor for ED)	+	Significant:
							Age
							Smoking
Cabete[17]	Portugal	135	61.5% (ED)	+	NA	NA	Significant:
							Age
							Height
							Diabetes
Ji S[18]	China	191	52.9% (ED)	-	+	NA	Significant:
							Hypertension
							Hyperlipidemia
							Age
Molina-Leyva[19]	Spain	40	53.7% (SD)	+	+	+	Significant:
							Age
							Anxiety
Molina-Leyva[20]	Spain	79	41.8% (SD)	-	+	-	Significant:
							Age
							Smoking
Turel Ermertcan[21]	Turkey	39	NA	+	-	-	NA
Bardazzi[22]	Italy	120	51.6% (ED)	+	NA	+	Not significant:
							Diabetes Mellitus, smoking, hypertension
Wojciechowska-Zdrojowy[23]	Poland	76	43.8% (ED)	NA	NA	+	Significant:
							Age
							Not significant:
							Cardiovascular diseases
							Diabetes
							Significant:
							Genitourinary diseases
							Duration of psoriasis
Goulding[24]	United Kingdom	92	58% (ED)	-	NA	NA	Significant:
							Age
							Hypertension
Egeberg[25]	Denmark	26,536	12.8% (ED)	+	NA	+	NA
Meeuwis[26]	Netherlands	278	NA	NA	NA	NA	Significant:
							Genital psoriasis
Sampogna[27]	Italy	244	34.4–67.9% *4 questionnaires were used	NA	NA	+	Significant: Age
Hidradenitis suppurativa							
Alavi[28]	Canada	17	NA	NA	NA	NA	NA
Janse[29]	Netherlands	66	52% (ED)	NA	NA	-	NA
Kurek[30]	Germany	NA	NA	NA	NA	-	NA
Lichen simplex							

(continued)

Table 1. Continued

Article	Country	Number of participants	SD or ED prevalence	Association with psoriasis	Association with depression	Association with disease activity	Association with other factors
Juan[31]	Taiwan	5,611	3.37% (SD)	NA	+	NA	Significant:
			*Incidence				Diabetes Mellitus
							Hypertension
							Hyperlipidemia
							Cardiovascular disease
							Anxiety
Vitiligo							
Sukan[32]	Turkey	26	11.5% (SD)	NA	-	NA	NA
Chronic urticaria							
Sukan[32]	Turkey	16	31.2% (SD)	NA	+	NA	NA
Atopic dermatitis							
Egeberg[25]	Denmark	26,536	6.7% (ED)	+	NA	+	NA

ED = erectile dysfunction; SD = sexual dysfunction.

Risk of Bias in Individual Studies

The methodological quality of the studies was assessed with the Newcastle-Ottawa Scale, developed for case-control and cohort studies.[14] In the case of cross-sectional studies, an adapted scale was used.[15] One reviewer, L.P., assessed the quality of the studies. Using this method, points were awarded to each publication, related to the selection of the study group, the comparability of the study groups and the ascertainment of the outcomes. The score ranges from 0 to 9, with scores >5 representing good-quality studies (scores per study are presented in Tables 1–3).

RESULTS

A total of 9,735 references were identified. After removing 2,851 duplicates, 6,884 articles were eligible for title/abstract screening, resulting in 289 articles eligible for full-text reading. A total of 27 articles fulfilled the inclusion criteria for cIMD (see Figure 1 and Table 4).

Results are presented per disease (when available) and were divided into 4 categories (*sexual function, reproductive hormones, fertility outcomes, and pregnancy and offspring outcomes*).

Sexual Function

Sexual function in men with cIMD was the most common outcome found in our search, these studies represent 74% of the total included studies in this SR (for in-depth information, see Table 1).

The importance of this topic is illustrated by the results from a European multicenter study where 24.9% of male patients diagnosed with a dermatologic disease reported sexual difficulties that were strongly associated with depression and anxiety. The highest prevalence of sexual difficulties was found in patients diagnosed with hidradenitis suppurativa (HS) (66.7%), blistering disorders (34.9%), and psoriasis (34.8%).[27]

Psoriasis

Sexual function in psoriasis was studied in 14 studies that included 29,410 patients with a mean age of 41.07 years. Cross-sectional studies were the most frequent study type, and the overall quality of these studies was graded as "good quality." To assess sexual function, 8 of the studies used the International Index of Erectile Function (IIEF). Other tools also used were the Massachusetts General Hospital-Sexual Functioning Questionnaire in 2 studies and the Sexual Quality of Life-Men in 1 study. Disease activity in psoriasis was reported using the Psoriasis Area and Severity Index (PASI) that combines the assessment of the severity of the skin lesions and the affected area into a single score in the range of 0 (no disease) to 72 (maximal disease).[16-26,41-43]

Using validated questionnaires, the prevalence of SD in psoriasis (including ED) ranged from 34.4% to 81%.[16-25,43] When compared with a control group, the prevalence of SD was significantly higher in patients with psoriasis. Using the IIEF questionnaire, the highest prevalence of ED was reported by Tasliyurt et al.[16] In their study, a prevalence of 81.08% was found in a population of 37 patients with psoriasis (mean age: 45.19 ± 13.82 years, mean PASI: 8.25 ± 4.42) compared with 53.57% in 28 healthy men (mean age: 40.89 ± 12.91 years); this difference was statistically significant ($P = .018$). IIEF scores had a significant negative correlation with age, body mass index, and PASI scores. Depression, older age, and smoking were found to be independent risk factors for ED.

In the study from Cabete et al,[17] the prevalence of ED (IIEF-5 score $\leq$ 21) was higher in patients with psoriasis than in controls (61.5% vs 43.8%, $P = .001$). Furthermore, it was

Table 2. Description of characteristics and key findings of studies regarding reproductive hormones

Study	Number of cases/ controls (mean age in years)	Main findings	Study type and quality assessment (NOS)
Psoriasis			
Caldarola[33]	Cases: 50 (34)	• Testosterone was found to be significantly decreased in patients with psoriasis compared with the control group (3.7 ± 1.3 vs 4.8 ± 1.2 ng/mL, respectively).	4
	Controls: 50 (33.4)	• Estradiol (E2) levels were higher in patients with psoriasis than in the control group (43.8 ± 8.1 vs 29.1 ± 8.2 pg/mL).	Cross-sectional
Cemil[34]	Cases: 47 (55.9 ± 4.1)	• Testosterone was found to be significantly decreased in patients with psoriasis compared with the control group (3.9 ± 1.8 vs 5.1 ± 1.2 ng/mL, respectively).	4
	Controls: NA	• Estradiol (E2) levels were higher in patients with psoriasis than in the control group (37.5 ± 17.1 vs 29.9 ± 8.7 pg/mL).	Cross-sectional
		○ Inverse correlation was detected between PASI and serum level of estradiol in the psoriasis group.	
Saad[35]	Cases: 15 (53)	Observational study.	Case series
	Controls: 131 (NA)	15 men diagnosed with late-onset hypogonadism and psoriasis.	
		Treatment with testosterone undecanoate every 12 wk for up to 93 mo was associated with:	
		• Testosterone levels rose significantly to a eugonadal state.	
		• PASI declined from 19.3 ± 2.3 to 1.8 ± 0.4 ($P < .0001$).	
		• Serum C reactive protein levels decreased significantly over the first 24 mo.	
Tehranchinia[36]	Cases: 43 (34.1 ± 10.5)	• Testosterone levels were not statistically different between the 2 groups.	4
	Controls: 42 (31.8 ± 8.9)	• Patients with psoriasis had significantly higher levels of leptin than healthy controls (5.4 vs 2.7 ng/mL, respectively) and lower levels of follicle-stimulating hormone (1.4 vs 2 IU/L).	Cross-sectional
		○ A positive correlation was reported between serum leptin levels and disease activity.	
Atopic dermatitis			
Ebata[37]	Cases: 40 (24)	Serum levels of testosterone, free testosterone, and estradiol were significantly lower and serum levels of LH were significantly higher in male patients with atopic dermatitis	4
	Controls: 40 (24)		Cross-sectional

LH = luteinizing hormone; NOS = Newcastle-Ottawa Scale; PASI = Psoriasis Area and Severity Index.

reported that patients with psoriasis had a 2.69- and 5.3-fold increased risk of having mild-moderate and moderate-severe ED, respectively.

In a study from Poland, 42% of patients diagnosed with psoriasis reported that sexual activity decreased owing to their skin problems. ED was diagnosed in 43.8% of these patients and its severity was correlated with age ($r = -0.42$; $P \leq 0.001$) and with disease activity ($r = -0.26$: $P = .03$).[23]

Psoriasis was found to be an independent risk factor for ED (odds ratio of 2.28 [95% confidence interval, 1.40−3.27]) in 1 study[17] and with SD in 2 studies.[18,19] No association was reported in any study.[21]

The association between disease activity and SD was further analyzed in 8 studies. 6 studies reported an association between disease activity and SD.[16,20,22,23,25,43] Conversely, in 2 studies, such an association was not significant.[19,21]

The association between SD and depression, a known factor that adversely affects male sexual function, was analyzed in 5 studies. An association between depression and the presence of SD was reported in 3 studies.[18-20] No association between depression and SD in patients with psoriasis was reported in any study.[21]

In a study that included 191 patients with psoriasis, Ji et al[18] reported that severe depressive symptoms increased the risk of ED. Similarly, Molina-Leyva et al[19] reported that depression was significantly associated with ED and that psoriasis per se was not independently associated with ED.

No significant association between depression and SD was reported in a study that included 70 men from Turkey (39 diagnosed with psoriasis and 27 healthy controls; mean age, 41.42 and 41.77 years, respectively). Interestingly, total IIEF scores were not correlated with disease activity (PASI).[21]

Table 3. Description of characteristics and key findings of studies regarding fertility

Study	Number of cases/ controls (mean age in years)	Main findings	NOS quality assessment and study type
Psoriasis			
Caldarola[33]	Cases: 50 (34)	Total sperm count, sperm motility and percent of spermatozoa with normal morphology were significantly reduced in patients compared to controls.	4
	Controls: 50 (33.4)	• Sperm concentration, n × 10^6/mL: 18.6 ± 11. 6 vs 62.8 ± 20.5	Cross sectional
		• Total motility, %: 29.7 ± 22.7 vs 60.2 ± 10.2	
		• Normal morphology, %: 13.3 ± 9 vs 32.9 ± 5.5	
Heppt[38]	Cases: 27 (37.5)	• Only 4 (14.8%) patients with psoriasis showed normozoospermia at baseline.	5
	Controls: NA	• 85.2% of the patients had at least 1 sperm/seminal abnormality, including 2 patients showing an azoospermia.	Cohort
		• 48.1% of the patients showed semen parameters indicating a genital tract inflammation.	
Grunnet[39]	Cases: 20 (32.4)	16 of 20 patients with psoriasis (80%) treated with topical glucocorticoids or methotrexate had abnormal semen parameters.	3
	Controls: 10 (NA)		Cross sectional
Liu[40]	Cases: 31 (22)	Semen quality did not differ between patients and controls.	4
	Controls: 14 (22)		Cross sectional

NOS = Newcastle-Ottawa Scale.

Other relevant factors associated with SD were increasing age, smoking, and hypertension.[16-20,23,24,43] Bardazzi et al[22] reported that patients with psoriasis with ED were younger and had a more severe form of ED in comparison with patients without psoriasis diagnosed with ED.

Communication between patients and healthcare professionals was analyzed in 2 studies from the United Kingdom. Only 9% of patients with psoriasis had been previously asked by a healthcare professional about erectile problems, whereas 68% admitted dissatisfaction with their erectile ability and wanted more information on this topic.[24] Similarly, in a study from the Netherlands that included 278 men diagnosed with psoriasis (mean age, 53.9 ± 12.3 years), only 9% of patients believed that there was sufficient attention given by their doctors to possible sexual problems and 43% thought that healthcare professionals should ask more frequently about possible sexual problems.[26]

3 studies used diagnosis codes to report the prevalence or incidence of SD in patients with psoriasis. Data from 1,593 patients with psoriasis from the United States (aged 18–42 years) reported that a diagnosis of SD (International Classification of Diseases-9 and International Classification of Diseases-10 codes) was present in 7.2% of men on systemic medications compared with 3.6% of those treated with topical or no medications, this difference was statistically significant.[41]

A recent observational nationwide study from Egeberg et al[25] included 1,756,679 Danish men from which 1.5% were diagnosed with psoriasis. The prevalence of ED was 12.8% for patients with psoriasis compared with 8.7% in the general population. The risk of ED was significantly increased in patients with mild psoriasis (adjusted hazards ratio 1.14; 1.09–1.20) and severe psoriasis (adjusted hazards ratio 1.17; 1.04–1.32).

A nationwide study from Taiwan reported a significantly higher incidence of SD (3.03%) among 12,300 patients (median age, 46 years) than that among age-matched controls (2.34%) during 7 years The most prevalent SD was ED.[42]

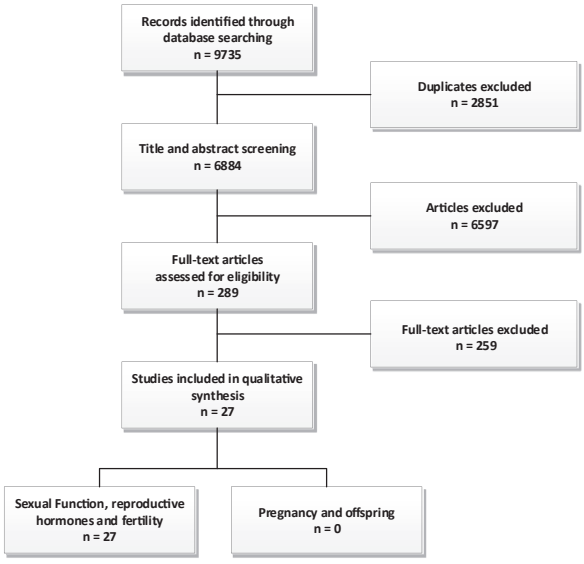

Figure 1. Flow diagram for study selection.

Table 4. Number of studies included per disease and topic

Disease	Total number of studies	Sexual function	Reproductive hormones	Fertility	Pregnancy outcomes
Psoriasis	21	13	4	4	0
Hidradenitis suppurativa	3	3	0	0	0
Lichen simplex	1	1	0	0	0
Vitiligo	1	1	0	0	0
Chronic urticaria	1	1	0	0	0
Atopic dermatitis	2	1	1	0	0

Hidradenitis Suppurativa

Sexual function in HS was reported in 3 studies. The IIEF questionnaire was used in all 3 studies. The quality of these studies was graded as "good quality." These studies included data on 103 patients (mean age of 41.6 years) and 42 healthy controls (mean age of 37.8 years). The prevalence of SD in HS was reported in one study. Overall, compared with healthy controls, patients with HS reported more sexual function problems that contribute to a lower quality of life. No association was found between disease activity and SD.

In a cross-sectional study from Canada that included 17 patients with HS (mean age, 40.47 ± 15.49 years) and 22 healthy age-matched control, significant differences in sexual function assessments were identified. Patients with HS had significantly lower Sexual Quality of Life Questionnaire for Use in Men scores ($P < .001$) and lower IIEF scores ($P = .019$). The authors concluded that SD is an important contributor to impaired quality of life in patients with HS.[28]

A multicenter cross-sectional study from the Netherlands (n = 66; mean age, 48.4 ± 12.3 years) reported a prevalence of ED of 52%. No association was reported between the IIEF total score and age of onset, duration of disease, Visual Analogue Scale-pain score, Physician Global Assessment score, Hurley stage, or Dermatology Life Quality index 58% of men with HS indicated that their sexual activity declined after disease onset.[29]

SD was more severe in 20 patients with HS compared with 20 age-matched controls as evidenced by a lower IIEF total score (42.6 ± 27.1 vs 62.6 ± 10.8, $P = .01$). No significant correlation between disease activity and the IIEF was reported.[30]

Table 5. Research recommendations

Sexual function	Use standardized screening questionnaires (IIEF).
	Case-control studies and well-designed prospective cohort studies are encouraged over cross-sectional studies.
	Consider relevant comorbidities and potential confounders (depression, anxiety, disease activity).
	Collaboration with experts in the field of sexology is encouraged.
Sperm quality	Use standardized methods to report sperm quality (WHO) (primary endpoint).
	DNA fragmentation index could provide more information regarding male fertility potential and can be considered as a secondary endpoint.
	Ideally, technicians should be blinded regarding the drug-exposure.
	RCTs are ideal but case-control and well-designed prospective cohort studies are also encouraged over cross-sectional studies.
	Consider disease activity, relevant medication history, comorbidities, and potential confounders (age, smoking, varicocele).
Reproductive hormones	Use standardized methods to measure hormones.
	RCTs are ideal but case-control and well-designed prospective cohort studies are also encouraged over cross-sectional studies.
	Consider disease activity, relevant comorbidities and potential confounders (age, medication history).
Pregnancy and offspring outcomes	Collect data prospectively or report cases with all the relevant information. eg,
	• Source of the information, indication, disease activity, clear description of medication use and timing paternal age.
	• Regarding pregnancy/child outcome; pregnancy outcome, gestational age, birthweight, infant health, genetic testing, follow up period,
	• Partner's relevant medical history.

IIEF = International Index of Erectile Function; WHO = World Health Oraganization.

Lichen Simplex

From 2000 to 2004, 5,611 male patients (mean age, 49.46 years) were diagnosed with lichen simplex in Taiwan. The incidence of SD in this group was higher than in the general population (3.37 vs 1.74 per 1,000 person-years). After adjusting for age and comorbidities and using data from 22,444 age-matched patients without lichen simplex as controls, patients with lichen simplex had a 1.74-fold greater risk of developing ED compared with controls ($P < .001$).[31]

Vitiligo

The prevalence of SD was not significantly different among patients with vitiligo and healthy controls (11.5% and 16%) in 1 study from Turkey that included 26 patients and 25 healthy controls (mean age: 35.8 and 35.9 years, respectively).[32]

Chronic Urticaria

The prevalence of SD was not significantly different among patients with chronic urticaria and healthy controls (31.2% and 16%) in a study that included 26 patients and 25 healthy controls from Turkey (mean age: 38.6 and 35.9 years, respectively).[32]

Atopic Dermatitis

In the study from Egeberg et al,[25] patients diagnosed with atopic dermatitis were also included. Interestingly, patients with atopic dermatitis had a lower prevalence of SD than the general population (6.7% vs 8.7%, respectively).

Reproductive Hormones

Regarding reproductive hormones, 5 studies were identified. The quality of these studies was graded as /+ "low quality" (for in-depth information, see Table 2).

Psoriasis

The androgenic status of 50 patients (mean age, 34 ± 8.4 years) with moderate psoriasis (PASI: 8 ± 5.5) was investigated by Caldarola et al.[33] Testosterone and sex hormone—binding globulin were significantly decreased in patients compared with age-matched controls (n = 50). Estradiol (E2) levels were higher in patients than controls.

An association between disease activity and low estradiol levels was reported by Cemil et al.[34] In a cross-sectional study that included 47 patients and 20 controls (mean age: 42.87 ± 15.56 and 38.05 ± 10.14 years, respectively), serum testosterone levels were significantly decreased in patients with psoriasis compared with controls (392.29 ± 181.91 ng/mL and 506.91 ± 117.7 ng/mL, respectively). Estradiol levels were significantly increased in patients with psoriasis (37.52 ± 17.16 vs 29.9 ± 8.77), and an inverse correlation was detected between PASI and estradiol levels in patients with psoriasis ($P < .05$).

In an observational study, testosterone replacement therapy declined PASI scores by >75% within 2 years in 15 patients diagnosed with psoriasis and late-onset hypogonadism. This was an observational study without controls. The possible role of testosterone as an anti-inflammatory agent is discussed.[35]

Leptin, a hormone secreted by the adipose tissue that plays an important role in reproductive function, was found to be significantly higher in patients with psoriasis (n = 43, mean age 34.09 ± 10.53) than that in age-matched healthy controls (n = 42). This was associated with lower level of follicle-stimulating hormone in patients compared with controls. Serum concentrations of luteinizing hormone, total testosterone, sex hormone—binding globulin, and prolactin were comparable among the 2 groups. In patients with psoriasis , disease activity and duration were significantly correlated with log-transformed leptin levels (adjusted $R^2 = 0.50$, $F = 21.87$, $P < .0001$).[36]

Atopic Dermatitis

The prevalence of hypogonadism was significantly higher in 40 patients diagnosed with atopic dermatitis than that in age-matched healthy controls. This was evidenced as patients had lower serum levels of testosterone, free testosterone (447 ± 96 vs 593 ± 149 ng/dL and 14.6 ± 3.2 vs 20.0 ± 5.1 pg/mL, both $P < .001$), and higher levels of luteinizing hormone than controls (4.57 ± 1.6 vs 3.11 ± 1.2 mIU/mL, $P < .001$).[37]

Fertility

Psoriasis

Regarding fertility parameters, 4 studies that reported sperm analysis results were identified. The quality of these studies was graded as "low quality." Sperm analysis abnormalities in patients with psoriasis were reported in 3 of 4 studies (1 study included untreated patients, 1 study included patients treated with methotrexate, and 1 study did not report treatment characteristics of the patients) (for in-depth information, see Table 3).

Sperm analysis was performed in 27 untreated patients (mean age of 37.5 years) with moderate to severe psoriasis (mean PASI score, 11.05). Interestingly, 85.2% had at least 1 sperm/seminal abnormality and 48.1% showed parameters indicative of genital tract inflammation.[38]

Grunnet et al[39] reported sperm analysis abnormalities in all 10 patients with severe psoriasis treated with topical corticosteroids included in their study. Based on semen quality, 30% were classified with "severely impaired fertility" (oligospermia 70%, asthenospermia 90%) and 30% were unwillingly childless. In contrast, sperm analysis was normal in 40% of the patients included in their comparison group (n = 10) patients with severe psoriasis treated with methotrexate, this was statistically significant ($P = .04$).

In the study from Caldarola et al,[33] semen analysis was also performed. Sperm count, motility, and morphology were significantly reduced in patients compared with controls. 50% of patients showed 1 or more seminal parameter abnormalities.

Sperm quality was investigated in 31 young Chinese soldiers diagnosed with psoriasis (aged 18—24 years). Compared with a

group of 14 healthy volunteers from the same population, conventional sperm analysis and the measurement of sperm nuclear DNA fragments werecomparable among the 2 groups.[40]

Pregnancy and Offspring Outcomes

No articles were identified.

DISCUSSION

Sexual Function

Patients with psoriasis, hidradenitis suppurativa, and lichen simplex have a higher prevalence of SD. Along with the classical risk factors, a positive correlation between psoriasis disease activity and SD was reported in several studies. This finding invites a discussion about how inflammation secondary to psoriasis can contribute to the development of SD in a young population.

Although there is evidence suggesting an influence of disease itself (via inflammation) in the development of SD, we were not able to conclude whether the disease itself plays a role in this association. After carefully analyzing our data, we concluded that performing a meta-analysis was not ideal. Our main reason behind this decision was that the type of studies included and the extracted heterogeneous data might lead to erroneous assumptions.

Epidemiologic, clinical, and basic science studies are needed to investigate the association between sexual function and cIMD. These studies should be executed in such a way that results can be compared among different populations.

Before there is more research on this topic and to improve the overall quality of it, agreement should be pursued on the definitions and diagnostic tools to use. Discussion on these issues between experts from different fields such as andrology, sexology, dermatology, and Epidemiology is needed. Such an agreement will have a positive effect on future research projects trying to summarize the available data (see also Table 5, research recommendations to conduct future research on these topics).

Adult men consider sexual health as a highly important aspect of quality of life,[44] thus dermatologists with a commitment to improving patient's overall health should address sexual concerns with their patients and partners.

Reproductive Hormones

In psoriasis, evidence suggests a possible association between disease activity and abnormalities in the reproductive endocrine axis. This is a topic where surprisingly few studies were found. Nonetheless, these studies provide interesting information; inflammation secondary to disease activity, via aromatase activity stimulation, might contribute to the development of hypogonadism in these men. Consequently, hypogonadism can be in part responsible for the high prevalence of SD in this population. The anti-inflammatory effects of testosterone have been previously described and low testosterone levels are correlated with increased expression of inflammation markers.[45] Nonetheless, in men diagnosed with cIMD, a valid estimation of the prevalence of hypogonadism, and the influence that this has on the development of the disease is still unknown. More research is needed to fully understand the role of reproductive hormones on cIMD.

Fertility

Sperm quality can be impaired in patients diagnosed with psoriasis (independent of treatment), and this could be associated with disease activity. Systemic inflammation can cause impaired spermatogenesis by mechanisms that have not been fully elucidated. For men diagnosed with psoriasis and a desire to become a father, disease activity should be monitored before and during the conception period. Importantly, medication is not the only factor that can contribute to impaired fertility in men diagnosed with psoriasis.

Pregnancy and Offspring Outcomes

Considering the extensive list of diseases included in this SR, the complete lack of studies included in this section warrants discussion. The paternal contributions to pregnancy are vital for a successful pregnancy. These men need to receive proper counseling to limit the potential negative effects of disease and/or medication on a future pregnancy. Nonetheless, currently, there is no enough information regarding the possible influence of paternal cIMD on pregnancy and offspring outcomes.

Strengths and Limitations

Several limitations should be addressed. First, a limited amount of studies that included a small number of participants were identified. In addition, studies about sexual function and fertility in men with cIMD suffer from an inconsistent methodological quality mainly because a wide variety of screening questionnaires and/or diagnostic tools were used. In consequence, the definition of SD and ED was not uniformly reported. Altogether, these limitations contributed to heterogeneous data, which we consider to be too large to perform a meta-analysis. Finally, relevant comorbidities that can also have a direct effect on sexual function such as depression and anxiety were not analyzed or reported in all studies.

Although we were able to provide a summary of the available information, we consider that the major strength of this SR is its ability to identify a large knowledge gap in this topic. Regarding fertility and pregnancy outcomes, the complete lack of information available should be acknowledged and prioritized for future research plans.

CONCLUSION

Evidence suggests that male SRH can be impaired in a significant proportion of men diagnosed with psoriasis. Nonetheless, for the other cIMD included in this SR, information on this topic is scarce, and no strong conclusions can be drawn other

than more research is needed and that this is still an important neglected topic in dermatology. Future research on this topic can provide us with relevant scientific information that can help us understand the role of inflammation in SRH.

We encourage dermatologists to consider male SRH in their clinical practice. Timely detection, referral, and treatment of SD and fertility problems can have a significant impact on the quality of life of patients and reduce the use of costly medical care. To achieve this, dermatologists and patients must have the opportunity and necessary tools to discuss this topic.

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REFERENCES

1. Glasier A, Gülmezoglu AM, Schmid GP, et al. Sexual and reproductive health: a matter of life and death. **Lancet 2006;368:1595-1607.**
2. Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. **J Urol 1994;151:54-61.**
3. Martin JA, Hamilton BE, Sutton PD, et al. Births: final data for 2004. **Natl Vital Stat Rep 2006;55:1-101.**
4. Eisenberg ML, Li S, Cullen MR, et al. Increased risk of incident chronic medical conditions in infertile men: analysis of United States claims data. **Fertil Steril 2016;105:629-636.**
5. Calmasini FB, Klee N, Webb RC, et al. Impact of immune system activation and vascular impairment on male and female sexual dysfunction. **Sex Med Rev 2019;7:604-613.**
6. Fijak M, Pilatz A, Hedger MP, et al. Infectious, inflammatory and 'autoimmune' male factor infertility: how do rodent models inform clinical practice? **Hum Reprod Update 2018;24:416-441.**
7. Takeshita J, Grewal S, Langan SM, et al. Psoriasis and comorbid diseases: epidemiology. **J Am Acad Dermatol 2017;76:377-390.**
8. Shlyankevich J, Chen AJ, Kim GE, et al. Hidradenitis suppurativa is a systemic disease with substantial comorbidity burden: a chart-verified case-control analysis. **J Am Acad Dermatol 2014;71:1144-1150.**
9. Perez-Garcia LF, Te Winkel B, Carrizales JP, et al. Sexual function and reproduction can be impaired in men with rheumatic diseases: a systematic review. **Semin Arthritis Rheum 2020;50:557-573.**
10. Gabrielson AT, Le TV, Fontenot C, et al. Male genital dermatology: a primer for the sexual medicine physician. **Sex Med Rev 2019;7:71-83.**
11. Ermertcan AT. Sexual dysfunction in dermatological diseases. **J Eur Acad Dermatol Venereol 2009;23:999-1007.**
12. Wu T, Duan X, Chen S, et al. Association between psoriasis and erectile dysfunction: a meta-analysis. **J Sex Med 2018;15:839-847.**
13. Bramer WM, de Jonge GB, Rethlefsen ML, et al. A systematic approach to searching: an efficient and complete method to develop literature searches. **J Med Libr Assoc 2018;106:531-541.**
14. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute; 2013. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed August 25, 2020.
15. Modesti PA, Reboldi G, Cappuccio FP, et al. Panethnic differences in blood pressure in Europe: a systematic review and meta-analysis. **PLoS One 2016;11:e0147601.**
16. Tasliyurt T, Bilir Y, Sahin S, et al. Erectile dysfunction in patients with psoriasis: potential impact of the metabolic syndrome. **Eur Rev Med Pharmacol Sci 2014;18:581-586.**
17. Cabete J, Torres T, Vilarinho T, et al. Erectile dysfunction in psoriasis patients. **Eur J Dermatol 2014;24:482-486.**
18. Ji S, Zang Z, Ma H, et al. Erectile dysfunction in patients with plaque psoriasis: the relation of depression and cardiovascular factors. **Int J Impot Res 2016;28:96-100.**
19. Molina-Leyva A, Molina-Leyva I, Almodovar-Real A, et al. Prevalence and associated factors of erectile dysfunction in patients with moderate to severe psoriasis and healthy population: a comparative study considering physical and psychological factors. **Arch Sex Behav 2016;45:2047-2055.**

20. Molina-Leyva A, Almodovar-Real A, Carrascosa JC, et al. Distribution pattern of psoriasis, anxiety and depression as possible causes of sexual dysfunction in patients with moderate to severe psoriasis. **An Bras Dermatol 2015; 90:338-345.**
21. Turel Ermertcan A, Temeltas G, Deveci A, et al. Sexual dysfunction in patients with psoriasis. **J Dermatol 2006; 33:772-778.**
22. Bardazzi F, Odorici G, Ferrara F, et al. Sex and the PASI: patients affected by a mild form of psoriasis are more predisposed to have a more severe form of erectile dysfunction. **J Eur Acad Dermatol Venereol 2016;30:1342-1348.**
23. Wojciechowska-Zdrojowy M, Reid A, Szepietowski JC, et al. Analysis of sexual problems in men with psoriasis. **J Sex Marital Ther 2018;44:735-745.**
24. Goulding JM, Price CL, Defty CL, et al. Erectile dysfunction in patients with psoriasis: increased prevalence, an unmet need, and a chance to intervene. **Br J Dermatol 2011;164:103-109.**
25. Egeberg A, Hansen PR, Gislason GH, et al. Erectile dysfunction in male adults with atopic dermatitis and psoriasis. **J Sex Med 2017;14:380-386.**
26. Meeuwis KA, de Hullu JA, van de Nieuwenhof HP, et al. Quality of life and sexual health in patients with genital psoriasis. **Br J Dermatol 2011;164:1247-1255.**
27. Sampogna F, Abeni D, Gieler U, et al. Impairment of sexual life in 3,485 dermatological outpatients from a multicentre study in 13 European countries. **Acta Derm Venereol 2017; 97:478-482.**
28. Alavi A, Farzanfar D, Rogalska T, et al. Quality of life and sexual health in patients with hidradenitis suppurativa. **Int J Womens Dermatol 2018;4:74-79.**
29. Janse IC, Deckers IE, van der Maten AD, et al. Sexual health and quality of life are impaired in hidradenitis suppurativa: a multicentre cross-sectional study. **Br J Dermatol 2017; 176:1042-1047.**
30. Kurek A, Peters EMJ, Chanwangpong A, et al. Profound disturbances of sexual health in patients with acne inversa. **J Am Acad Dermatol 2012;67:422-428.e1.**
31. Juan CK, Chen HJ, Shen JL, et al. Lichen simplex chronicus associated with erectile dysfunction: a population-based retrospective cohort study. **PLoS One 2015;10.**
32. Sukan M, Maner F. The problems in sexual functions of vitiligo and chronic urticaria patients. **J Sex Marital Ther 2007; 33:55-64.**
33. Caldarola G, Milardi D, Grande G, et al. Untreated psoriasis impairs male fertility: a case-control study. **Dermatology 2017;233:170-174.**
34. Cemil BC, Cengiz FP, Atas H, et al. Sex hormones in male psoriasis patients and their correlation with the psoriasis area and severity index. **J Dermatol 2015;42:500-503.**
35. Saad F, Haider A, Gooren L. Hypogonadal men with psoriasis benefit from long-term testosterone replacement therapy - a series of 15 case reports. **Andrologia 2016;48:341-346.**
36. Tehranchinia Z, Niroomand M, Kazeminejad A, et al. Leptin and sex hormones in psoriasis and correlation with disease severity. **Iran J Dermatol 2014;17:43-48.**
37. Ebata T, Itamura R, Aizawa H, et al. Serum sex hormone levels in adult patients with atopic dermatitis. **J Dermatol 1996; 23:603-605.**
38. Heppt F, Colsman A, Maronna A, et al. Influence of TNF-alpha inhibitors and fumaric acid esters on male fertility in psoriasis patients. **J Eur Acad Dermatol Venereol 2017;31:1860-1866.**
39. Grunnet E, Nyfors A, Brogaard Hansen K. Studies on human semen in topical corticosteroid treated and in methotrexate treated psoriatics. **Dermatologica 1977;154:78-84.**
40. Liu H, Li J, Yu L. Effects of acitretin on semen quality and reproductive hormone levels in patients with psoriasis vulgaris. **Dermatol Sin 2017;35:55-58.**
41. Orrell KA, Nardone B, Serrano L, et al. Psoriasis and sexual dysfunction in young adult males: a cross-sectional study in a large U.S. population. **J Invest Dermatol 2017;137:S27.**
42. Chen YJ, Chen CC, Lin MW, et al. Increased risk of sexual dysfunction in male patients with psoriasis: a nationwide population-based follow-up study. **J Sex Med 2013; 10:1212-1218.**
43. Sampogna F, Gisondi P, Tabolli S, et al. Impairment of sexual life in patients with psoriasis. **Dermatology 2007; 214:144-150.**
44. Flynn KE, Bruner DW, Cyranowski JM, et al. Sexual satisfaction and the importance of sexual health to quality of life throughout the life course of U.S. adults. **J Sex Med 2016; 13:1642-1650.**
45. Bianchi VE. The anti-inflammatory effects of testosterone. **J Endocr Soc 2019;3:91-107.**

SUPPLEMENTARY DATA

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