

Research Article

Open Access, Volume 4

ISSN: 2691-7785

# Qualitative Systematic Review on the Bio-Psycho-Socioeconomic Impact of Hidradenitis Suppurativa/Acne Inversa

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#### **Abstract**

Hidradenitis Suppurativa or Acne Inversa (HS) is a chronic, inflammatory, recurrent integumentary disease, with periods of exacerbation, related to metabolic comorbidities, affecting the well-being, quality of life and mental health of patients, in addition to negatively influencing oral health and women's health levels as well. It often presents little responsiveness to conventional dermatological treatments. With the aim of estimating the biopsychosocial and economic impact on patients' lives, a qualitative systematic review was planned. The results were similar to clinical practice and also with several qualitative reviews, i.e. low efficiency. It was observed few studies of good quality, low number randomized clinical trials, and quantitative systematic review, as well. Thus, (HS) has not yet been mapped into the Evidence-Based paradigm and justifies the low assertiveness of therapeutic modalities conventionally instituted to date, as most of them are still structured empirically.

Under this circumstance, and due experience and achieviments with these patients at the Instituto da Pele/Departamento de Dermatologia da Escola Paulista de Medicina da Universidade Federal de São Paulo/UNIFESP/Brazil (Monson 2019) [1], was decided to expand spectrum the research, and to add Oral and Systemic Health and Women's Health, simultaneously to the conventionally studied biopsycho-social parameters.

The results were not surprising and revealed the importance of expanding scientific research on HS. As implications for practice, we sought to qualitatively map knowledge to help organize a comprehensive minimum protocol for HS care beyond the conventionally adopted parameters, and include ways of measuring the quality levels of oral health and women's health with aimed at the quality of life of these patients.

Thus, a more realistic and assertive management could be given to the target population, as well as the adoption of complementary therapeutic modalities (according to WHO parameters), and applied in a co-intervention regime, to control these new sets of comorbidities that have been considered by the present study with the objective of increasing the levels of efficacy, effectiveness and safety by Good Clinical Practices. Even though we still do not have the methodological conditions to establish Guidelines for HS, we at least strive to make care for these patients increasingly humanized and inclusive.

Manuscript Information: Received: Feb 01, 2024; Accepted: Mar 18, 2024; Published: Mar 25, 2024

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**Citation:** Augusto OC, Monica O, Giulia M, Donato S, Carlos M, et al. Qualitative Systematic Review on the Bio-Psycho-Socioeconomic Impact of Hidradenitis Suppurativa/Acne Inversa. J Surgery. 2024; 4(1): 1149.

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#### Introduction

Hidradenitis Suppurativa (HS) or Acne Inversa is a chronic, inflammatory, skin disease with periods of exacerbations or relapses. Poorly understood and debilitating, the disease presents varying degrees of refractoriness to conventional dermatological treatments [2]; It affects men and women of different age groups, reduces the quality of life, well-being and mental health of patients, in addition to being frequently associated with low levels of human development [3]. Clinically, it manifests as multiple papules, nodules and abscesses in flexural areas of the body such as armpits, inguinal and perigenital regions and perineum [4], as well as in non-flexural areas such as legs, dorsal and pectoral regions, ears and penis [5]. HS can also manifest in unusual locations such as the abdomen, amputation stump, cesarean scar, chest, dorsal region of the foot, eyelids, knees, post-auricular region and scalp [6]. There are reports of involvement of the follicular portion of the pilosebaceous units [7] and genetic predisposition [8], and associations with significant comorbidities such as smoking, obesity, metabolic syndrome and diabetes mellitus [9,10].

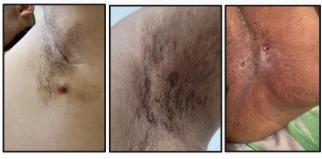
#### Theoretical foundation

It is believed that acne conglobata, hidradenitis suppurativa and perifolliculitis capitis are due to follicular occlusion resulting from hyperkeratinization of the intradermal follicular portion of the hair follicle [11].

Anatomically, the hair follicle is found in the surface regions of the skin, except lips, palms and soles; It is made up of three segments (upper or infundibulum, middle or isthmus, lower or bulb), and performs thermoregulation and wound healing functions [12]. Although its intrinsic mechanism of pathogenicity has not yet been completely elucidated, it is inferred that the formation of the lesion is related to follicular hyperkeratosis within the pilosebaceous unit, characterizing HS as a hair follicle disease [13] associated with secondary inflammation of the apocrine glands [14].

The pathophysiology is not yet fully understood, the histopathological findings show that the initial lesion of HS is an occlusive infundibulitis with a predominance of T cells in the lymphocytic cell population [15]. The disease is multifactorial, recurrent and scarring, and keratotic occlusion of the hair follicle may be the initiating event [16]. Follicular hyperkeratosis and perifollicular lymphocytic and subepidermal inflammation appear to be the initial patterns favoring cyst formation [17]. Such events, driven by factors such as genetic predisposition (changes in genes that encode essential elements of the y-secretase complex - PSENEN, PSEN1 or NCSTN) [18] or external factors such as skin microbiome, obesity, smoking and mechanical friction. The microbiome of damaged skin differs significantly when compared to normal skin, and an altered microbiome plays a relevant role in the onset of HS [18]. Furthermore, intrinsic defects in keratinocyte function favor inflammation in HS. Keratinocytes recruit high concentrations of immune cells to the injured epidermis and the interaction between chemokines (CCL2, CCL3 and CXCL3), neutrophils, CD8 T cells and natural killer cells favors the inflammatory condition in the epidermis [20]. Add to this the changes undergone by the stem cells of the hair follicles and mainly by the cells of the external root sheath, culminating in the activation of the ATR/CHK1 pathway and the consequent increase in the number of micronodules and





Hidradenite supurativa - illustrations

the presence of cytoplasmic ssDNA and finally the activation of the IFI16/STING pathway and production of type I IFNs [21].

The rupture of the diseased follicle favors the release of its contents, that is, keratin fibers, dermal debris and molecular patterns associated with damage and pathogens (DAMP, PAMP), attracting more inflammatory cells. It is known that the cycles repeat themselves, the inflammation becomes chronic, favoring the formation of scars and tunnels as well as the formation of cavities that unite or deepen, creating conditions for infections and accumulation of materials that result in suppurative and foul-smelling secretions. It is possible that a bidirectional communication between the skin microbiome and the patient's immune response in skin damaged by HS favors a positive diet that accounts for the chronicity of inflammation, tissue destruction and exacerbation of the disease [22].

Regarding etiology, it is believed that HS may be the result of an association of causes such as genetic predisposition, environmental, hormonal and microbiological factors that act as risk factors. Numerous scientific studies associate HS with mutations in y-secretase genes and changes in the Notch signaling pathway [8]; changes in the skin microbiome [23]: elevations in pro-inflammatory cytokines [24]; changes in the innate immunity system [25]; the influence of hormonal factors, especially androgens [26]; physical factors such as mechanical stress [27] or environmental factors such as obesity and smoking [28]. Recent work has sought to establish, albeit broadly, a relationship between the disease and social and economic factors [29].

The exact prevalence of HS is unknown. HS is a disease of young adults with a predominance of females [30]; typically occurs after puberty [31]; it is more common in the second and third decades of life, rare before the beginning of adolescence, and the

prevalence is lower in elderly people [14]. It is rarely observed in younger children and when it occurs, it is more common in children with a positive family history [32], and tends to be more severe in men.

It is estimated that HS has an estimated prevalence of 1% of the world population. Prevalence estimates in North Hemisphere range from <1 to 4% [10]. In the US, HS disproportionately affects women, young adults and African Americans [33]. In Australia, the prevalence of HS has been estimated at 0.67%. The individuals were predominantly female, young, obese, smokers, unemployed or with lower purchasing power [3]. In the Brazilian population, the prevalence of HS was estimated at 0.41%. The age group from 13 to 24 years of age was the most affected, and females were the most affected. Cross-sectional descriptive study with retrospective analysis of 194 patients, between 2005 and 2015, in, 74% of the cases were female [34].

Age at the time of diagnosis varied between 10 and 67 years. 33% were diabetic; 55% were obese; and 61% were smokers. Hurley stage II was the most common at the time of diagnosis; and the average time between the onset of the disease and diagnosis was 9 years [35].

The scientific literature contains conflicting data on the epidemiology of HS. The prevalence disease depends on a variety of factors. Taking into account where and how data is collected, an extremely significant bias can be observed, highlighting a difficulty in collecting and extrapolating data [36].

The overall expression of the disease is disproportionate to the estimated prevalence. The severity of the disease is described according to Hurley's three categories with the majority of cases meeting criteria for mild or moderate disease [31].

### Materials and methods

To assess the degree of impact HS of bio-psycho-socio-economic risk factors, the present Qualitative Systematic Review was planned. The study in question aims to analyze the influence of socioeconomic markers on the occurrence, severity and chronification of HS, as well as the relationship between such risk factors and the occurrence of the disease, in addition to innovative aspects on the topic such as the impact of HS on women's health and correlation with oral health levels.

To evaluate the methodological quality of the included studies, the Higgins Bias Risk Analysis Tool for Randomized Clinical Trials (Higgins 2011) and the AMSTAR Scale 2 (A Measurement Tool to Assess Systematic Reviews 2) were applied [37], created to evaluate the methodological quality of Quantitative Systematic Reviews retrieved by search strategies.

The study in question aimed to analyze the influence of socioeconomic markers on the occurrence, severity and chronification of HS, as well as the correlation between such risk factors and the occurrence of the disease, in addition to evaluating new aspects on the topic such as the impact of the disease on women's health, as well as the correlation with patients' oral health levels. To this end, a basic research question of a PICOT question (Problem, Intervention, Control, Result and Time) was organized. To this end, MsSH (Medical Subjects Headings) were selected and included Hidradenitis Suppurativa, Acne Inversa and Verneuil's Disease.

**PICOT question:** Which are the Bio-Psycho-Socioeconomic risk factors that most interfere in the Evolution and Quality of Life of Individuals with Hidradenitis Suppurativa?.

Submitted via Webliography in the electronic databases Pubmed, Google Scholar and Cochrane Library, using specific search strategies, in association with the Boolean operators OR, AND and NOT. The following primary studies were selected (Case-Control Studies, Observational Studies and Randomized Clinical Trials). Searches for qualitative and quantitative secondary clinical studies were also carried out in specific electronic databases. Only articles in English published between 1990 and 2023 were included in this study. Studies published in non-scientific newspapers and magazines, narrative reviews, theses, and monographs were excluded. Among the selected articles, preference was given to those with clearer analyzes related to the topic in question, that is, articles that established some relationship between socioeconomic level and HA and/or comorbidities, seeking to clarify the interrelationships between lifestyle of people and the diseases that affect them and how these diseases can be interconnected as causes or consequences of each other in a relationship of interdependence.

#### **Results**

According to the review protocol, only one secondary clinical research was retrieved from COCHRANE LIBRARY. A Quantitative Systematic Review that fully completed the items of the AMSTAR 2 Scale, however two unfavorable aspects were observed (outdated review and not analyzing in detail the bio-psycho-socioeconomic aspects of the participants) and thus not meeting the project inclusion criteria. Also in COCHRANE LIBRARY, 3 ongoing randomized clinical trials were retrieved, with results that have not yet been conclusive or published:

- 1. Etude de l'efficacité et de la tolérance du L35 versus placebo dans le traitement de l'hidradénite suppurée (Maladie de Verneuil) Hidradénite suppurée. EUCTR2006-005405-67-FR. https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2006-005405-67-FR, 2007 | added to CENTRAL: 31 March 2019 | 2019 Issue 3.
- 2. Etude comparative randomisee intra-individuelle de l'efficacite du traitement d'hidradenite suppuree ou maladie de verneuil par injections sous cutanee de toxine botulinique versus placebo verneuil2006. EUCTR2007-000534-39-FR. https://trialsearch.who.int/Trial2.aspx? TrialID=EUCTR2007-000534-39-FR, 2007 | added to CENTRAL: 31 March 2019 | 2019 Issue 3.
- 3. The effect of Botulinum Toxin type A in patients with axillary Suppurative Hidradenitis. RBR-4sp5w6. https://trialsearch.who.int/Trial2.aspx?TrialID=RBR-4sp5w6, 2020 | added to CENTRAL: 31 October 2020 | 20 20 Issue 10.

The result is due to the scarcity and low quality of current scientific production on the subject. Therefore, it was decided to carry out this review using a multifactorial analysis of bio-psychosocioeconomic risks, with 12 observational studies, with more than 100 participants, in addition to 6 observational studies with less than 100 participants.

The latter were chosen randomly, which resulted in 20 studies in total, with a total of 3712 participants with those related to the epidemiology of HS, and subjected to a pre-established research

protocol. 18 studies were listed in the tables, except the study on Oral and Systemic Health and Women's Health. The extracted data such as age, gender, race/color/ethnicity, education, income and degree of severity of HS, according to the Hurley Classification, 1989 (Table 1) were stratified with the participation of two more examiners, and later arranged in tables. Among the main comorbidities and/or triggering or aggravating factors, smoking and obesity were given greater importance. The study on Oral and Systemic health totaled 102 participants [38]. The women's health study did not calculate the total number of participants [39].

| Tahla 1. | Hurley | classification  | stage ch  | aracteristics  |
|----------|--------|-----------------|-----------|----------------|
| Table 1. | nullev | CIASSIIICALIOII | Stage CII | aracteristics. |

| Stage     | Characteristics   |
|-----------|---|
| Stage I   | Formation of abscesses, single or multiple, absence of fistulas and scars.  |
| Stage II  | Recurrent abscesses, single or multiple, sparsely separated, with the presence of fistulas or scars.                        |
| Stage III | Presence of multiple abscesses, diffuse involvement between them, and interconnected fistulas throughout the affected area. |

**Table 2:** Study, participantes and soci aspectos socioeconômicos.

| Study  | Participants | Gender                                 | Etnics   | Scholarity   | Job   |
|--|--------------|--|--|--|---|
| Lorite-Fuentes, I. et al. 2022 [40].                   | 221          | Male: 59 (26.30%)<br>Fem: 162 (73,30%) |  |  |   |
| Andrade, et al. 2015 [35].                             | 123          | Male: 32 (26%)<br>Fem: 91 (74%)        | Caucasian: 94 (76%)<br>No-caucasian: 22 (18%)<br>Unknown: 7 (6%)                       |  |   |
| Katoulis, et al. 2017 [41].                            | 152          | Masc: 60 (39.5%)<br>Fem: 92 (60.5%).   |  |  | Public Job: 13, Privat Job: 55<br>Liberal job: 29, House wives:<br>15, Students: 16, Pupils: 5,<br>Retirement: 4, Jobless: 15 |
| Kluger, N; Ranta, M; Serlachius,<br>M. 2017 [42].      | 26           | Male: 10 (38.5%)<br>Fem: 16 ((61,5%)   | Caucasian: 25/26 (96,2%)<br>African descendent: 1 (3,8%)                               | High School or College:<br>57,5%   | Annual Earnings between € 25.000 e 59.999: 58,3%; Jobless: 16 (61,5%)   |
| Delany, et al. 2017 [43].                              | 150          | Male: 45 (30,0%)<br>Fem: 105 (70,0%)   | Caucasian: 143 (95,3%)<br>Black: 1 (0,7%)<br>Asian: 1(0,7%)<br>Others: 5 (3,5%)        |  | Students: 16, Working: 76<br>Jobless: 32, Temporarely Inc: 4<br>Permanent Inc: 10, Others: 12                                 |
| Schultheis, M. et al. 2023 [44].                       | 553          | Male: 120 (21,7%)<br>Fem: 433 (78,3%)  |  | N= 508:<br>Hig School: 35,2%<br>Professional Qualification:<br>40,0% College: 24,8%                  | Employment relationship: 68,7% Jobess: 31,3%  |
| Loo, et al. 2018 [45]                                  | 62           | Male: 52 (83,9%)<br>Fem: 10 (16.1%)    | Malaysian: 44 (71,0%)<br>Chinese: 7 (11,3%)<br>Hindu: 10 (16,1%)<br>Others: 1 (1,6%)   | Primary: 1 (1,6%) Secondary: 35 (56,5%) Diploma: 12 (19,4%) Degree: 11 (17,7%) Masters/PhD: 3 (4,8%) |   |
| Hammud, A; Avitan-Hersh, E;<br>Khamaysi, Z. 2023 [46]. | 164          | Male: 96 (58,5%)<br>Fem: 68 (41,5%)    | Jewish: 93 (57%)<br>Arab: 71 (43%)   |  |   |
| Choi, E; Cook, A; Chandran, N S.<br>2018 [47].         | 58           | Male: 34 (58.6%)<br>Fem: 24 (41,4%)    | Chinese: 24 (41,4%)<br>Malaysian: 7 (12,1%)<br>Hindu: 17 (29,3%)<br>Others: 10 (17,2%) |  |   |
| Yuksel, M; Basim, P. 2019 [48].                        | 208          | Male: 142 (68,3%)<br>Fem: 66 (31,75)   |  | 0 to 8 yo: 70 (33,7%)<br>8 to 16 yo: 138 (66,3%)   |   |
| Alsadhan, H. et al. 2022 [49].                         | 183          | Male: 101<br>Fem: 82                   |  |  |   |
| Hayama, K. et al. 2020 [50].                           | 300          | Male: 219 (73%)<br>Fem: 81 (27%)       |  |  |   |
| Chu, CB; et al. 2021 [12].                             | 161          | Male: 110 (68,3%)<br>Fem: 51 (31,7%)   | Caucasian: 02 (1,24%)<br>Taiwanese: 159 (98,76%)                                       |  |   |
| Vazquez, et al. 2013 [51].                             | 268          | Male: 79 (29,5%)<br>Fem: 189 (70,5%)   | Caucasian: 241 (90,3%)<br>No Caucasian: 26 (9,7%)<br>Unknown: 1                        | >12 yo: 139 (57.9%)<br>12 to 57 yo (23,8%)<br><12 yo: 44 (18,3%)<br>Unknown: 28                      |   |
| Kamat, D; Gaba, S; Kumaran, M S.<br>2021 [52].         | 22           | Male: 10 (45,4%)<br>Fem: 12 (54,4%)    |  |  |   |

| Schrader, A. M. R. et al. 2014 [53]. | 846 | Male: 232 (27,4%)<br>Fem: 614 (72,6%) |   |  |
|--------------------------------------|-----|---------------------------------------|---|--|
| Wang, Z S. et al 2022 [54].          | 87  | Male: 67 (77,0%)<br>Fem: 20 (23,0%)   | Chinese: 75 (86,2%)<br>Outros: 12 (13,8%) |  |
| Fabrocini, G. et al., 2016 [55].     | 27  | Male: 8 (29.6%)<br>Fem: 19 (70.4%)    |   |  |

 Table 3: Study, sample, main triggering/aggravating factors and HS severity.

| Estudo   | Amostra | Smoking  | Obesity  | HS Severity  |
|--|---------|--|--|--|
| Lorite-Fuentes, I. et al. 2022 [40].                   | 221     | Smokers: 127 (57,46%)  | BMI (Kg/m²) : 29,65  | Hurley I: 65 (29,41%)<br>Hurley II: 86 (38,91%)<br>Hurley III: 70 (31,67)                    |
| Andrade, et al. 2015 [35].                             | 123     | Smokers: 75 (61%)<br>No-Smokers: 42 (34%)<br>Unknown: 6 (5%)                                   | Yes: 55%<br>No: 12%<br>Unknown: 33%  | Hurley I: 26 (21%)<br>Hurley II: 59 (48%)<br>Hurley III: 38 (31%)                            |
| Katoulis, et al. 2017 [41].                            | 152     | Smokers: 110 (72,4%)<br>Ex-Smokers: 11 (7,2%)<br>No-Smokers: 31 (20,4%)                        | BMI <20: 3<br>BMI 20-<25: 35<br>BMI 25-<30: 35<br>BMI 30-<35: 44<br>BMI 35-<40: 22<br>BMI ≥ 13             | Hurley I: 40 (26,3%)<br>Hurley II: 68 (44,7%)<br>Hurley III: 44 (29,0%)                      |
| Kluger, N; Ranta, M; Serlachius, M. 2017 [42].         | 26      | Active Smokers: 10 (385%)<br>Ex-Smokers: 10 (38,5%)<br>No-Smokers: 6 (23,1%)                   | BMI < 25: 4 (15,4%)<br>BMI > 30: 13 (50%)  | Hurley I: 13 (50%);<br>Hurley II: 11 42,3%)<br>Hurley III: 2 (7,7%)                          |
| Delany, et al. 2017 [43].                              | 150     | Active Smokers: 84 (56,0%)<br>Ex-Smokers: 33 (22,0%)<br>No Smokers: 33 (22,0%                  | BMI ≥ 25 kg/m2: 81,8%  | Hurley II: 50,4%   |
| Schultheis, M. et al. 2023 [44].                       | 553     | Active Smokers: 353 (63,83%)<br>Ex-Smokers: 97 (17,54%)<br>No Smokers: 103 (18,62%)            | BMI: 32,2 ±7,27  | Hurley I: 72 (13,0%);<br>Hurley II: 343 (62,0%);<br>Hurley III: 138 (25,0%)                  |
| Loo, C H. et al. 2018 [45].                            | 62      | Yes (Smokers /<br>Ex-Smokers ): 29 (46,8%)<br>No (Never Smoked): 33 (53,2%)                    | BMI ≥ 27,5: 30 (48,4%);<br>BMI 23 – 27.4: 15 (24,2%)<br>BMI 18,5-22,9: 9 (14,5%)<br>BMI < 18.5: 8 (12,9%). | Hurley I: 15 (24,2%)<br>Hurley II: 38 (61,3%)<br>Hurley III: 9 (14,5%).                      |
| Hammud, A; Avitan-Hersh, E; Khamaysi, Z. 2023<br>[46]. | 164     | Smokers: 90 (55%)  | Overweights: 46 (28%).   | Hurley I: 33 (20,0%)<br>Hurley II: 83 (51,0%)<br>Hurley III: 48 (29,0%)                      |
| Choi, E; Cook, A R; Chandran, N S. 2018 [47].          | 58      | Yes: 19 (35)   | BMI < 25: 10 (38)<br>BMI 25-30: 9 (38)<br>BMI > 30: 19 (38)  | Hurley I: 22 (37,9%)<br>Hurley II: 30 (57,1%)<br>Hurley III: 6 (10,3%).                      |
| Yüksel,M; Basim.2019 [48].                             | 208     | Smokers: 126 (60.6%)<br>No Smokers: 82 (39,4%)   | BMI < 18,5: 1 (0,5%)<br>BMI 18,5-25: 59 (28,4%)<br>BMI 25-29: 92 (44,2%)<br>BMI ≥ 30: 56 (26,9%).          | Hurley I: 67 (32,2%)<br>Hurley II: 118 (56,7%)<br>Hurley III: 23 (11,1%).                    |
| Alsadhan, H. et al. 2022 [49].                         | 183     | Smokers: 43  | Overweights: 46<br>Obese: 48<br>Morbid Obesety: 63   | Hurley I – Moderada:<br>98<br>Hurley II e III – Grave:<br>85                                 |
| Hayama, K; et al. 2020 [50].                           | 300     | No: 85 (28,3%);<br>Yes: 123 (41,0%)<br>Unknown: 92 (30,7%).                                    | Yes: 48 (16,0%)  | Hurley I: 69 (23%)<br>Hurley II: 109 (36,3%)<br>Hurley III: 121 (40,3%)<br>Não informado: 1. |
| Chu, CB. et al. 2021 [12]                              | 161     | Active Smokers: 54 (36,0%)<br>Ex-Smokers: 4 (2,7%)<br>No Smokers: 92 (61,3%)<br>Uninformed: 11 | Normal weight: 51 (38,1%)<br>Over weight: 42 (31,3%)<br>Obese: 41 (30,6%)<br>Uninformed: 27                | Hurley I: 69 (42,9%)<br>Hurley II: 68 (42,2%)<br>Hurley III: 24 (14,9%).                     |

| Vazquez, et al. 2013 [51].                | 268 | No Smokers: 79 (29,8%)<br>Active Smokers: 153 (57,7%)<br>Ex-smokers: 33 (12,5%)                    | BMI < 25: 49 (19,2%)<br>BMI 25,0-29,9: 66 (25,9%)<br>BMI 30,0-34.9: 49 (19,2%)<br>BMI 35.0-39,9: 49 (19,2%)<br>BMI 40,0-49,9: 33 (12,9%) | Hurley I: 160 (59,7%);<br>Hurley II: 102 (38,1%)<br>Hurley III: 6 (2,2%)   |
|---|-----|--|--|--|
| Kamat, D; Gaba, S; Kumaran, M. 2021 [52]. | 22  | Active Smokers: 3 (13,6%)  | BMI 19-25: 8 (36,3%)<br>BMI 25-29,9: 10 (45,4%)<br>BMI ≥ 30: 4 (18,1%)   | Hurley I: 3 (13,6%)<br>Hurley II: 7 (31,8%)<br>Hurley III: 12 (54,4%0.     |
| Schrader, A. M. R. et al. 2014 [53].      | 846 | Active Smokers: 595 (70,7%)<br>Ex-Smokers: 119 (14,2%)<br>No Smokers: 127 (15,1%)<br>Uninformed: 5 | BMI ≥30.0: 263 (32,3%)<br>BMI > 25.0-29,9: 256 (31,5%)   | Hurley I: 385 (45,5%)<br>Hurley II: 351 (41,5%)<br>Hurley III: 110 (13,0%) |
| Wang, et al. 2022 [54].                   | 87  | Smokers: 30 (34,48%)<br>Ex-Smokers: 13 (14,94%)<br>No Smorkers: 44 (50,6%)                         | BMI < 18,5: 3 (3,4%)<br>BMI 18,5-23,9: 31 (35,6%)<br>BMI 24,0-27,9: 24 (27,6%)<br>BMI > 28: 29 (33,3%)                                   | Hurley I: 22 (25,3%)<br>Hurley II: 52 (59,8%)<br>Hurley III: 13 (14,9%)    |
| Fabbrocini, D. et al., 2016 [55].         | 27  | Current Smoker: 14 (51.8%)   |  |  |

#### **Discussion**

Thus, given the scarcity of epidemiological data on HS, and high heterogeneity among the studies retrieved, some studies clearly pointed out the demographic aspects of the disease. Then, subgroup analyzes were carried out as detailed below:

Gender and race or ethnicity were the most discussed data. Individual or family income and education do not appear in the protocols or in clinical trials, and there is a lack of establishing correlations between the factors causing or aggravating the disease and the outcomes observed.

A total of 3,611 patients with hidradenitis suppurativa were included in the 18 studies analyzed. The studies revealed demographic data for 1,476 (40.88%) men and 2,135 (59.12%) women. Only 1,099 patients had data related to race, color or ethnicity mentioned.

Data gaps allowed the following distribution: 505 were identified as white; 50 were identified as non-white, Afro-descendant or black; 36 were classified as unknown or other; 344 were identified as Asian, Malayan, Chinese, Indian and Taiwanese, and 164 were mentioned as Arab and Jewish.

Regarding Education, of the 18 articles, only 5 studies dealt with the subject, but the way the data were placed makes a more precise analysis difficult. Only 4 articles dealt with the subject of work/occupation, referring to 881 patients with HS, of whom 236 were clearly defined as unemployed.

Regarding smoking, all 18 articles make reference. 3,115 patients had their data clearly informed while 496 had, for unidentified reasons, their information neglected. Smokers and exsmokers totaled 2,358 patients, while non-smokers totaled 757. Among the 17 articles that emphasize the issue of obesity, some provided only average data.

The way the data was placed, considering the unknown and uninformed, only 614 patients were clearly identified as having a BMI>30 kg/m². 17 articles used the Hurley Classification to assess disease severity. Of these, 2 articles generated ambiguity in their interpretation. 15 articles provided clearer information allowing the following distribution: 1,061 patients were classified as Hurley I; 1,525 with Hurley II, and 664 patients were referred with Hurley III.

# Hidradenitis suppurativa and socioeconomic status

The Organic Health Law (Law 8,080/90) in force in Brazil provides for the conditions for the promotion, protection and recovery of health, the organization and operation of the corresponding services and other provisions. The law sets out the determining and conditioning factors for health as food, housing, basic sanitation, the environment, work, income, education, transport, leisure and access to essential goods and services for health.

The National Commission on Health Determinants establishes social determinants as the social, economic, cultural, ethnic/racial, psychological and behavioral factors that influence the occurrence of health problems and their risk factors in the population; while the World Health Organization (WHO), in relation to social determinants of health, classifies them as conditions in which people are born, grow, live, work and age, including the health system.

Socioeconomic level (SES) refers to an individual's social position in relation to other members of society [56]; plays a significant role in determining an individual's quality of life, health, social position, and class [57]; it is one of the main factors that influence the health status of a nation [58]. NSE can be classified into two types: objective NSE and subjective NSE. This can be assessed using methods such as the MacArthur Scale.

Objective SES refers to three different aspects, namely income, education and occupation, while subjective SES refers to the perception that people have regarding their position in the social hierarchy in relation to other individuals. The level of education is one of the indicators of socioeconomic level. People with low knowledge are more prone to poor health, have less understanding of their health problems and treatment, and are at greater risk of hospital admissions [59].

The relationships between socioeconomic status and health, social and financial inequalities are current issues. The socioeconomic link and health, whether individual or collective, has already been widely debated. However, among the 18 scientific works listed in this study, only three mention the profession, employment relationship and/or income of patients affected by Hidradenitis suppurativa. A descriptive epidemiological study of HS involving 152 cases emphasizes occupation: thirteen pa-

tients (8.5%) worked in the public sector; 29(19.0%) were self-employed, 35(36.2% worked in the private sector; 15(9.9%) were housewives; 16(10.6% were students; 5(3.3%) were students; 4 (2.6% were retired; and 15(9.9%) were unemployed [41]. A review of medical records involving 26 patients emphasizes income, limiting itself to mentioning that "58.3% had an annual income between 25,000 and 59,999 euros" and that "in total, 16 patients (61.5%) were unemployed" [42]; while a cross-sectional epidemiological study with 150 patients, showing that, of the 143 patients who filled out the questionnaires, 49.7% were employed at the time of the survey; 21.3% were unemployed, while 9.4% were unemployed due to temporary or permanent disability [43]. Both studies, in their conclusions, did not establish a direct relationship between socioeconomic status and HS.

Although controversial, socioeconomic level is a critical determinant of health outcomes. A study involving 27,614 patients with HS observed that low socioeconomic status was found in 6,195 patients (22.4%).

HS was associated with lower socioeconomic status, in crude analysis (Odds Ratio 85, 95 CI: 1%, 80.1-90.1). The association, in multivariate analysis, proved to be more modest (Odds ratio 13.95; CI: 1%, 9.1-16), and concludes that the modest association between SH and low socioeconomic status may not be a determining factor for the development of the disease [29]. In contrast, a self-reported population-based cohort of 56,084 respondents found a general prevalence for HS of 2.1% (CI: 95%, 2.0-2.2) and highlights that patients with HS had a lower socioeconomic status lower than controls (P<0.001) [40]. Low socioeconomic status may be a risk factor for the development of HS as it may be associated with an unhealthy lifestyle such as smoking and obesity, factors that have been widely studied and related to the development and chronicity of the disease [61]; while differences in socioeconomic status between racial groups constitute one of the main factors contributing to racial disparities in health [62].

Cause or consequence of HS, low socioeconomic status may be associated with worse results in physical and mental health, and in people's quality of life. Groups of low socioeconomic status may, on the one hand, face increased levels of health impairment, and on the other, face lower levels of health-related quality of life [63].

A cross-sectional study based on a registry of 13,538 patients diagnosed with HS showed a mean age of 44 years, more frequently in women, single people, lower education and lower income, and a high prevalence of overweight, obesity and smoking in pregnant women [64].

Low socioeconomic level can translate into increased financial expenses for patients who require routine medical consultations, more expensive medications, hospitalizations, more intensive post-operative care and/or higher costs with dressings and return consultations for follow-up. Furthermore, the higher costs can also be passed on to health plans, and to public health policies, that is, States or nations, both through expenses resulting from surgical claims or loss of life in the full working age range.

Another expression of socioeconomic level is elevations in inflammatory factors. Cytokines such as TNF- $\alpha$ , IL-1B and IL-10, among others, are involved in the pathogenesis of HS [65]. IL-6 is

a cytokine with a molecular weight between 21 and 30 kDa, little reported in studies related to HS, however the upregulation of IL-6 appears to be involved in some inflammatory diseases such as rheumatoid arthritis and Crohn's disease [66]. On the other hand, IL-6 appears to be related to socioeconomic status. Aging itself may be related to an increase in inflammatory cytokines. Unfavorable social and economic conditions are associated with the increase in these substances, and in particular, with the increase in IL-6 [67]. Parents' low level of education is associated with their children's state of inflammation during adolescence, a fact that is partly explained by adiposity. Parental education is inversely associated with increased levels of IL-6 [68].

Social inequalities can translate into health inequalities. Socioeconomic level and inflammation levels (CRP and IL-6) are associated. Smoking and obesity as behavioral processes explain this association. People with low socioeconomic status exhibit higher levels of inflammatory markers, leading to the conclusion that socioeconomic inequalities can be translated into inequalities in physical and mental health [69]. In obesity (BMI>30 kg/m²) an average increase in ESR, CRP and IL-6 levels can be observed [70] while serum IL-6 levels are increased in patients with HS Hurley II and III, which suggests that IL-6 may play a role in the development of HS [71] and that serum IL-6, CRP and ESR may be considered effective markers in assessing the severity of HS [72].

### Hidradenitis suppurativa and gender

Does HS have a predilection for the female sex? Does sexual gender determine which regions of the body are affected by the disease? Epidemiological studies, the most diverse, attempt to clarify the geographic distribution of HS between countries and highlight the distribution of the disease between men and women. A controversial subject, the prevalence of HS varies greatly between different geographic regions as well as between sexes. In American and European populations, where epidemiological studies are most carried out, evidence points to a higher prevalence in females, that is, for every three women, only one man is affected by the disease [73]. The opposite can be observed in East Asia, where HS was found to be more common in men and few with a positive family history [74], more precisely in Korea, where a predominance of male patients was observed reaching a relationship male/female ratio of 2.5:1 [75] and in peninsular Malaysia, where a male predominance was found among patients with an earlier age of onset and more severe disease [45].

The onset time of the disease differs between men and women. The prevalence is higher in the fourth and fifth decades of life, but the onset of the disease can date back to puberty or the immediate post-puberty period. HS is rare in children and pre-pubertal children, and when it occurs, it may be due to hormonal disorders and genetic susceptibility [76] or unknown etiology [77].

Women have an earlier onset of the disease compared to men, and are less likely to have the more severe form of the disease [78], while men develop the disease later, but are more likely to have the more severe form. compared to women [75]. Regarding distribution, men develop lesions more frequently in the glutes, perianal and atypical regions and a history of severe acne, while women develop predominantly inguinal and breast lesions and a more frequent family history of HS [53]. The severity of the disease appears to be associated with male sex, duration of the disease

ease, obesity and smoking [53]. The two environmental factors most involved in the development of HS are also factors implicated in the severity and possibly in the distribution of the disease between the sexes. Obesity and smoking appear to be associated with more severe disease [75].

HS has a negative impact on the exercise of sexuality in both men and women. In a systematic review, the prevalence of sexual dysfunction varied between 51 and 62% and, considering erectile dysfunction, a specific type of sexual dysfunction that impairs penile erection, the prevalence varied between 52 and 60%, in a universe of 42,729 patients with HS, with women being most affected by sexual suffering [79]. HS affects the sexuality of both patients and their sexual partners.

A cross-sectional study including 34 single patients and 28 patients in stable relationships and their partners showed that women with Hidradenitis suppurativa had a high prevalence of sexual dysfunction (13/32, 40.6%) while men had a high prevalence of erectile dysfunction (19/30, 63.3%). Male partners had a high prevalence of erectile dysfunction (10/17, 58.8%) while only one female partner had sexual dysfunction (1/11, 9.1%) [80]. Multicenter study involving 13 European countries, 23.1% of 3,485 patients with various skin conditions reported sexual problems. Impairment was higher in patients with HS, prurigo, bullous diseases, psoriasis, urticaria, eczema, skin infections or pruritus, and sexual impact was more widely related to depression, anxiety and suicidal ideation [81]. Therefore, HS is strongly associated with sexual problems such as sexual dysfunction in women and erectile dysfunction in men [82].

## Hidradenitis suppurativa and ethnicity

Epidemiological studies related to HS generally originate in developed, Western, predominantly white/Caucasian countries. Demographic information, such as education and occupation, is scarce, and epidemiological data from developing and underdeveloped countries are very limited.

There is racial and ethnic underrepresentation in research and clinical trials. 246 clinical trials were analyzed. 215(87.4%) reported racial data. Hispanics and Latinos were underrepresented, and Black/African Americans were underrepresented even when accounting for prevalence rates [83]. Patients from ethnic-racial minorities with chronic inflammatory skin diseases, more precisely black and Hispanic people, are disproportionately affected by numerous obstacles to care [84]. As previously stated, social determinants have important influences on health and favor health disparities in different ways. Health disparities are understood as differences in the incidence, prevalence, severity and number of diseases experienced by less privileged populations [85].

Considering the influence of race on HS, African Americans face significant disparities in disease severity, emergency room visits, hospitalizations, and surgeries [86]. Mean HS prevalence rates were highest among African-American populations (1.3%), lowest among Hispanic/Latinos (0.07%), and intermediate among Caucasian populations (0.75%) [87].

There is a paucity of data exploring the distribution of race and ethnicity in randomized controlled clinical trials for HS [88]. African Americans had a prevalence up to 3.1 times higher than whites/Caucasians [89].

Evidence demonstrates a higher prevalence of HS in dark-skinned patients, a higher prevalence of comorbidities, greater severity, and greater difficulties in accessing effective medical care [90]. Considering health disparities, a targeted review focusing on race and ethnicity concluded that for black/African Americans, 29 of 38 health disorders revealed a considerable excess in incidence, prevalence or severity. After sickle cell anemia, multiple myeloma and hidradenitis suppurativa showed the highest excesses in frequency [91].

The cytokines TNF- $\alpha$ , IL-22, IL-23, IL-17, IL-27 and IL-10, in subgroup analysis by race, showed higher concentrations in African-American patients [92]. A greater delay in diagnosis is observed in non-white patients. Another fact to be observed among these patients is the fact that medical consultations are more frequent with surgeons than with dermatologists [93]. Black patients with HS may use health services more frequently and have a greater severity of the disease [94].

African Americans are more likely to have clinical visits for HS than whites [95]. Differences were observed in the medical care and procedures provided to black patients when compared to white patients.

Blacks received more Metformin and nonsteroidal anti-inflammatory drugs during HS-associated visits and were more likely to undergo complex surgical excision [96]. A greater number of hospitalizations due to HS was observed in black patients [97]. A retrospective cohort study recorded a total of 3,079,332 hospital admissions of patients with Inflammatory Bowel Disease (IBD), including 4,369 patients with concomitant HS. IBD-HS patients were significantly younger, mostly African American women, more prone to smoking, obesity, diabetes mellitus, depression, and anemia [98]. Obesity and metabolic syndrome are predisposing and/or aggravating factors for HS. They are also a problem commonly faced by African-Americans, which may partly explain the higher prevalence of HS in this racial group.

When talking about race and HS, it is known that there is an extensive gap of ethnic and racial heterogeneity in epidemiological research data, just as it is common knowledge that racism is a reality in our environment and an important determining factor of health. Racism, whether structural, cultural, institutional or individual, affects health through different paths. Systematic review of empirical research on racism and health showed an association between self-reported racism and health problems in oppressed racial groups with negative results in the areas of mental health and health-related behaviors [99].

The analysis of 62 empirical articles, focusing on racial discrimination and health among Asian-Americans, showed that racial discrimination was related to worse health status, more precisely to mental health [100]. In a systematic review involving 121 studies in which African-American, Latino and Asian populations were most frequently included, strongly significant associations were found between racial discrimination and mental health (depression and anxiety) [101]. Perceived discrimination can be translated into significant stress responses and/or unhealthy behaviors or even the absence of participation in healthy behaviors [102].

Internalized racism (in which people internalize racist attitudes, beliefs, stereotypes, ideologies about an ethnic-racial

group or someone) is negatively associated with health through decreases in self-evaluation of the positive core, increases the relationship between stressors and health problems, mediates between discrimination and health, or can be a protective strategy against health problems [103]. Racism proves to be an extremely stressful factor in the lives of the less privileged, bringing with it negative consequences for physical and mental health. Intergroup and intragroup racism play a role in morbidity and mortality rates in African American populations [104]. Stress, by stimulating the hypothalamic-pituitary-adrenal axis, stimulates the production of cortisol and consequently changes in the immune system.

It is known that dysregulation of the immune system is one of the elements involved in the onset and chronicity of hidradenitis suppurativa.

A dearth of research addressing disparities and the role of social determinants of health remains a constant even as data suggests that people of color have a higher risk of developing HS compared to white people.

#### Hidradenitis suppurativa and education

Epidemiological studies that establish a relationship between HS and education are practically non-existent. A population-based study, seeking to determine the incidence of HS and associated factors, observed that 18.3% (44 of 268 patients with HS) had less than 12 years of education, and 28 patients had their education level declared as unknown, possibly due to are not included in the analyzed census data [51]. Another cross-sectional study, involving 26 patients, shows that only 57.5% of them had secondary or higher education, leading to the conclusion that 42.5% had only primary education [42]. A cross-sectional, multicenter study with 62 patients describes that 36 (58.1%) of them had only completed primary and secondary education [45]. While another, when evaluating the clinical and demographic characteristics of HS cases, highlights that 70(33.7%) of the 208 patients listed in the work, had only 0 to 8 years of school studies [48].

When characterizing the heterogeneity of comorbidities among 13,667 HS patients, another study highlights that the highest level of education achieved by 83% (11,338) of these patients was less than a bachelor's degree [105] and more, in a cross-sectional study involving 1,301 individuals, 206 were officially diagnosed with HS, among which, 23 patients with severe HS and 24 patients with mild HS, had only primary and/or secondary education [106].

It is known that the level of education is related to socioeconomic position. This, in turn, is an indicator of physical and mental health in modern societies. Low education can translate into lower positions in socioeconomic hierarchies, and can be related to situations of inferiority, generating physical and mental consequences directly related to health status, in addition to deprivation of material goods [107]. Furthermore, when it comes to HS, the level of education can be observed from two aspects: on the one hand, people with greater knowledge may have an earlier perception of the disease and thus seek medical services earlier, and in a more efficient way it is clearer to adopt care and treatment measures for HS; which may, on the other hand, not occur with people with a lower level of education.

The functional incapacity, taboo, stigma, low self-esteem and

social isolation generated by the disease can be better managed, avoiding greater negative impacts on their academic activities and/or individual work. It should be noted that in a cross-sectional study involving 206 patients with HS, only 17 patients had a master's/doctorate degree, and that, in this context, only 6 of them had progressed to the severe form of the disease, while 11 had mild HS [106] leading to the conclusion that the level of education can directly influence the diagnosis, treatment and control of HS. An early diagnosis interferes with the progression of the disease.

# Hidradenitis suppurativa and work/occupation

Hidradenitis suppurativa is a chronic disease that directly affects the patient's quality of life in all its aspects. Patients with HS often suffer from anxiety disorders, depression, social isolation, sexual dysfunctions and difficulties in performing their work functions. The severity of the disease, the number of decompensations, the locations and the number of skin areas affected are factors that influence the patient's well-being. Stigma, common among HS patients, exerts a strong psychosocial influence. Pain, itching, bad odor, disfiguring scars as well as the public's lack of knowledge about HS contribute to stigmatization [108]. Chronic pain, whether mild or moderate, and quality of life are factors associated with loss of productivity at work [109].

HS is a disease that has a major impact on the patient's professional life. A substantial loss of work capacity and productivity is observed. HS is a debilitating disease that affects individuals of working age [110]. The severity of the disease, depressed mood and intense pain cause a decrease in work capacity and productivity [111]. Presenteeism, reduced overall productivity at work and impaired activity correlate positively with greater disease severity and low quality of life [112]. Newly diagnosed patients with HS had significantly slower income growth and greater risk of leaving work compared to controls, while patients with HS, in general, had more total days lost from work, higher total annual indirect costs, and lower annual income when compared to controls [113]. Hidradenitis suppurativa negatively impacts productivity as well as professional career progression. Other facts already known on the subject are that patients with HS have high rates of unemployment, low annual income, decreased ability to work and losses in work productivity. This compromise in production leads to indirect socioeconomic costs caused by lower employability rates, absenteeism and decreased productivity [111].

In addition to the losses related to the reduction of the workforce, another negative aspect of HS can be observed in the high costs and/or expenses for patients with the disease. The use of healthcare resources associated with the management of patients with HS is high. The average annual cost of HS was €6,791 per patient. Loss of productivity, biological treatment and informal care accounted for 53.3%, 21.5% and 9.2% respectively. There were 26 days of absence from work due to absenteeism and 63 days due to presenteeism. Male gender, more severe HS, gluteal involvement and associated inflammatory bowel disease accounted for higher direct medical costs while lower education and worse quality of life accounted for higher indirect costs [114].

Regarding expenses related to HS, considering limited and non-homogeneous data, the average total cost caused by the disease per patient/year ranged from \$258 to \$8,078. Increase was observed in case of surgical intervention, disease progression,

failure of antibiotic efficacy and comorbidities. Higher costs were noted for hospital care, followed by outpatient care and emergency services [115]. Regarding the use of emergency services and hospitalizations, patients with HS made more use of these resources when compared to patients with Psoriasis [116], and in the HS-IBD association, they were more likely to develop sepsis, greater length of stay and higher total hospital costs [98]. HS is associated with large costs related to hospital care for young patients, of full working age, and high costs of National Health Service resources [117].

#### Hidradenitis suppurativa and smoking

Smoking is one of the main preventable risks to general health. It is a condition, in itself, very important for the development of many health problems with the most varied outcomes and dimensions, and when enhanced by conditions such as obesity and depression, there is a greater risk of illness. Tobacco use can affect all organs and systems in the human body. Tobacco and its constituents affect the skin through external and internal exposure, which can be evidenced by a list of skin and mucous signs resulting from its use as well as the increased incidence and/or exacerbation of numerous skin diseases [118]. Skin aging, contact dermatitis, psoriasis, hair and hair follicle diseases are on this list, and some of them may characterize a dose-dependent pattern. Smoking, even light and intermittent smoking, brings substantial health risks, lower health-related quality of life compared to nonsmokers, and a variable list of signs and symptoms [119].

Tobacco smoking has substantial local and systemic adverse effects on the immune system, respiratory system, skin, and soft tissues [120].

The systemic effect of chronic smoking (>40 cigarettes/day; >5 years) on the cutaneous elastic fiber system can account for wrinkling and loss of skin elasticity, that is, chronic smoking significantly increases the hardening of the dermis and of the epidermis due to the significant remodeling of the elastic fiber network [121]. Several studies associate smoking with Hidradenitis suppurativa. Up to 98% of HS patients are active smokers, and these tend to have higher scores and, consequently, greater severity of the disease [122]. There is a much higher prevalence of smoking, up to 90%, among patients with HS [123]. Current (active) smoking favors a greater number of body areas affected by HS compared to patients with HS who are non-smokers or who have stopped smoking [124].

Smoking may also be related to the risk of injury due to pressure. Active (current) smokers and ex-smokers have approximately 1.5 times greater risk of developing lions resulting from pressure compared to non-smokers [125].

Regarding socioeconomic status, patients with Hidradenitis suppurativa are more likely to have a low social and economic status compared to patients without HS [29]. Regarding educational level, poor health perception and early initiation of smoking in groups with less education were the main predictors of educational differences in smoking maintenance [126].

The prevalence of smoking is higher among less favored groups, and less favored smokers may face greater exposure to the harm caused by cigarettes, that is, among individuals with low socioeconomic status, acceptance of smoking is greater and at-

tempts to quit smoking have increased. greater probability of failure [127]. Regarding social and economic disparities in intentions to quit, attempts to quit smoking and abstinence, it is observed that smokers with lower education or income are less likely to report the intention to quit smoking compared to those with higher education or income [128]. In Brazil, considering socioeconomic inequalities, there is a higher prevalence of current (active) smoking among those with less education, in the non-white population and among those who did not have health insurance, and an unhealthy behavior score was higher in the extracts of lower education, in the non-white population, among those who did not have health insurance, and higher smoking rates among males [129].

Relating socioeconomic level, smoking cessation services and smoking cessation behavior in Brazil, it is highlighted that smokers with a higher socioeconomic level visit a medical service 1.54 times more often than those with a lower socioeconomic level, and had 1.65 more opportunities to receive guidance on quitting smoking [130].

The social and economic characteristics of the areas in which they live seem to influence the behavior of smokers in attempts to quit smoking. It is possible that there is a relationship between the deprivation of the place where one lives and the smoker's status. Some attributes of living in a deprived area can contribute to worse smoking profiles and a lower prevalence of smoking cessation [131].

Smoking is shown to be one of the main contributing factors to socioeconomic disparities in health. The opposite can also be observed. In a succinct analysis, considering the gaps in knowledge, factors involved in the development of HS such as smoking, obesity, depression and socioeconomic status seem interconnected. Cross-sectional study involving 212 patients diagnosed with HS between 1981 and 2001, analyzed after a 22-year segment (range 12-32) demonstrates that smoking and obesity were significantly associated with a lower self-reported remission rate of Hidradenitis suppurativa [132], while advanced age and non-active (current) smoking were important factors associated with a positive response when starting HS treatment with first-line measures such as topical and oral antibiotics, intralesional corticosteroids and antiseptics [133].

The mechanism by which smoking triggers Hidradenitis suppurativa is unclear. It is known that nicotine appears to influence genetic predisposition, favoring the formation of follicular plugs through an inflammatory process mediated by neutrophils [34]. Nicotine stimulates the sweat gland, favoring the engorgement of the glandular ducts [134], modifying their activity as they begin to produce pro-inflammatory cytokines such as Interleukin (IL)-8 and TNF- $\alpha$  [124] and consequent inflammatory reaction. Nicotine also negatively influences by suppressing the notch signaling pathway, and thus, mechanisms such as intercellular communication, regulation and cell differentiation, which allows the emergence of inflammatory diseases such as HS [124]. Smoking interferes with innate and adaptive immunity and plays dual roles in regulating immunity, exacerbating pathogenic immune responses or attenuating defensive immunity, and thereby exerting effects on chronic inflammation and autoimmunity [135].

### Hidradenitis suppurativa and obesity

Obesity has been characterized as a global public health problem in recent decades. It has been showing an increasing prevalence in the last two decades [136], substantially among children and adolescents in both developed and developing countries, even taking into account a slowdown in the increase in obesity in so-called first world countries [137].

This prevalence has increased globally in the last 40 years, from less than 1% to 6-8% among children of both sexes, from 3 to 11% among men, and from 6 to 15% among women considering the time elapsed between 1975 and 2016 [138].

Obesity, also recognized for its association with a wide variety of skin and systemic diseases as well as for its association with psychiatric illnesses such as anxiety and depression [139], constitutes a broad threat to national or global public health considering the incidence, prevalence and economic burden it entails [140]. Excessive healthcare spending, loss of productivity, loss of economic growth resulting from reduced number of days worked, lower productivity, higher mortality and permanent disability must be considered [140]. Approximately 60-70% of individuals who suffer from obesity can exhibit a variety of skin changes. Such changes have been related to mechanical friction, infections and hypertrophic conditions of the skin [141] and it should be noted that obesity is a disease and a risk factor for the occurrence of several other diseases, whether as a causal factor or as an aggravating factor [142]. Changes in skin barrier function, sebaceous glands and sebum production, sweat glands, lymphatic system, collagen structure and function, wound healing, as well as changes in microcirculation and macrocirculation and subcutaneous fat can be observed in obesity [139].

As a result of an increase in adipokines, chemokines and cytokines, obesity is characterized by metabolic changes with subsequent accumulation of adipose tissue and an inflammatory state, thus affecting skin homeostasis and activating immune cells and consequently favoring chronic inflammatory diseases [143]. Genetic and environmental factors are widely implicated in the origin of obesity. The types of food ingested, the socioeconomic level added to behavioral factors such as sedentary lifestyle are important environmental factors, while leptin, a hormone produced by adipocytes, and Pro-Opiomelanocortin (POMC) are the genetic factors most involved in obesity [139]. Leptin's function is to carry information about the body's fat reserves to the neurons of the hypothalamic arcuate nucleus. These, in turn, stimulate the POMC gene, which responds with the production of the prohormone pro-opiomelanocortin, involved in energy homeostasis. It is known that changes in the POMC gene, generally caused by Single Nucleotide Polymorphisms (SNPs), cause changes in the signaling pathway and thus, causing a negative impact on the regulation of energy expenditure and food intake, that is, favoring energy consumption excess, hypertrophy and inflammation of adipose tissue.

Obesity favors an increase in the intertriginous surface area of the skin, skin-to-skin friction, increased sweat production and retention and consequently skin maceration, as well as hormonal changes expressed by the relative excess of androgens [144]. Excess androgens contribute to thickening of the hair shaft and consequently to follicular obstruction. Thus, obesity acts on the

genesis and chronicity of HS either through mechanical factors such as friction and/or through hormonal influences as observed in Polycystic Ovary Syndrome and Insulin Resistance [34].

In the association between obesity and socioeconomic status, it is stated that socioeconomic status is a determining factor in the prevalence of obesity. In developed societies, socioeconomic level is largely related to the prevalence of obesity: the lower the social class, the greater the obesity, while in developing societies, the higher the socioeconomic level, the greater the obesity [145]. Both obesity and socioeconomic status are negatively associated in high-income countries, and positively associated in middle- and low-income countries. Factors such as the introduction of solid foods and family behaviors may explain the link between socioeconomic status and obesity. Parental education and early pediatric nutrition appear to explain the relationship between socioeconomic status and obesity [146].

The highest rates of obesity occur among population groups with higher rates of poverty and lower education.

The link between poverty and obesity may be a consequence of the low cost of high-calorie foods and the high palatability of foods rich in sugar or fat [147]. Educational level, higher financial earnings and consumption of certain food groups can reduce the risk of obesity [148]. A high level of education can promote knowledge about the benefits of physical activity and the consumption of balanced meals and their impact on the quality of health. A higher income favors greater access to resources for better health, such as purchasing healthier foods, more time for leisure and sports, as well as greater access to health services [148]. Lower education level and income, lower property values in the region of residence, and shopping at low-cost stores were consistently associated with a higher risk of obesity, while higher socioeconomic status, living in wealthier neighborhoods, shopping in Higher-cost stores have been linked to a protective effect on obesity risk [149].

Other elements, within the spectrum of socioeconomic level, that influence obesity are sex and age. Increasing age increases the risk of obesity.

Weight gain is expected in men and women until the age group of 50-60 years. But after the age of 50, women have a higher prevalence of obesity when compared to men [148].

The epidemiological relationships between SH and obesity are evident. Cross-sectional study included 396 participants (339 women and 57 men), of whom 241(60.9%) were overweight or obese, and 227(57.3%) were active smokers. The majority of patients had Hurley stages II (263, 66.4%) and III (76, 20.3%) HS, and the increase in HS stage was related to obesity and some disease locations such as genitals, pubis, gluteal fold and inguinal regions [150]. Retrospective cohort included 102 patients (38 women and 64 men). 68.4% had BMI≥25; 76.5% were active smokers; and Hurley stages II and III were found in 53.1 and 33.3% of patients respectively [151]. And a retrospective review of medical records including 149 patients (113 women and 36 men) showed that 80.9% of them were overweight or obese, 39.5% were active smokers or ex-smokers and Hurley stages II and III were diagnosed in 36.5 and 33.9% of cases [152].

### Hidradenitis suppurativa and chronic inflammatory diseases

HS is defined as a chronic inflammatory disease, often associated with other inflammatory diseases or factors that cause and/or chronify inflammation. Smoking is an important triggering factor for HS [153]. Cigarette smoke, with its most varied chemical substances, activates pro-inflammatory cytokines found in tissues damaged by HS, activates nicotinic Acetylcholine (nAChRs) and Aryl Hydrocarbon (AHRS) receptors and suppresses the Notch signaling pathway [124].

An increase in TNF- $\alpha$ , IL-1, IL-6, IL-8, GM-CSF is observed; a reduction in the levels of anti-inflammatory cytokines such as IL-10; an increase in IgE levels; an activation of the activity of macrophages and dendritic cells; and an increase in the production of antibodies such as citrulated proteins observed in Rheumatoid Arthritis, and increased anti-dsDNA titers in Systemic Lupus Erythematosus [154]. Smoking tobacco causes systemic immunomodulatory effects as it releases reactive oxygen species from the smoke responsible for a chain of harmful effects on normal inflammatory function, reducing phagocytosis and bactericidal activities, and increasing the release of proteolytic enzymes, thus interfering with the process of renewal of connective tissue and promoting its degradation [123].

Exposure to air pollutants is associated with damage to various organs of the body and a variety of skin diseases. The inflammatory state is a common feature in many skin diseases [155]. A cytosolic multiprotein complex, the inflammasome, promotes the maturation of pro-inflammatory cytokines IL-B and IL-18, reinforcing pollution-induced skin damage, and damaging the skin barrier appears to facilitate an increase in the production of reactive oxygen species, promoting oxidative stress and activate the Aryl Hydrocarbon Receptor (AhR) and inflammatory cytokines [156].

An increasing number of comorbidities are observed in patients with Hidradenitis suppurativa. Rheumatoid Arthritis (RA), collagen vascular diseases, Psoriasis, Pyoderma gangrenosum and Crohn's Disease (CD) are some of the inflammatory conditions listed [157]. The association between HS and Crohn's disease is well known. In a cross-sectional analysis of 51,340 patients with HS, the prevalence of Crohn's disease was 2.0% (1025/51,340) compared with 0.6% (113,360/18,404,260) among those without HS. (P<001). The prevalence was higher among white patients (2.3%), aged between 45 and 64 years (2.4%), non-obese (2.8%) and smokers (2.3%) [158]. An increased prevalence and risk of Crohn's disease and ulcerative colitis was observed in patients with Hidradenitis suppurativa, possibly due to the sharing of a common immunopathogenesis in CD and HS [159]. Patients with a history of inflammatory bowel diseases have a nine times greater risk of developing HS than the general population [160].

Evidence suggests that common inflammatory pathways, such as IL-1 and TNF- $\alpha$ , may be dysregulated in both HS and Spondylitis. The prevalence of inflammatory arthritis appears to be increased in patients with HS, especially in severe cases [161].

Psoriasis as a comorbidity of HS has been discussed, but the association between the two diseases is not yet entirely clear. Psoriasis and HS appear to result from the existence of a common inflammatory pathway manifested by increased expression of IL-12/23 and TNF- $\alpha$  [162]. Positively regulated cytokines such

as TNF- $\alpha$ , Interferon- $\gamma$ , IL-1 $\alpha$ /B, IL-6, IL-8 and IL-17 can cause an inflammatory process in both diseases, and HS-Psoriasis coexistence can favor a greater prevalence of concomitant psychiatric and cardiovascular diseases [163,164] and greatly increase the severity of the disease, requiring more aggressive treatment [165]. Analysis of health insurance data from about 7 million individuals concluded that the prevalence and incidence of HS were 68/100,000 and 10.1/100,000 respectively, and about 6% of patients with HS had Psoriasis as a concomitant disease [164]. A study involving 68,836 patients with psoriasis and 68,836 control cases showed that the prevalence of HS was higher in patients with psoriasis compared to controls. Patients with concomitant psoriasis and HS were, for the most part, younger, with a higher prevalence of obesity and smoking when compared to patients with psoriasis alone [166].

The association between HS and Arthritis is rare and most frequently affects peripheral joints [167]. Despite the low risk of the association, when compared to patients without HS, patients with HS have an increased risk of developing rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis [168].

The epidemiological association between HS and Rheumatoid Arthritis does not seem to be firmly established despite the observation of the existence of common points in the interaction of T and B cells and in the activation of pro-inflammatory cytokines in both diseases, such as TNF- $\alpha$ , IL-6 and IL-1 [169]. Although the exact underlying mechanisms of this association remain unclear, patients with Hidradenitis suppurativa have a three-fold increased risk of developing inflammatory arthritis, whether ankylosing spondylitis or rheumatoid arthritis [170].

# Hidradenitis suppurativa and mental health (Psychiatric Diseases)

Socioeconomic level (SES) or social class is an important factor in determining psychological outcomes [171]. Having a low socioeconomic status in childhood appears to contribute to the development of depression in adulthood. Low SES in childhood may influence depressive symptom burden in midlife through a combination of economic stress, restricted social resources, and physical symptoms seen in adulthood [172]. The consequences of financial difficulties accumulated over time constitute risk factors for physical and mental health evident in youth and continuing into adulthood and senility through chronic diseases such as depression, obesity and diabetes mellitus [173].

In developed countries, the prevalence and impact of depressive disorders are associated with certain characteristics, including socioeconomic level. Adopting health measures is effective in reducing depressive disorders in low-SES populations in the short and long term [174].

But when compared to higher SES, low SES was associated with less promising outcomes in depression treatments. Cognitive Behavioral Therapy, interpersonal psychotherapy and pharmacotherapy demonstrated lower rates of improvement in patients with low SES compared to patients of medium SES treated under the same conditions [175].

Low socioeconomic status and negative complications are risk factors for prenatal anxiety and depression, preterm birth and birth weight. Low SES increases the adverse impact of previ-

ous negative events on anxiety and depressive symptoms during pregnancy, and measures against anxiety and depression during pregnancy should be targeted with greater particularity towards unemployed pregnant women, with less education and low income [176].

Lower education and lower family income have an important impact on psychiatric status, favoring a worsening in sleep quality. The mental health of individuals with low socioeconomic status is important in maintaining physical health. Low socioeconomic status implies more vulnerable mental health and, consequently, more harmful effects on sleep quality. Less education can be translated into fewer economic and social resources, favoring stressful life experiences and culminating in anxiety and depression. Insomnia is perceived as a comorbidity of depression, and individuals who suffer from insomnia have elevated levels of psychiatric distress or somatic anxiety [177].

Low socioeconomic status and mental illness (depression and anxiety) have a bidirectional cause and effect relationship. Psychiatric illnesses can reduce employment and consequently income, while psychological interventions can generate economic gains. Negative economic patterns favor mental illness, but combating poverty improves mental health [178].

Parents' education and family income are important factors in children's lives. Children from highly educated and high-income families are exposed to a lower level of childhood trauma [179], while children from lower-SES families may meet more criteria for mental disorder when compared to children from high-SES families [180]. Adverse childhood experiences may be associated with lower education, and greater risks of depression, smoking and drug use [181].

SES can determine people's behavior and lifestyle. Individuals of low socioeconomic status are more likely to choose health risk behaviors or ignore health prevention behaviors [182]. Social conditions subsequent to low education seem to increase the risk of prevalence of disorders among non-Latino whites and of persistent mood and substance use disorders among ethnic-racial minorities [183].

And morbidity resulting from chronic diseases and early mortality are more evident in individuals of low SES when compared to people of higher SES [184].

The effect of SES and/or social inequalities on public health is evident, whether physical or mental health. SES is associated with a significant impact of diseases in the general population [185].

Defined as education level, income level or even neighborhood level, SES may reflect the incapacity for work commonly observed in chronic diseases such as Hidradenitis suppurativa. Inability to work, however, can translate into limited income and resources, and therefore into deprivation, regardless of the level of education.

HS is a polysymptomatic inflammatory condition with a negative effect on the physical, social and emotional well-being of patients [186]. The recurrent and debilitating aspect of the disease negatively influences their physical and psychological aspects as well as their quality of life. The involvement of anogenital regions seems to be more related to compromised quality of life, while

the involvement of exposed areas of the skin by HS seems to be more related to stigmatization [187]. The bad smell causes significant damage to the quality of life in patients with HS [188]. Fear of stigmatization favors social isolation. The bad smell, scars, itching and pain encourage shame and irritability [189].

HS is always referred to as chronic painful follicular disease. Chronic pain, of varying intensity, is the most bothersome symptom of HS. Pain, whether chronic or acute, possibly the most impactful symptom of the disease, is associated with physical limitations such as reduced mobility and sleep, and psychological changes such as irritability, depression, loss of control and the ability to communicate painful experiences, as well as such as changes in social relationships such as social isolation, intimacy problems and compromising social responsibilities [190]. Pain, itching, bad odor, stigmatization, and sleep disorders have an important effect on the quality of life and mental health status of people with HS [191]. Physical pain and feelings of shame are strongly associated with psychological distress in HS and a feeling of powerlessness over one's own body [192]. Cross-sectional study involving 1,795 patients, in which pain was assessed using a numerical scale, 83.6% of patients reported the presence of pain. 77.6% of patients reported mild pain. Women and smokers reported more intense pain, and pain intensity was greater in those patients with multiple areas of skin affected by HS [193]. The vicious circle characteristic of HS is identified as the factor responsible for pain, purulence, tissue destruction and scars [194]. Pain in HS is a mixture of acute pain (nociceptive) and chronic pain (neuropathic) possibly resulting from inflammation of the affected tissues (injured areas) and damage caused directly to the nerves, and the perception of pain can be associated with depression, anxiety and disease severity [195].

HS, like other inflammatory dermatoses, is associated with mental comorbidities, mainly Depression and Anxiety. Metaanalysis involving 28 studies related to Depression and HS, and 12 studies related to Anxiety, showed a prevalence of 21% (95% CI [17-25] in relation to Depression, and 12% (95% CI [6-17] in relation to Anxiety in patients with HS with wide variations in both cases, demonstrating that patients with HS have a high impact of Depression and Anxiety [196]. In a prospective study with 51 patients with HS, 29.4% presented mental symptoms, mainly symptoms of depressive disorder. HS patients were predominantly young, female, with a history of high incidence of nicotine and alcohol use, a positive family history of paternal alcohol dependence, and with more serious psychosocial impairments such as less education [197]. In a cross-sectional study involving 1,795 patients, pain was reported in 83.6% of cases. 77.6% of cases reported mild pain; women and smokers reported more intense pain; pain was more severe in patients with multiple affected areas, and worse in those patients with the most severe form of the disease [198]. Chronic pain is associated with a significantly higher prevalence of Depression (20.2%) when compared to the general population (9.3%) [199].

Psychiatric disorders are more observed in patients with immune-mediated chronic inflammatory diseases when compared to the general population [200]. Systematic review and meta-analysis including 40,307 patients with HS, showed an overall prevalence of Depression of 16.9% (95% CI: 9.9%-27.2%), and a prevalence of Anxiety of 4.9% (95% CI: 1.7%-13.2%) [201]. It is

estimated that one in four adults with HS has depression, and one in five has anxiety [202]. A higher proportion of bipolar disorders was found in patients with HS, and a tenfold increase in the prevalence of Schizophrenia [203].

In a cross-sectional study with 114 patients with HS, symptoms suggestive of Depression were found in 47 of them (41.2%), with no significant difference in the incidence of Depression in female and male distribution, and without correlation between the incidence and severity of Depression and Anxiety about the severity of the disease [204]. Cross-sectional analysis of 38,140 adult patients and 1,162 pediatric patients with HS, showed a prevalence of depression among adults with HS equivalent to 30.0% (95% CI [29.6-30.5] compared to 16.9% (CI: 95, 16.7-17.1) among the controls. Among children and adolescents with HS, the prevalence of depression was equivalent to 11.7% (95% CI: 10.0-13.7) compared with 4.1% (95% CI: 3.6-4.7) among controls [205].

Mental illnesses or comorbidities negatively affect clinical illnesses while stimulating other psychiatric illnesses, consequently worsening patients' quality of life. The interactions between the body and mind are relevant. Many skin diseases have a psychosomatic aspect. Evidence suggests the existence of biological mechanisms underlying a bidirectional link between mood disorders and many clinical illnesses [206]. The nervous system and the skin derive from the ectoderm and remain intertwined throughout life. Neural receptors in the skin may constitute the largest sense organ in the body [207]. Tissues of the same embryonic origin, once stimulated, react in a similar way. Skin and brain are in permanent interaction through psychoneuroimmunoendocrine mechanisms and behaviors [207]. Skin deficiencies and disorders are often an early sign of a psychiatric disorder [208].

Psychiatric and dermatological disorders therefore have a complex relationship. Psychosomatic disorders summarize dermatological diseases stimulated or aggravated by emotional stress, while secondary psychiatric disorders can be a consequence of certain disfiguring skin diseases with subsequent psychological suffering. Primary psychiatric disorders induce the appearance of certain skin changes such as trichotillomania, factitious dermatitis, neurotic excoriations, parasitic disorders and dysmorphophobia. In this interrelationship, psychological factors such as stress and negative emotions can influence the emergence and worsening of skin disorders, and on the other hand, psychological disorders can be the result of some skin diseases [209]. Skin, mental health and the central nervous system are interconnected. Individuals with HS often suffer from Depression and anxiety. Other associated psychiatric disorders include substance abuse, psychotic and bipolar disorders, and suicide risk [191].

# Hidradenitis suppurativa and oral and systemic health

Oral manifestations are found with high frequency in cases of concomitant autoimmune, autoinflammatory, systemic chronic diseases. General dysregulation of IL-17 may thus contribute to host changes that lead to oral microbial dysbiosis. Interestingly, a key role for the IL-17 pathway in the pathogenesis of HS has recently emerged, strengthening the possible relationship between HS and oral lesions. Furthermore, HS shares etiopathogenetic similarities with oral lesions, as genetic susceptibility, environmental factors, and immunopathological mechanisms can lead to a dysregulation of the inflammatory response [38].

Common immune-mediated oral diseases include rheumatic disorders, ulcerated and erythematous lesions such as recurrent aphthous stomatitis, erythema multiform and drug-related ulcerations, lichenoid lesions, vesiculobullous lesions, benign migratory glossitis, desquamative gingivitis, and orofacial granulomatosis. Most of these lesions, as well as HS, which is characteristically relapsing, persist and recur frequently, and may be the first clinical signs or symptoms of the general disease [38].

Dental prophylaxis and dental consultations are extremely important to maintain quality of life and good digestion, two parameters that are particularly important in patients with chronic diseases. Dental-dermatological cooperation must be improved to create ad hoc in-hospital integrated care pathways for HS patients, especially those who are biologic candidates who have to undergo a mandatory oral health assessment. Dental prophylaxis should be promoted every 3 months in patients with HS and further studies are needed to understand the impact of HS therapies on oral comorbidities (i.e., epigenetics [31-33] and resistome) [38].

As results a total of 102 patients (44.0±0.9 years, body mass index 27.0±2.2 kg/m²) were enrolled. Remarkably, 48% and 43% did not undergo at least an oral hygiene or a dental visit each year, respectively. Oral disorders were found in 55.9% of patients with HS, in particular 39.2% had caries and 46.7% reported at least one missing tooth. The main oral manifestations in patients with HS were recurrent aphthous stomatitis (N=19, 19.2%), amalgam tattoo (N=14, 14.1%), leukoplakia (N=11, 11.1%), nicotinic stomatitis (N=9, 9.1%), papilloma (N=8, 8.1%), and geographic tongue (N=8, 8.1%). Whilst the main predictor of oral pathological conditions was Hurley staging (P=0.0276), multivariate regression analysis indicated that gender and International Hidradenitis Suppurativa Severity Score System (IHS4) were the main predictors for the presence of caries and number of missing teeth [38].

Today we already have strong enough scientific evidence to affirm that risk factors such as smoking and neuropsychic disorders affect oral and systemic health levels in different clinical scenarios certified for psoriasis. Using the principles of specificity and sensitivity, we can state that there are great possibilities for HS to also be subject to such complications, after all this is also an inflammatory dermatosis.

# Hidradenitis suppurativa and the repercussions on women's health

HS is particularly prevalent in women of childbearing age and can have diverse psychological and physical consequences. Paradoxically, studies point to cases of HS that showed significant improvements during pregnancy, presumably related to gestational hormones, and that around 90 days after birth, the conditions worsen again [210]. The chronic and debilitating nature of this disease can lead to significant impairments in patients' sexual health and overall quality of life. There are qualitative systematic reviews that have examined gender differences in the impact of HS on sexual health. Additionally, we review gaps in the sexual health management of patients with HS and outline recommendations to appropriately address sexual concerns and optimize care [82].

Sexual distress is defined as negative emotions about sex, such as regret, frustration, guilt, and unhappiness [188,162,81]. On the

other hand, sexual dysfunction refers to deficiencies in the physical aspects of sexual activity, such as lubrication, penetration, maintenance, orgasm, and resolution. Impaired sexual health includes sexual distress and sexual dysfunction.

Patients with HS often report impairments in sexual health resulting from the psychological and physical consequences of having this disease [189]. Contributing psychological deficiencies include depression, embarrassment, fear of contagion, and shame. Physical disabilities include pain, drainage, itching, scarring, and bad odor [189].

Studies on other chronic dermatological diseases, such as psoriasis, have found that compromised sexual health is particularly prominent in women [211]. Few studies have specifically investigated how women's and men's sexual health may be affected differently by HS.

This review examines the existing literature on gender differences in sexual health in patients with HS, identifies gaps in practice, and provides strategies to improve sexual health care.

HS is a highly burdensome chronic disease that is significantly associated with deficiencies in sexual health in several validated instruments in male and female patients. The sexual health burden caused by HS appears to be greater for women. Additional studies are needed to further elucidate the differential impact of HE on sexual disability by gender. This may also shed light on specific interventions that may be beneficial for women or men. Impairments in quality of life due to sexual health can be mitigated with proactive medical questioning and counseling about sexual health in all patients with HS, regardless of the presence of genital lesions. Sexual health should be addressed when evaluating the severity of HS and treatment outcome. Increasing awareness about sexual disability in HS is essential to optimize care.

# Hidradenitis suppurativa and Severity, treatment and quality of life

According to the World Health Organization, quality of life refers to "an individual's perception of their position in the world, in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". Seeking a better quality of life implies seeking improvements, whether in physical, mental, and emotional well-being, in health, education, purchasing power or in personal relationships with friends or family.

The impact of Hidradenitis suppurativa on the quality of life of patients, spouses, family members and/or caregivers is widely discussed. Many aspects of the disease contribute to this reduction. Several instruments are being created to measure these aspects, some better evaluated, others less so. The Dermatology Life Quality Index (DLQI) is the most used and specific instrument in Dermatology.

Other instruments include: HIDRAdisk, HSIA, HiSQoL, HSQoL-24, Skindex, Euroqol 5-Dimensional Questionnaire (EQ-5D) and Short Form 36 Questionnaire (SF-36), Hospital Anxiety and Depression Scale (HADS), Hospital Depression Inventory Bek (BDI), Major Depression Inventory (MDI), Female Sexual Function Index (FSFI-6), 5-Item International Index of Erectile Function (IIEF-5), Visual Analogue Scale (VAS) and Numerical Scale (NRS).

The latter assess the severity of symptoms [212]. The Harley classification, the HS-PGA and the Modified Sartorius Scale (MSS) are widely used to assess disease severity [213].

HS is observed as one of the worst dermatoses as it causes immense impairment of patients' quality of life. It is characterized by debilitating pain, purulent secretion, unpleasant odor and itching, factors associated with disastrous social and economic consequences, higher rates of depression, stigmatization and suicide [214] as previously discussed. The severity of the disease, the number of exacerbations and the location of the lesions are identified as the main factors responsible for the worsening of quality of life. The greater the intensity of the signal or symptom, the worse the general quality of life or specific dimensions of quality of life, whether sexual suffering, anxiety, depression or sleep [212]. Female sex, less education and genital involvement are also factors associated with worse health-related quality of life [215]. The mean Family Dermatology Life Quality Index Questionnaire (FDLQI) for partners of 50 patients with HS was 8.7±6.8, indicating a moderate impact of HS on their lives. The partners' quality of life was significantly correlated with the severity of the disease [216]. Both patients and cohabitants experience significant impairment in quality of life. DLQI scores were associated with the presence of negative affectivity, typical type D personality traits and cohabitants' anxiety, while FDLQI scores were associated with patient depression and cohabitant anxiety [217]. Patients with more severe HS tend to have a worse quality of life. The time dedicated to care and the emotional suffering generated are two factors responsible for reducing the caregiver's quality of life [218]. Women are related to a high prevalence of sexual dysfunction, and men, to a high prevalence of erectile dysfunction, as are male partners [219].

Numerous treatment measures show a positive response in the health-related quality of life of patients. Most of the assessment instruments developed so far aim to measure the response to treatment.

As HS is a heterogeneous and multifactorial disease, it is important to establish different interventions that seek to improve patients' quality of life while at the same time being able to be properly measured. Several clinical and surgical treatments have been proposed in this regard.

Biological and immunomodulatory products have shown important reductions in DLQI scores. The anti-Interleukin (IL)-17 monoclonal antibody, Secukinumab, at a dose of 300 mg, subcutaneously, once a week for five weeks, and then every four weeks for 24 weeks, favored a reduction in the DLQI score of 13 to 7 [211]. Ustekinumab, in an intravenous infusion adjusted for weight, followed by a subcutaneous maintenance dose of 90 mg every eight weeks, over a period of sixteen weeks, enabled an improvement in DLQI in 71.42% of the 14 patients [220]. Moderate to marked improvement in the modified Sartorius score was achieved at week 40 in 82% of the 12 patients who completed the protocol with Ustekinumab 45 or 90 mg at weeks 0, 4, 16 and 28 [221]. With adalimumab, a TNF- $\alpha$  inactivator, 77% (n=78/101) of patients reported improvement in PGA-HS scores and significant improvements in DLQI scores [222]. The count of the number of lesions, the International Hidradenitis Suppurativa Severity Score System (IHS4), the Visual Analogue Scale (VAS) of pain decreased throughout the study, and the DLQI was reduced from 11.9 at week 0 to 6.6 at week 0. week 96 [223]. A multicenter cohort study involving 389 patients with HS treated with Adalimumab also showed an improvement in quality of life. HiSCR was achieved in 43.7% and 53.9% of patients at weeks 16 and 52 respectively, and significant reductions in DLQI and Visual Analogue Scale pain were observed between weeks 0 and weeks 16 and 52 [224].

Greater efficacy was observed in cases of HS treated with an increase in the dose of Adalimumab from 40 mg to 80 mg, subcutaneously, once a week [2]. The use of Adalimumab 160 mg, subcutaneously, at the beginning of the study, 80 mg in week 2, 40 mg in week 4 and 40 mg in subsequent weeks provided a reduction in the modified Sartorius score of 74.93, before the start of treatment, to 39.86 at week 10 (P<0.0001) as well as the Hidradisk mean value from 77.3 at the beginning of treatment to 51.86 at week 10 (P<0.0001) [225]. Hidradisk also showed significant improvements, but more evident in men (69.8±6.2-49.6±10.8) than in women (80.7±6.0-72.3-6.7) with P<0.001 [226].

Apremilast, 30 mg twice daily demonstrated efficacy, but showed no significant difference in DLQI between the treatment and placebo groups at week 16 [227]. In contrast, Apremilast was effective in improving pain and quality of life in patients with mild to moderate HS. Significant improvement was observed in DLQI scores (11.6 to 5.4, P<0.01) after 24 weeks of treatment [228].

Antibiotics remain the first line of treatment for HS. A comparative, retrospective study evaluated 52 patients with mild, moderate and severe HS divided into two groups. Group A (26) patients received 300 mg of Limecycline per day and group B (26 patients) received the Clindamycin/Rifampicin combination, 600 mg, twice a day, for ten weeks. Both groups showed significant improvement in IHS4, pain Visual Analogue Scale (VAS) and DLQI compared to baseline, although the improvement was more evident in group A [229]. In the comparison of Clindamycin versus the Clindamycin/Rifampicin association, 60 patients with mild, moderate and severe HS were divided into two groups. Group A (Clindamycin/Rifampicin) and group B (Clindamycin), evaluated after 8 weeks of treatment. The two groups showed similar improvements in the IHs4 score, while the DLQI and Visual Analogue Scale pain scores showed a more significant improvement in group B [230].

In the treatment of HS, the combination of Intense Pulsed Light (IPL) and Radio Frequency (RF), after 12 weeks, showed a greater reduction in the number of lesions when compared to the groups treated with LIP or RF alone. The improvement in DLQI was significantly greater in the group treated with the combination of intense pulsed light and radiofrequency [231].

Botulinum Toxin type B, when compared to the placebo group, provided an improvement in the DLQI from 17, at the beginning of treatment to 8, in 3 months (P<0.05), possibly due to the reduction in the total number of lesions, thus improving, the quality of life of patients with HS [232].

Treatments with intralesional corticosteroids, two intralesional injections of Triamcinolone and Leucomycin guided by Ultrasound, at the beginning and after 2 weeks, provided a significant improvement from 36.2 at the beginning of the study to 53.9, on the SF-36 scale (Bodily Pain Scale). Short-Form Health Survey) in

the fourth week after intralesional therapy [233].

Regarding surgical treatment, in a study with one hundred and forty-nine patients treated with surgical intervention, Sartorius scores showed a significant improvement in relation to baseline values (P<0.001). 83 patients achieved a DLQI MCID and 75 patients achieved an NRS for MCID; while in the 19 patients who underwent combined clinical and surgical treatment, 9 achieved significant improvement in pain scores, DLQI and NRS, MCIDs and Sartorius [234].

Comparative study between the use of artificial dermis and pedicled perforator flaps after radical surgery, evaluating quality of life using the SF-36 Scale, showed a significant increase in quality of life both in the use of artificial dermis and in the use of perforator flap, but the effect was considered greater when using the perforator flap (P<0.001).

DLQI showed a reduction in the impact of HS on patients' quality of life in both groups, but once again the reduction in the impact of HS was greater in the perforator flap group [235]. Wide local excisions followed by reconstructions with pedicled perforator flaps, which 26 patients with HS Hurley III underwent, enabled a reduction in DLQI from 21.31±4.79 before the first surgery to 5±2.95 after the last segment (P<0.0001) [236].

Considering surgical results and the impact of major surgery on the quality of life, impairment of activity and sexual health of patients with HS, questionnaires answered by 39 patients with 171 survey responses concluded that patients with HS Hurley I and II had lower wound closure time when compared with HS Hurley III (P=0.005). DLQI and ASEX scores did not show significant improvement during the six months of study, but activity and general work impairment improved considerably after surgical treatment [237].

The use of the HS Burden of Disease (HSBOD) score showed that even with surgical intervention in HS, patients' quality of life continues to suffer impacts in the five domains evaluated, that is, symptoms and feelings, daily activities, leisure, work and school, and personal relationships [238]. However, surgical treatment has revealed great potential in improving the quality of life of patients with the severe form of HS. In a systematic review, 33 articles were selected, including 286 patients and 387 flaps. 15.1% of flaps presented at least one complication, but pedicled perforator flaps proved to be reliable and reproducible in the reconstruction of defects caused by HS, as they were associated with effective reconstruction, with lower morbidity and faster recovery [239]. Surgical treatment effectively improves the quality of life related to post-surgical health [240,241].

# Final considerations: Practical and research implications

Analyzing the influence of social factors on health, the importance of time, place and people's way of life is observed. Education, work, income and racial contextualization, shaping behaviors and lifestyles, stand out as important factors determining health. It is known that poverty and health have always been related, and currently social and economic influences on health constitute an important point of discussion.

Countless information has been accumulated; Knowledge gaps have been highlighted and research priorities have been highlighted. Health in general goes far beyond medical care, and re-

sults from the interaction, complex or not, of multiple factors. It is important to remember how the conditions in which they live, reside or work can, directly or indirectly, influence people's health status, and how behaviors and choices, individual or collective, political or not, can have a direct impact on health.

Education, work and income are important social factors. It is known that the greater the social disadvantage, the greater the precarious health. A higher educational level can translate into a better occupation, a more profitable profession, greater employment opportunities, higher income, higher economic resources (wealth) and consequently better health conditions, that is, better housing and neighborhood conditions, better nutritional conditions and lower levels of stress factors. Living or not living in areas with better infrastructure conditions or more favorable conditions (schools, transport, piped/treated water, adequate medical care, job offers) provide better health conditions, create and signal socioeconomic and ethnic-racial disparities.

Social relationships based on the exchange of trust favor security, lower rates of violence and social infractions and consequently, lower rates of chronic diseases such as anxiety and depression, which provides improvements in health indicators in general, even considering the particularities of each individual.

Work, in its physical and psychosocial aspects, has a great influence on health status. Work-related illnesses can result from several factors: repetitive movements, inadequate posture or conditions, psychological pressure or high-stress situations, excessive and excessive lifting of weight or strenuous work, sedentary lifestyle or physically inactive functions, pressure for results or goals unattainable, harassment in the workplace, high-stress situations; On the other hand, opportunities and resources arising from work, such as lectures and training that reinforce the need and correct use of Personal Protective Equipment (PPE), worker training, periodic exams, paid leave or vacation, flexible schedules or shifts, programs that provide well-being in the workplace, such as workplace gymnastics, health plans and retirement benefits, are extremely beneficial for health as a whole. A well-conducted and/or paid job can translate into better benefits, greater financial security and, consequently, better living conditions, while lower remuneration or lower salaries can translate into fewer healthrelated benefits or unfavorable living conditions.

It is known that educational level creates employment opportunities. Higher education can translate into higher employment rates, employment with better physical and psychosocial working conditions, better remuneration and greater benefits, greater perceived personal control and, consequently, better health conditions and health-related behaviors. Unemployment, in turn, can translate into worse health conditions and higher morbidity and mortality rates. Greater education can translate into greater social support and, consequently, better physical and mental health conditions. Knowledge about health, behaviors and adoption of healthy habits in the daily routine provided by higher educational levels enable more adequate management of medical care and health promotion policies. Hidradenitis suppurativa, even though it is not considered an occupational disease, can be aggravated by the exercise of some professions. Just remember how much absenteeism, presenteeism at work or lack of opportunities at work can harm people with HS.

In addition to educational level, greater economic resources provide easier access to goods and services, which can translate into better health conditions.

Race and ethnicity are other factors that can positively or negatively influence health. Racism and/or social structures associated with it can often limit resources or opportunities for people or institutions. Blacks, Latinos, or people with less education are more likely to live in less favored areas, where the lack of infrastructure or better resources contributes to more unfavorable health outcomes. Fact to remember is how a person's race or ethnicity can determine their place in different social classes.

Chronic HS disease negatively influences the patient's physical, social and psychological functions, often severely affecting their quality of life in all its aspects. HS, depending on the classification, involves greater financial expenses, feelings of shame and anguish, social isolation, loneliness, low self-esteem, anxiety and depression. The HS-BNSE relationships are evident even if the causal link is not entirely clear. The two main determining or aggravating factors of HS, smoking and obesity, have a broad relationship with BNSE, as previously demonstrated. Limited social and financial resources are directly related to HS. Such limitations may be the result of the difficulty the patient had in achieving a better level of education or employment or may be the result of loss of ability to work or loss of employment due to the negative effects of the disease.

HS can favor the loss of independence. The chronicity of the disease or the lack of hope for a cure generates hopelessness, and the feeling of dependence can generate dissatisfaction with life, anxiety, depression, mood disorders, and even attempts against one's own life.

In addition to smoking and obesity, anxiety and depression, frequently observed in HS patients, may also have their origins or chronicity favored by BNSE, and lower socioeconomic position implies a greater possibility of experiences with negative emotions. The BNSE can also affect the implementation of strategies to combat the disease, whether due to the consequences of low education and/or the lack of financial resources that provide adequate medical assistance, purchase of medicines and even the assimilation and practice of prophylactic measures related to the disease illness.

Furthermore, BNSE is generally associated with a maladaptive coping style, that is, linked to feelings of denial, social isolation and self-blame, which in turn favor more unfavorable health outcomes. In this context, it is important to remember the importance of strengthening resilience through which patients with HS can adopt a more adaptive coping style, that is, a lifestyle where even in the face of BNSE, the search for social support, help, acceptance and positive evaluation provide a better quality of life.

In conclusion, we sought to summarize how social factors influence HS, whether through triggering factors and/or aggravating factors such as smoking, obesity, anxiety, depression and other comorbidities such as chronic inflammatory diseases, observing as a point, often common to these diseases, the direct influence of BNSE. Despite the evidence, the causal link between BNSE and HS still needs to be clarified, and the limitations of this study must be considered.

With the aim of estimating the biopsychosocial impacts on patients' lives, this qualitative systematic review was prepared, and the results were compatible with the observed clinical reality and, as implications for practice, it is strongly recommended to adopt applied treatment modalities in a co-intervention regime, with the aim of increasing the levels of efficacy, effectiveness and safety of services through Good Clinical Practices. As implications for research, studies of better methodological quality are suggested, such as randomized clinical trials.

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