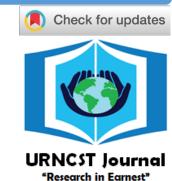
### REVIEW

### Applications of Lifestyle Medicine in the Management of Hidradenitis Suppurativa: A Literature Review

Sourianne Okwo Ebwil, HBc [1]\*

[1] Faculty of Science, University of Toronto, Mississauga, ON, Canada L5L 1C6

\*Corresponding Author: <a href="mailto:sourianne@gmail.com">sourianne@gmail.com</a>



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Abstract

**Introduction:** Hidradenitis Suppurativa (HS) is an inflammatory skin condition characterized by the formation of pusdischarging abscesses under the skin in axillary, inguinal, gluteal, and perianal body sites. Modifiable risk factors such as obesity and smoking have been associated with exacerbation of HS severity. Despite this, research on the clinical application of lifestyle medicine for the improvement of HS symptoms remains scarce. The goal of this review was to evaluate benefits of lifestyle medicine in improving HS symptoms.

**Methods:** A total of 8 articles that examined the associations of smoking cessation, diet modification and weight-loss with HS improvement were investigated. These publications came from cohort studies and intervention trials and were appraised using the Critical Appraisal Skills Programme checklist.

**Results:** HS patients following a brewer's yeast free diet reported significant decrease in HS abscesses and a severe immune reaction to the substance. The Paleolithic and Anti-Inflammatory diet alongside the reduction of foods high in carbohydrates, sugars, and dairy were also associated with improved HS symptoms. Zinc gluconate supplementation demonstrated improved inflammatory nodules and decreased boil count in patients. No correlation between HS and weight-loss or smoking cessation were observed.

**Discussion:** Based on the results, eating patterns resembling the Paleolithic and Anti-Inflammatory diets may lower levels of systemic inflammation in HS patients by reducing the production of TNF-  $\alpha$  cytokines present in HS lesions. Increased levels of antioxidants paired with fewer levels of pro-oxidant properties present in both diets are suggested to help improve the course of the disease in some patients.

**Conclusion:** Further intervention trials and cohort studies must be conducted investigating the effects of smoking cessation, weight-loss and diet in HS severity to determine the integration of lifestyle medicine pillars in clinical practice. No correlations between smoking cessation and weight-loss with HS were established due to limited clinical evidence. Intervention trials beyond exclusionary diets need to be conducted to elucidate the role of nutrition in HS exacerbation and alleviation.

**Keywords:** Hidradenitis Suppurativa; skin inflammation; lifestyle medicine; smoking cessation; weight-loss; diet; paleolithic diet; anti-inflammatory diet; exclusionary diet

### Introduction

Hidradenitis Suppurativa (HS) also known as acne inversa is a progressive inflammatory skin condition characterised by the formation of pus-discharging abscesses in axillary, inguinal, gluteal and perineal body sites [1]. HS frequently starts with the development of pea-sized lumps that rupture and leak pus at the surface of the body site. HS lesion size and frequency varies on condition severity, and this is commonly evaluated using the Hurley staging system [1]. The HS staging system is divided into three stages. Stage 1 is characterized by singular inflammatory nodules with no sinus tract formation while stage 2 includes multiple abscesses in different areas of the body. At this stage, inflamed nodules and abscesses may start to interconnect and form sinus tracts under the skin [1]. Finally, in Stage 3 multiple interconnected abscesses with deep sinus tracts often impairing physical movement are observed [1].

The prevalence of HS is estimated to be as high as 4.10% worldwide though the aetiology of HS remains unknown [1]. Several factors have been hypothesized to contribute to the pathogenesis of HS including hyperkeratosis, hormonal dysregulation, genetic predisposition, and immune response to bacteria [2]. Other risk factors for HS are sex, obesity, and tobacco smoking. [3] The sex pre-disposition of HS can vary according to ethnicity and geographical location. HS is found to likely develop in African-American and biracial individuals to three times more compared to other races. Disease

incidence is also disproportionately larger in adolescent women compared to other sex and age groups [1]. This variation is likely to be due to genetic, hormonal and immune differences among different races and sexes [4].

Treatment options for HS differ across stages of that range from antibiotic treatment, condition corticosteroids, steroid injections to biological agents like Humira and in more severe cases, surgery [2]. While the topical and systemic drug treatments have demonstrated significant symptom improvement, complete response rates in patients are low and lesion relapses are common [3]. As a result, patients frequently explore alternative methods for symptom alleviation beyond conventional therapy such as lifestyle medicine [5]. As an emerging field in clinical practice, lifestyle medicine is a medical approach that integrates lifestyle interventions for preventative health and for management of chronic conditions and illnesses. This medical specialty uses evidence-based behavioral intervention and is divided into six pillars: (1) healthy eating, (2) frequent physical activity, (3) sleep improvement, (4) stress management, (5) reduction of risky substances (tobacco smoking, alcohol, etc.), and (6) the formation of social relationships.

Scientific and medical literature strongly support the correlation of daily habits with both short-term and long-term health [6]. Empirical evidence suggests regular physical activity, healthy body weight maintenance, smoking cessation, and nutrition education to promote health [6]. Subsequently, an individualized treatment plan combining both conventional and lifestyle medicine can be used to address patients living with chronic illness. Increased treatment burden in patients with chronic conditions, as well as low treatment response rates for conditions such as HS, make lifestyle medicine a prospective area of research for additional therapeutic approaches to symptom improvement [7].

For this reason, this review aimed to evaluate and appraise studies that investigated pillars of lifestyle medicine particularly, diet, tobacco cessation and weight loss in HS symptom improvement. Additionally, this review aimed to provide evidence for clinical implementation of lifestyle medicine to help treat and manage HS and other chronic inflammatory skin disorders.

### Methods

### Inclusion and Exclusion Criteria

Primary literary searches were conducted on PubMed. Searches were filtered by research study design (observational studies and intervention trials) and by age of participants (19-44 years old). Patients in each study were diagnosed with HS using the Hurley stages. The keywords "hidradenitis suppurativa and diet", "hidradenitis suppurativa and smoking cessation", "hidradenitis suppurativa and weight loss" OR "hidradenitis suppurativa and lifestyle intervention" were applied in PubMed searches.

### Research Design

This critical appraisal conducted a complete examination of observational intervention studies investigating the role of diet, weight-loss and smoking cessation in HS symptom alleviation. The goal was to determine the strengths, weaknesses, credibility and result significance of these studies to infer on the clinical practice of lifestyle medicine for HS. Each study examined were appraised using the Critical Appraisal Skills Programme (CASP) checklist (adapted from Guyatt GH, Sackett DL and Cook DJ).

A total of 121 studies (41 HS and diet, 23 HS and smoking cessation, 28 HS and weight-loss and 29 HS and lifestyle interventions) were retrieved. A manual search was conducted to ensure that no articles were missed. The manual search retrieved an additional 6 articles that met the criteria. The CASP checklist was applied to evaluate the methodology of these articles and the final number of studies appraised and included in this review were eight articles (7 investigating diet interventions and HS improvement and 1 investigating the effect of weight loss in symptom alleviation) (Figure 1). A narrative synthesis was conducted to summarize the methodology, outcome measures, intervention and significant results of each article.

### Results

PubMed search results yielded 121 articles. After removing duplicates, titles and abstracts were reviewed for relevancy resulting in 24 full text articles assessed for eligibility using the exclusion/criteria detailed above. A total of eight articles remained for a quality appraisal using the CASP checklist as shown in <u>Tables 1</u>, <u>Table 2</u> and <u>Table 3</u>.

The studies included in this review investigated the relationship between nutritional supplements, exclusionary dietary interventions, and weight-loss with HS severity. Participant characteristics were adults older than 19 years old mostly diagnosed with Hurley stage I and II of HS. It has been reported that a vast majority of the participants were female; however, demographic data for some studies did not include age and gender. HS Severity was measured using different indicators most notably the Hidradenitis Suppurativa Assessment tool, the International Hidradenitis Suppurativa Severity Score System and the HS Sartorius Score. HS improvement was commonly measured by calculating the number of abscesses, boils and/or fistulas before and after dietary or weight-loss lifestyle interventions. For studies that examined diet, blood IgG sensitivity testing was used to determine any food triggers or sensitivities in participants. It is to note that some studies had comparators to the intervention, while others recorded changes in HS patients before and after administering lifestyle interventions (Table 4).

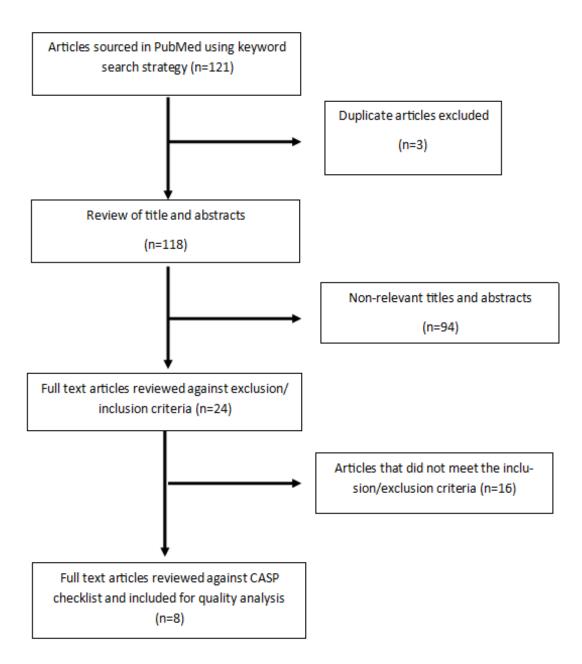


Figure 1. Flow chart of the selection of reviewed articles following CASP model (created with Microsoft Word).

CASP Cohort and Observational Checklist [30]	Hessam et al. (2016)	Cannistra et al. (2013)	Kurzen and Kurzen (2019)	Damiani et al. (2019)	
Did the study address a clearly focused issue?	Yes	Yes	Yes	Yes	
Was the cohort study recruited in an acceptable way?	Yes	Yes	Yes	Yes	
Was the exposure accurately measured to minimize bias?	Yes	Yes	Yes	Yes	
Have the authors identified and taken account all important confounding factors in the design and/or discussion of the study?	Yes	Yes Yes		Yes	
Was a follow up of subjects Yes completed?		Yes	Yes	Yes	
Was the follow up of subjects long enough?	Can't tell (3-month follow-up; minimal follow up time for cohort studies)	Yes (12 months)	Can't tell (follow up time after intervention is not mentioned)	No (1 month)	
How precise are the results? Can't tell (no CI given)		Can't tell (no CI given. Authors provided images of disease improvement in patients before and after intervention)	Can't tell (no CI given, subjective and qualitative measurements used)	95% certainty (CI)	
Do you believe the results?	u believe the results? Can't tell (due to lack of a CI and minimal follow up time). Can't tell (lack of CI)		Can't tell	Can't tell (short follow up time)	
Can the results be applied to the local population?	Yes (reflective of HS prevalence)	Yes (reflective of HS prevalence)	Can't tell	No (small sample size)	
Do the results of this study fit with other available evidence?	Can't tell (due limited studies	Can't tell (due limited studies investigating HS and	Can't tell (due limited studies investigating HS	Can't tell (due limited studies investigating HS and lifestyle	

 Table 1. Quality appraisal using CASP cohort and observational study checklist (n =4)

CASP Cohort and Observational Checklist [30]	Hessam et al. (2016)	Cannistra et al. (2013)	Kurzen and Kurzen (2019)	Damiani et al. (2019)
	investigating HS and oral zinc gluconate supplementation available)	brewer's yeast-free diets available)	and lifestyle factors)	factors)
Does the study have implication for practice?	No (further research needed; lack of available evidence)	No (further research needed; lack of available evidence)	No (further research needed; lack of available evidence)	No (further research needed; lack of available evidence)

Abbreviations used: CI = Confidence Interval

CASP Case-control Checklist [31]	Aboud et al. (2020)	Velluzzi et al. (2022)
Did the study address a clearly focused issue?	Yes	Yes
Did the authors use an appropriate method to answer their question?	Yes	Yes
Were the cases recruited in an acceptable way?	Yes	Yes
Were the control selected in an acceptable way?	Yes	Yes
Was the exposure accurately measured to minimise bias?	Yes	Yes
(a) Aside from the experimental intervention, were the groups treated equally?	Yes	Yes
(b) Have the authors taken account of the potential confounding factors in the design or analysis?	No (bias in self-evaluative questionnaire was not considered)	Yes
How precise was the estimate of the treatment effect?	Can't tell (no CI given)	Can't tell (no CI given)
Do you believe the results?	Can't tell	Can't tell
Can the results be applied to the local population?	Yes (sample reflective of HS prevalence)	Yes (sample reflective of HS prevalence)
Do the results of this study fit with other evidence?	Can't tell (lack of evidence available)	Can't tell (lack of evidence available)

### **Table 2.** Quality appraisal using CASP case-control checklist (n=2)

Abbreviations used: CI = Confidence Interval

CASP Qualitative-study Checklist [32]	Mackalis et al. (2020)	Barrea et al. (2019)		
Was there a clear statement of the aims of the research?	Yes	Yes		
Is a qualitative methodology appropriate?	Yes	Yes		
Was the research design appropriate to address the aims of the research?	Yes	Yes		
Was the recruitment strategy appropriate to the aims of the research?	Yes	Yes		
Was the data collected in a way that addressed the research issue?	Yes (both subjective and objective ratings of symptom severity and improvement between different lifestyle interventions were collected)	Yes (differences between HS patients and control group in Med. Diet adherence were collected and evaluated by a Kolmogorov-Smirnov test)		
Has the relationship between researcher and participants been adequately considered?	Can't tell (not specified)	Can't tell (not specified)		
Have ethical issues been taken into consideration?	Yes	Can't tell (not specified)		
Was the data analysis sufficiently rigorous?	Yes	Yes		
Is there a clear statement of findings?	Yes	Yes		

**Table 3**. Quality appraisal using CASP qualitative study checklist (n=2)

Abbreviations used: CI = Confidence Interval

### **Table 4.** Characteristics of included studies (n= 8)

Author & Year of Study	Study Design	Sample Size	Outcome Measures	Intervention	Comparator	Duration	Significant Results
Hessam et al. (2016)	Retrospective CS	n=66 (>18y/o); (18M, 48 F)	Number of nodules and fistulas	Zinc supplementation (50mg)	N/A	BID for 12 wks	<ul> <li># of nodules significantly decreased from 7.3 ±</li> <li>5.1 to 5 ± 4.4 (p &lt; 0.001).</li> <li># of new boils significantly decreased from 3 to 1 (p=0.0009).</li> </ul>
Cannistra et al. (2013)	Prospective CS	n=12 (5M, 7F)	Flare-up or boil relapses after surgery and following the yeast-free diet	Exclusionary diet eliminating brewer's yeast	N/A	12 mths	Skin lesion regression observed over the 12-month treatment period. Recurrence of skin lesions

Author & Year of Study	Study Design	Sample Size	Outcome Measures	Intervention	Comparator	Duration	Significant Results
							following accidental consumption.
							$22.9 \pm 10.9$ U/mL IgG reaction to yeast.
Aboud et al. (2020)	Retrospective CCS (followed for	n=185 (43 M, 142 F)	Brewer's yeast sensitivity tested using IgG	Exclusionary diet eliminating brewer's yeast	Control group (no exclusionary	6 yrs	Up to 80% improvement of HS symptom recorded > 6 months.
	6 years)		sensitivity. Patient self-report on flareup and stabilization of HS.		diet)		87% saw a resurgence of HS flares after eating a restricted food.
Barrea et al. (2019)	Cross- sectional OS	n=82	PREDIMED score and disease severity	n=41 HS patients Assessment of Med. Diet Adherence	n=41 healthy participants Assessment of Med. Diet Adherence	N/A	Low adherence to the Med. Diet compared to control.
Kurzen and Kurzen (2019)	Retrospective CS	n=40 (24 M, 16, F)	Correlation between disease severity and dietary restrictions and/or influence of certain food compounds	N/A	N/A	2 yrs	HS improvement after gluten free diet and low dairy/ carbohydrate intake was reported.

Author & Year of Study	Study Design	Sample Size	Outcome Measures	Intervention	Comparator	Duration	Significant Results
Velluzzi et al. (2022)	CCS	n=70	Severity of disease using the Sartorius Score compared to adherence to the Mediterranean diet	Compared HS patient results (n=35; 22F, 13 M)	Healthy participants (n=35; matched by sex and age)	12 mths	Results report a low adherence to the Mediterranean diet in HS patients and an excess of simple carbohydrates and saturated fats compared to the control.
Damiani et al. (2019)	Cross- sectional CS	n= 55 (24 M, 31 F)	Disease severity using the IHS4 after Ramadan	N/A	N/A	N/A	HS severity index decreased from $11.00 \pm 5.88$ before Ramadan to $10.15 \pm 6.45$ after Ramadan.
Mackalis et al. (2022)	SS using Likert scale	n=591	Measured disease severity (assessed with the Hidradenitis Suppurativa Symptom Assessment tool) after lifestyle intervention	N/A	N/A	N/A	<ul> <li>56% saw an improvement in their symptoms after adopting the Paleo, Gluten-free and anti- inflammatory diet.</li> <li>Reduced sugar, dairy and chocolate consumption reported high HS improvement.</li> </ul>

Abbreviations used: CS = Cohort Study; CSS = Case-Control Study; SS = Survey study; OS = Observational study; M = male; F = female; mth=months; yrs=years; y/o=years old; wks=weeks; BID=twice daily; IHS4= International Hidradenitis Suppurativa Severity Score System; Med. Diet = Mediterranean Diet

Findings suggest that certain diets were associated with HS improvement. Participants who followed a brewer's yeast free diet for 12 months demonstrated skin lesion regression. However, it has been observed that accidental or voluntary consumption of yeast resulted in the recurrence of abscesses [8]. An alimentary intolerance to brewer's yeast was recorded after participants reported an average reaction of  $22.9 \pm 10.9$  U/mL to the substance [8]. Similarly, when given a brewer yeast free diet on patients with frequent flareups, 70% of participants experienced HS lesion regression. Subsequently, a significant improvement of HS symptoms in less than 6 months has been reported [9]. Food intolerances to wheat and cow's milk were reported to be as high as 29% in participants [9]. In a survey study, 56% of participants reported to experience high symptom relief of HS when sugar and dairy consumption were reduced with the Paleolithic and Antiinflammatory diets [5]. Nutritional supplements were suggested to improve HS severity in patients with the number of inflammatory nodules and boils reported significantly decreasing from 7.3  $\pm$  5.1 to 5  $\pm$  4.4 (p < 0.001) and 3 to 1 (p=0.0009) after a 12-week supplementation of zinc gluconate twice daily [10].

The association between patient adherence to the Mediterranean diet and improvement in HS severity was not clearly defined. It has been observed that there was a low adherence to the Mediterranean diet and an excess consumption of simple carbohydrates and saturated fat in HS patients compared to the control group [11]. Likewise, patients with a low adherence to the Mediterranean diet had a higher HS Sartorius score (59.38. ± 13.02) compared to HS patients who had higher adherence to the Mediterranean diet (p < 0.001) [12]. These findings did not associate adherence to the Mediterranean Diet with HS symptom improvement. In a study conducted by Damani et al. 2019, HS severity index was reported to decrease from  $11.00 \pm$ 5.88 before Ramadan to  $10.15 \pm 6.45$  after Ramadan in 55 patients [13]. Disease severity improvement was associated with topical and systemic antibiotic treatment and not weight-loss.

In sum, the elimination of brewer's yeast, sugar and dairy was associated with the improvement of HS. Zinc gluconate supplementation as well as the Paleolithic and Anti-Inflammatory diets demonstrated significant symptom improvement and boil reduction in examined patients. Weight-loss was not associated with HS improvement in patients.

#### Discussion

Hidradenitis suppurativa (HS) is a complex and inflammatory skin condition marked by the formation of abscesses, lesions and boils in body sites prone to friction [15]. Smoking, and obesity are risk factors associated with the exacerbation of HS symptoms. As a result, lifestyle medicine may be a therapeutic approach to reduce HS severity in patients. This review investigated the

Eating patterns resembling the Paleolithic and Anti-Inflammatory diet were associated with reduced skin inflammation. The elimination of brewer's yeast and reduction of carbohydrates, dairy, and sugar contributed to reduced abscess frequency and high levels of symptom relief in patients [5,8,9]. Both diets have lower glycemic loads by avoiding sugar, dairy and foods high in carbohydrates, including bread and baked goods made with brewer's yeast [14]. Instead, the diets are characterized by high intakes of fruits, vegetables, lean meats, fish and nuts that have shown to contain antioxidants and fewer prooxidant properties [14,16]. A diet high in antioxidant substances can reduce oxidative stress that has been suggested to induce the production of proinflammatory cytokines (TNF-  $\alpha$ ) present in HS lesions [14,17]. These cytokines play a key role in the cellular inflammatory processes of other skin conditions such as psoriasis by proliferating keratinocytes and creating epidermal plaques [18].

Dietary antioxidants present in both diets such as vitamin C, vitamin E, flavonoids (i.e: quercetin and kaempferol) and polyphenolic compounds (i.e. resveratrol and curcumin) are suggested to limit oxidative stress in tissues and contribute to improved health outcomes [12]. Contrastingly, excess consumption of refined sugars and processed carbohydrates have been associated with higher levels of oxidative stress in individuals [20]. To add, epidemiological studies and clinical trials on other inflammatory conditions such as Polycystic Ovary Syndrome (PCOS) have linked higher carbohydrate intake to low-grade chronic inflammation [12]. When effect of low glycemic load diets on patients with acne vulgaris were compared, it demonstrated significant lesion reduction suggesting role of high carbohydrate and sugar intake in acne pathogenesis [21]. Therefore, the Paleolithic and Anti-Inflammatory diets may lower levels of systemic inflammation in HS patients by reducing the production of TNF-  $\alpha$  cytokines triggered by oxidative stress responses. Presently, HS clinical research lacks evidence from intervention trials investigating the effects of the 2 diets on HS severity to support its clinical integration.

Multiple cellular studies have reported an increased number of active smokers in HS patients, suggesting a correlation between smoking and HS pathogenesis. Inhaled cigarette smoke is suggested to promote the production of TNF-  $\alpha$  by stimulating alveolar macrophages to secrete the cytokine in the body [22]. This leads to the induction of systemic inflammation and for HS patients, the exacerbation of existing lesions. Consequently, active smokers with HS may experience reduced efficacy of TNF- $\alpha$  inhibitor pharmaceutics such as Humira [17,23]. This is similar with another skin condition, psoriasis, wherein tobacco smoking is suggested to exacerbate existing

plaques and trigger the onset of the disease in some individuals [24]. Additionally, increased risk of cutaneous squamous cell carcinoma (SCC) has been associated with tobacco smoking [24]. Though numerous observational studies find a high prevalence of smoking among HS patients, limited cohort studies and intervention trials suggest smoking cessation to improve the course of the disease. Additional intervention trials need to be conducted on HS patients before suggesting tobacco cessation to reduce HS lesion sizes and frequency.

Growing evidence suggests obesity to play a role in the development of low-grade systemic inflammation [26]. Though obesity is suggested to be a risk factor for the onset of inflammatory skin conditions, the molecular mechanisms by which obesity trigger the development of skin diseases remain unclear [25]. Evidence hypothesize increased inflammatory cytokine production in adipocytes to trigger obesity-induced inflammation in individuals [25,26]. Increase of proinflammatory proteins in adipocytes are suggested to lead to keratinocyte hyperproliferation, which may exacerbate HS abscesses and lesions. In a cohort study led by Damiani et. al, HS improvement in patients practicing Ramadan were associated with topical and systemic antibiotic treatment [13]. The reduction of HS lesions was not linked to weight loss. Presently, HS literature suggesting weight-loss to be beneficial for symptom alleviation were observed in case report studies where statistical significance was not tested for [27-29]. While obesity is associated with chronic low-grade systemic inflammation, intervention trials on larger samples sizes are needed before determining weight-loss to provide HS symptom relief. More cohort studies and randomized clinical trials investigating weight-loss intervention, tobacco cessation and diet in HS improvement are warranted for the integration of these lifestyle medical pillars in clinical practice.

### Conclusion

Evidence-based approaches to behavioural interventions can be used to help develop individualized treatment plans and modify risk factors for chronic conditions and illnesses such as HS. Despite this, the application of lifestyle medicine in clinical practice is limited. This appraisal investigated the effects of smoking cessation, weight loss and diet modification on HS severity. Due to limited intervention trials and cohort studies examining smoking cessation and weight-loss in HS, correlations for these two lifestyle pillars were not established. A cohort study associated HS abscess reduction to topical and systemic antibiotics, not weight-loss [13]. Associations between the Paleolithic and Anti-Inflammatory diet paired with the reduction of foods high in carbohydrates, brewer's yeast, sugar, and dairy demonstrated increased scores of disease improvement in examined patients. The Palaeolithic and Anti-Inflammatory diets have been suggested to reduce HS inflammation and as a result, lesion size and frequency, but more studies supporting the effects of the Paleolithic and Anti-Inflammatory diet in HS patients need to be conducted. Overall, this study demonstrated the limited evidence on the effects of lifestyle medicine in HS research. Clinical advances in HS treatment continue to examine the involvement of follicular hyperkeratosis in the condition. Evidence outside of case reports investigating smoking cessation and weight-loss intervention is scarce; therefore, more studies examining the effects of lifestyle medicine in HS are needed to determine the integration of its pillars in clinical practice.

### List of Abbreviations Used

HS: Hidradenitis suppurativa CASP: critical appraisal skills programme PCOS: polycystic ovary syndrome TNF: tumor necrosis factor SCC: squamous cell carcinoma IgG: immunoglobin G CS: cohort study CSS: case-control study SS: survey study OS: observational study IHS4: International Hidradenitis Suppurativa Severity, Score System

### **Conflicts of Interest**

The author declares that they have no conflict of interests.

### **Ethics Approval and/or Participant Consent**

This study did not need ethical approval or participant consent to review and appraise research investigating lifestyle medicine in HS.

### **Authors' Contributions**

SOE: Drafting the work or revising it critically for important intellectual content, substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, and final approval of the version to be published.

### Acknowledgements

I would like to thank my mentor, Patricia Acosta for providing substantial contribution to the development of the manuscript with her writing assistance and guidance.

### Funding

This study was not funded.

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### **Article Information**

Managing Editor: Jeremy Y. Ng Peer Reviewers: Patricia Acosta, Katelyn Sushko Article Dates: Received Dec 10 22; Accepted Feb 04 23; Published Apr 14 23

### Citation

Please cite this article as follows: Ebwil SO. Applications of lifestyle medicine in the management of hidradenitis suppurativa: A literature review. URNCST Journal. 2023 Apr 14: 7(4). <u>https://urncst.com/index.php/urncst/article/view/455</u> DOI Link: <u>https://doi.org/10.26685/urncst.455</u>

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