Editorial

Addressing important knowledge gaps about the disease burden of hirsutism

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Hirsutism, defined as excessive terminal hair growth in an androgen-sensitive distribution in females, is a common dermatologic condition affecting 5% to 15% of reproductive-aged females worldwide (Hatch et al., 1981; Mimoto et al., 2018). Over the past 2 decades, patients with hirsutism have been more closely analyzed to better understand quantitative measurements and clinical scoring, racial and ethnic differences, associated clinical characteristics, and the psychosocial impact on quality of life (QoL; Azziz et al., 2003; Pasch et al., 2016; Wang et al., 2013). There is still, however, a need for basic awareness and characterization of this common skin finding among different populations worldwide.

In this 5-year, retrospective cross-sectional study performed at a single academic institution, Mahajan et al. (2021) report on the severity and associated demographic and clinical features of a small population of reproductive-aged Indian women with hirsutism (n = 122). Using the validated modified Ferriman–Gallwey (mFG) scoring system, patients were classified as having hirsutism with an mFG score of ≥8 and were further stratified for disease severity as mild (score: 8–16), moderate (score:17–25), or severe (score: >25). The authors report demographic and clinical features of these patients, including social characteristics, family history of hirsutism, menstrual and reproductive histories, and the presence of other associated clinical findings.

In this population, the mean mFG score was moderately severe at 17.95 (range, 4–36; standard deviation ± 10.58), with 46% of patients having mild hirsutism. The prevalence of hyperandrogenemia was low, seen in 9.8% of patients. This finding is consistent with the results of other studies, reiterating the common finding of discordance between clinical and biochemical signs of hyperandrogenism (Mueller et al., 2007). Patients with moderate-to-severe hirsutism scores were referred to gynecology or endocrinology and had higher rates of incomplete evaluation, which the authors attributed to high-cost concerns and urgency to forgo further evaluation and instead start therapy. As part of the study's methodology, patients with mild hirsutism were advised to pursue a watchful waiting approach, deferring specialty referral, and recommended to use topical eflornithine.

Twenty-two patients in this cohort were classified as having a diagnosis of polycystic ovary syndrome (PCOS). PCOS is the most common cause of hirsutism worldwide, accounting for up to 70% of all cases of hirsutism in some case series (Azziz et al. 2004b; Carmina et al., 2006). Established in 2003, the Rotterdam consensus criteria are the most widely accepted diagnostic criteria for PCOS in adults (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004), and require the presence of two of three of the following findings: presence of hyperandrogenism (either biochemical or clinical, with clinical hyperandrogenism defined as hirsutism), evidence of ovulatory dysfunction, and findings of polycystic ovarian morphology on transvaginal ultrasonography (Legro et al., 2013).

Mahajan et al. noted the presence of hyperandrogenemia in several of its study participants, but they did not clearly define the criteria by which patients in this cohort were given the diagnosis of PCOS. The investigators reported individual clinical findings, such as obesity (23.8%), morbid obesity (10.7%), polycystic ovarian morphology on ultrasonography (29.5%), striae (10.7%), clitoromegaly (2.5%), and elevated testosterone levels (16.4%), as individual features that could all be related to PCOS or other underlying endocrine conditions. A broad number of comorbidities and other associated clinical features were reported; the validity of the statistical significance of these associations for hirsutism is weakened by the lack of correction for multiple hypothesis testing, limiting conclusions for clinical practice and generalizability to other populations.

In the cohort described by Mahajan et al., there was a high prevalence of menstrual irregularities (47% in the group with completed records vs. 37% of those with incomplete investigation); only 22 patients were described as having menstrual abnormalities secondary to PCOS. The high prevalence of menstrual dysfunction could also be attributed to the vast majority of patients being of young menstrual age, in which physiologic oligomenorrhea or menstrual irregularities are common (Rosenfield and Barnes, 1993). Acne was also noted to be apparent in 46.7% of the patients in this study, which may also be due to the majority of study patients being adolescents.

Previously published data have shown acne to be a common feature of hyperandrogenism and PCOS and thus often used as screening marker (Balen et al., 1995; Franks, 1989; Sharma et al., 2012), but its ability to serve as a sensitive and specific clinical marker in PCOS has been questioned (Schmidt et al., 2016). Using the World Health Organization proposed classification of body mass index (BMI) in adult Asian patients, Mahajan et al. noted obesity (defined as BMI >25–30 kg/m^2) in 23.8% of patients and morbid obesity (defined as BMI >30 kg/m^2) in 10.7% of patients with full investigative records. These set points are different from other populations, in which the World Health Organization defines "overweight" as 25 to 29 kg/m^2 and "obese" as >30 kg/m^2.

The association between obesity and hirsutism was not well defined in this paper, especially given that 11.5% of the cohort were reported to not have hirsutism yet were still included in the study. What is described in the literature is a possible link between hirsutism and elevated BMI due to the prevalence of insulin resis-

tance and increased androgen production due to adiposity. Finally, Mahajan et al. make the conclusion that the high number of unmarried women in the study may be attributed to their hirsutism; however, no causality was determined. An important limitation to this assumption is that this finding may also be explained by the higher number of adolescents and individuals under the age of 20 years included in the study cohort.

The study by Mahajan et al. contributes valuable data to the characterization of patients with hirsutism worldwide and raises important questions regarding social stigma and QoL impact associated with hirsutism. In 2015, Hodeeb et al. found that, using the Dermatology Life Quality Index assessment, patients with hirsutism were most affected by the following areas: embarrassment and self-consciousness, influence on clothing, affected social or leisure activities, and problems with partners, close friends, and relatives (Hodeeb et al., 2015). The degree to which clinicians measure severity does not always correlate to the patient's perceived impression of their skin findings. Pasch et al. (2016) found that self-rated mFG scores in patients with PCOS were often higher than clinician assessments in all areas of the body except for the thighs. mFG self-assessments were on average 4.6 points higher than the clinician's assessment, and the higher degree of self-reported hirsutism was more strongly associated with worsening QoL assessments.

Higher Skindex-16 emotional and functional domain scores were also noted among patients with higher self-reported mFG scores, highlighting that QoL is greatly affected in females who perceive themselves as hirsute; this should not be overlooked by clinicians. Interestingly, this study also found that only patient self-reported ratings of hirsutism were strongly associated with depression, an association that was not seen with clinician-based scoring (Pasch et al., 2016). Another subtle yet important nuance of this study was the identification of a small subset of individuals whose self-reported scores were also significantly lower (less severe hirsutism) than that of clinician-based scoring. These rare outliers deserve mention as a reminder to clinicians to not assume potential QoL impact of moderate-to-severe hirsutism on the patient, even if hirsutism is the patient's main reason for seeking consultation with a dermatologist.

The stigma and QoL impact of hirsutism, as well as many other dermatologic conditions, is a critical knowledge gap for dermatologists, with only limited literature available. The reported significant impacts and association with depression may support prioritizing these and other patient-reported outcomes over clinician-rated metrics in clinical trials investigating hirsutism treatments. Further understanding of these impacts in different populations is another critical knowledge gap. For example, hirsutism may have both common and varied stigma, as well as impacts on QoL, which are wide-ranging across different cultural settings. As research continues to characterize this disease across populations, as done here by Mahajan et al., our foundational knowledge and understanding of disease impacts will grow.

This avenue of hirsutism investigation may require deeper examinations of disease burden, QoL impact, gender identity, and sociocultural standards of beauty. For example, two areas of significant controversy in the endocrine and dermatology literature that warrant further research in hirsutism are the calls to establish race- or ethnicity-specific mFG cutoffs and site-specific weighted mFG scores (Sendur and Yildiz, 2021). With more population-based studies, there is an emerging perspective that the standard mFG cutoff of ≥8 may not be appropriate in defining hirsutism in certain populations (e.g., East-Asian women; Welt et al., 2006; Zhao et al., 2011). Although race is a social construct, there has been mixed evidence that mFG cutoffs should be defined separately for different ethnicities to justify this proposal (Zhao et al., 2011). In one U.S.-based study, total mFG scores were comparable between white

patients and patients of East-Asian ethnicity with PCOS; however, there were subtle site-specific differences in the anatomic distribution of hirsutism in Asian females. Interestingly, Asian patients evaluated in this study were more likely to pursue laser hair removal as a treatment for hirsutism, which raises a number of questions regarding the motivations behind this trend (Wang et al., 2013).

There is limited data regarding associations between Fitzpatrick skin type (FST) scale and hirsutism in females with PCOS. Afifi et al. (2017) found significant differences in patterns, prevalence, and severity of hirsutism in a U.S. cohort of females with PCOS based on FST, with increased overall mFG scores and prevalence in patients with a higher FST. However, the conclusions stemming from this analysis are limited, and only few comparisons with this research are available due to most studies focusing on a single subset of an ethnic population rather than a diverse cohort. Further research, especially in large, diverse populations, will be needed to inform and justify the call for differential race- or ethnicity-specific mFG cutoffs.

Lastly, whether QoL is affected by the prevalence and severity of hirsutism involving certain anatomic sites of the body is not known and may deserve further attention. This issue has important historical context. In 1961, Ferriman and Gallwey were the first to create a hirsutism scoring system based on an analysis of 430 white females in London, ages 15 to 74 years (Ferriman and Gallwey, 1961). Their scoring system has now been adjusted to a modified version using just 9 of the 11 body areas that were first described. However, the 0-to-4 rating remains the same for all body sites scored. One hypothesis is that the QoL impact of hirsutism may be more significant when the affected area is in a more publicly visible place on the body (e.g., the face). This raises the question of whether a weighted site-specific mFG scoring system, one that rates facial hirsutism involvement higher than truncal involvement, may represent a more accurate way of measuring disease severity, as well as a way to track improvement over time.

QoL impact may also be heightened by site-specific involvement based on the emotional and functional impairment caused. Similar efforts are being explored in other areas of dermatology, including examining the differential QoL impact of alopecia (Creadore et al, 2021). Weighted scoring systems for site-specific involvement of hirsutism, as well as understanding differences between patient populations, may thus provide a more high-fidelity measurement of disease impact that helps us better understand the burden of this complex dermatologic condition.

Funding

None.

Study approval

None.

Conflicts of interest

None.

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Armaiti Mody MD
University of California, Davis Department of Pediatric Endocrinology, Davis, California

Kanade Shinkai MD, PhD*
University of California, San Francisco Department of Dermatology, San Francisco, California

*Corresponding Author.
E-mail address:* Kanade.shinkai@ucsf.edu *(K. Shinkai)*