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Follicular Occlusion Disorders in Patients with Crohn's Perianal Disease and the Relationship to Fistulizing Phenotypes

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Abstract

Background and Objectives: Perianal fistulizing Crohn's disease (pCD) is a challenging phenotype, often associated with significant morbidity and reduced quality of life. Follicular occlusion disorders (FODs), such as hidradenitis suppurativa (HS), share pathogenic mechanisms with CD, potentially influencing disease severity and treatment outcomes. This review aims to investigate the association between FODs and perianal fistulizing CD, exploring the underlying pathogenic mechanisms and the impact on fistula complexity and treatment strategies. **Methodology:** A comprehensive literature review was conducted, examining studies reporting on the prevalence, clinical characteristics, and pathogenic mechanisms linking FODs and perianal CD. The search included studies focusing on genetic predisposition, immune dysregulation, the role of the microbiome, and epithelial-mesenchymal transition (EMT). Studies assessing the impact of FODs on fistula complexity, treatment outcomes, and diagnostic and management strategies were also included. **Results:** The prevalence of FODs, particularly HS, appears to be higher in CD patients with perianal involvement. Shared genetic factors, such as mutations in the NOD2/CARD15 gene, and common inflammatory pathways involving TNF-*α*, IL-17, and IL-23 may contribute to the co-occurrence of these conditions. Alterations in the gut and skin microbiome, as well as the involvement of EMT,

further contribute to the pathogenesis of both CD and FODs. The presence of FODs may increase the risk of developing fistulizing perianal CD and influence fistula complexity and severity. Effective management requires a multidisciplinary approach, including medical therapies targeting inflammation and surgical interventions to address perianal sepsis. **Conclusion:** Follicular occlusion disorders, especially HS, exhibit a notable association with Crohn's disease, particularly in patients with perianal involvement. Shared pathogenic mechanisms, such as genetic predispositions, immune dysregulation, microbiome alterations, and epithelial-mesenchymal transition, underpin this relationship. The co-occurrence of FODs and perianal CD can significantly impact disease severity, quality of life, and treatment outcomes, necessitating a multidisciplinary approach to diagnosis and management. Future research should focus on elucidating the specific genetic and environmental factors that contribute to this association, as well as developing novel therapeutic strategies that target shared pathogenic pathways.

Keywords

Crohn's Disease, Perianal Fistulizing Crohn's Disease, Follicular Occlusion Disorders, Hidradenitis Suppurativa, Inflammatory Bowel Disease, Fistula Complexity, Epithelial-Mesenchymal Transition, Microbiome, Immune Dysregulation, NOD2 Gene, TNF-Alpha, IL-17, IL-23, Genetic Predisposition, Multidisciplinary Management, Perianal Sepsis, Chronic Inflammation, Cutaneous Manifestations

1. Introduction: Linking Two Chronic Inflammatory Conditions

Perianal fistulizing Crohn's disease (pCD) is a severe phenotype of Crohn's disease characterized by chronic abscess formation and fistulous tracts involving the anorectal and perineal regions [1]. These perianal fistulas represent a debilitating complication of Crohn's, affecting approximately one-third of patients over the course of disease [1]. The relentless drainage, pain, and occasional fecal incontinence from pCD can profoundly impair quality of life, impacting social activities, intimate relationships, and psychological well-being [2]. Management of pCD is challenging; fistulas are often complex and refractory to conventional therapies, contributing to high morbidity and healthcare burden [3].

Follicular occlusion disorders (FODs) are a group of chronic inflammatory skin conditions defined by follicular plugging and rupture, leading to recurrent nodules, abscesses, sinus tracts, and scarring. This group includes hidradenitis suppurativa (HS), acne conglobata, dissecting cellulitis of the scalp, and pilonidal cysts [4]. Among these, HS is the most commonly studied and severe, presenting with painful nodules and draining fistulae in apocrine gland-rich areas such as the axillae, groin, and perineal region [5]. Like pCD, HS follows a chronic relapsing course with frequent flares and significant quality-of-life impairment [6].

The rationale for investigating the connection between pCD and FODs stems from their shared clinical, genetic, and immunologic features [7]. Several epidemiological studies suggest that patients with Crohn's disease are significantly more likely to develop HS than the general population, with one population-based cohort reporting a ninefold increased risk [8]. Conversely, HS patients have also demonstrated a higher incidence of inflammatory bowel disease [8]. Moreover, co-localization of HS lesions and perianal Crohn's disease has been reported, suggesting a potential overlap in inflammatory pathways and tissue microenvironment [9]. Both diseases are associated with increased expression of TNF-α, IL-1β, IL-17, and IL-23, and both may respond to treatment with TNF-α inhibitors such as infliximab or adalimumab [10] [11].

Environmental and lifestyle risk factors such as smoking and obesity are also shared between pCD and FODs and may exacerbate disease severity and frequency of flares [12] [13]. Genetic susceptibility, particularly involving NOD2/CARD15 mutations in Crohn's and γ-secretase mutations in HS, suggest a hereditary component to these diseases' co-occurrence [14] [15]. This review aims to explore the co-occurrence of pCD and follicular occlusion disorders, particularly HS, by examining overlapping genetic, immunologic, and microbiome-related mechanisms. Understanding the interplay between these conditions is crucial for early recognition, accurate diagnosis, and optimized treatment. Enhanced awareness can lead to earlier initiation of effective therapies and improved quality of life for patients with this dual disease burden [1].

2. Methodology

A thorough search of the literature was performed using various databases, including PubMed, Google Scholar, and Scopus. Key search terms for the literature review included follicular occlusion disorders, hidradenitis suppurativa, fistula, perianal fistulizing Crohn's disease, Crohn's disease, inflammatory bowel disease, perianal sepsis, and cutaneous manifestations. No date restrictions were placed on the search for available data, as we aimed to perform a thorough review with pertinent information. A total of 80 studies were included in this review.

Study types utilized in this review include review articles, cross-sectional studies, case reports, observational studies, systematic reviews, meta-analyses, and original research. For this study, original research refers to pilot studies, cohort studies, population-based studies, morphological studies, histological studies, genetic association studies, experimental studies, surveys, and qualitative studies. Additionally, information from textbooks, handbooks, seminars, and clinical guidelines was included. All included studies must have involved adult patients.

Our objective was to identify the prevalence, clinical characteristics, and pathogenic mechanisms linking follicular occlusion disorders and perianal Crohn's disease. Specifically, studies focusing on genetic predisposition, immune dysregulation, the role of the microbiome, and epithelial-mesenchymal transition (EMT) were of primary interest. Secondarily, studies that surveyed the impact of follicular

occlusion disorders on fistula complexity, treatment outcomes, and diagnostic and management strategies were included.

Outcomes assessed for this manuscript included the genomics of the disease process as well as all involved cytokine expressions and biochemical pathways. Additionally, outcomes outlining population level data, including disease prevalence, response to treatments, and risk factors were of interest. Exclusion criteria when determining eligible studies included editorials, conference abstracts without complete data, non-English studies, and pediatric-only populations, defined as <18 years of age.

Once individual studies were identified using the aforementioned databases, a PRISMA flow diagram was used to identify studies most relevant to our inquiry [16]. A qualitative synthesis of existing literature was performed [17] [18]. After initial identification of relevant articles and material, a screening process was performed to remove duplicates and ensure the studies did not include any exclusion criteria. A minimum of two independent reviewers screened each article and literature source, examining the title, abstract, and full-text to ensure adequate and correct data as well as fulfillment of eligibility criteria. Discrepancies were resolved via discussion.

Data was extracted using a standardized Excel template that included study design, whether it met inclusion criteria, key outcomes, the patient population studied, and tools used to preserve study quality. The data extracted from each article included the various genetic factors contributing to the association between follicular occlusion disorders and Crohn's disease. Additionally, inflammatory pathways involved in and contributing to the co-occurrence of these conditions were explored. Further data examining the contribution of gut and skin microbiome to the pathogenesis of these conditions and their association was assessed. Finally, data about management strategies, pharmacological therapy, and surgical interventions was obtained. If there was conflict in the data obtained, conflict resolution was accomplished by designating a team of two reviewers to survey the information and include the data most strongly supported by the literature.

Quality assessment of included studies was performed independently by two reviewers. The JBI Critical Appraisal Tool was utilized to assess the quality of case reports, cross-sectional studies, cohort studies, systematic reviews, pilot studies, morphological studies, histological studies, surveys, qualitative studies, and experimental studies [19]. Quality assessment of genetic association studies was accomplished using the Q-Genie tool [20].

3. Epidemiology and Clinical Presentation: Understanding Overlap

3.1. How Common Are FODs in Patients with pCD?

A group of dermatologic conditions known as the follicular occlusion tetrad, comprising hidradenitis suppurativa (HS), acne conglobata, pilonidal cysts, and dissecting cellulitis of the scalp share a unifying pathophysiological mechanism: fol-

licular occlusion in areas rich in apocrine glands [4]. These disorders frequently overlap in risk factors, clinical presentation, and chronic inflammatory profiles. Despite their similarities, distinct anatomic sites of involvement and varying severities necessitate condition-specific management strategies [4]. Among these, hidradenitis suppurativa presents with the most systemic associations and has received increased attention due to its debilitating nature and strong links with metabolic and immune-mediated diseases.

Hidradenitis suppurativa (HS), also referred to as acne inversa, is a chronic, recurrent, and painful inflammatory skin condition that predominantly affects intertriginous areas. The disease is multifactorial, with contributing factors including obesity, polycystic ovary syndrome (PCOS), insulin resistance, and inflammatory bowel disease (IBD), particularly Crohn's disease (CD) [12]. In a cross-sectional study involving 158 IBD patients, Kamal *et al*. (2016) estimated the prevalence of HS at approximately 16% [9]. This aligns with findings from Dutch referral centers, where HS prevalence among IBD patients ranged from 16% to 23%, further supporting the association between these two chronic inflammatory conditions [21]. Similarly, in a Minnesota population-based cohort of 679 IBD patients, HS was associated with a ninefold increased risk of IBD, with the relationship more pronounced for CD (12-fold) [1]-[8]. These findings suggest a potential shared inflammatory pathway, contributing to both skin and gastrointestinal involvement.

This connection between hidradenitis suppurativa and Crohn's disease has been substantiated by large cohort studies. Garg *et al*. (2018) in an analysis of over 51,000 patients with HS, reported a CD prevalence of 2.0% compared to 0.6% among individuals without HS, highlighting a significant association [7]. Furthermore, three separate Dutch investigations reported HS prevalence of 26%, 17% and 15% in CD cohorts of 688, 102, and 634 patients respectively [21]-[23]. These elevated prevalence rates across diverse cohorts reinforce the strength of the relationship. In a related vein, Pogacnik and Salgado (2019) observed that CD patients with perianal fistulas are particularly prone to developing extraintestinal manifestations, including cutaneous disorders such as HS [24]. This raises the possibility that the anatomic and immunologic environment of perianal Crohn's disease may play a unique role in triggering hidradenitis suppurativa lesions.

Race-related differences also appear to influence this co-occurrence. A retrospective study by Kamal *et al*. (2016) found that Black individuals were disproportionately affected by both HS and CD [9]. One proposed biological explanation is the greater density of apocrine glands among individuals of African descent, which may contribute to increased HS susceptibility [13]. However, this biological explanation must also be considered alongside structural factors, such as healthcare access disparities and delayed diagnosis, which may exacerbate disease burden. The consistently elevated relative risks reported in population studies [1] emphasize the need for vigilance in detecting hidradenitis suppurativa in Crohn's disease populations, especially in high-risk groups.

Beyond the general overlap between hidradenitis suppurativa (HS) and Crohn's disease, recent studies have identified a particularly strong association between HS and perianal manifestations of CD. Kamal *et al*. (2016) in a retrospective review of patients with dual diagnoses of CD and HS, found that 73% (11 of 15) had HS lesions localized to the perianal region. Of these, 67% (10 of 15) had documented perianal CD [9]. Additionally, another study by Principi *et al*. (2016) reported the prevalence of HS in patients with perianal Crohn's disease to be approximately 17.3% [25]. This is significantly higher compared to the prevalence of HS in the general population, which is estimated to be around 1% [5]. These findings suggest that HS may preferentially localize to sites of active Crohn's involvement, especially in the perineal area, potentially due to the shared inflammatory microenvironment. The co-localization of Hidradenitis Suppurativa and perianal Crohn's Disease underscores the importance of thorough dermatologic and gastrointestinal evaluation in patients presenting with chronic perineal lesions.

3.2. How Do FODs Present in Patients with pCD?

While there are some commonalities among the elements of the follicular occlusion tetrad, there are also notable distinctions. Acne conglobata is a rare and severe type of acne that is characterised by sore nodules, abscesses, and numerous inflammatory papules that frequently combine to create foul odours that drain the tract. Lesions usually start on the upper limb and truck, although they often spread to the buttocks [26]. Dissecting cellulitis of the scalp, another component of the tetrad, is uncommon and presents with perifolliculitis of the scalp, deep and superficial dermal abscesses, the formation of sinus tracts, and severe scarring [27]. Although less common, it illustrates how follicular occlusion may present with distinct anatomical and pathological consequences depending on the region.

The pilonidal sinus, which results from entrapment of hair within the pilosebaceous unit, typically involves the sacrococcygeal area although it can occasionally affect the pubis, anterior perineum, or the hands of those in specific professions like hairdressers or dog groomers [26]. In contrast, hidradenitis suppurativa (HS) commonly presents with scarring, draining sinus passages, abscesses, and recurrent painful nodules in apocrine-rich areas such as the buttocks, groin, axillae, perineal and perianal regions, and the infra and intermammary folds [26]. The similarity of hidradenitis suppurativa symptoms to that of other follicular occlusion disorders necessitates a high index of suspicion and clinical differentiation, especially in complex cases involving inflammatory bowel disease.

Cutaneous manifestations of Crohn's disease frequently exhibit numerous clinical similarities with hidradenitis suppurativa (e.g., inflamed nodules and fistulas/tunnels), thereby presenting a diagnostic challenge [26]. However, clinicians can improve diagnostic accuracy by focusing on key distinguishing features, including topography of lesions, fistula location, presence of gastrointestinal symptoms, diagnostic imaging findings, and histological characteristics. Typical topography of HS lesions are axillae, groin, perineal, and perianal regions, buttocks, and

infra- and intermammary folds while preferred sites in cutaneous Crohn's disease are the perineum and perianal area. HS lesions are usually far from the anal canal and rectum. In HS, fistula lesions do not extend to the dentate line of the anal canal (no apocrine glands at or above the dental line) [1], whereas, in Crohn's disease, fistulas are typically intersphincteric [26]. In addition, patients with perianal fistulizing Crohn's disease may have gastrointestinal symptoms or unexplained biological abnormalities such as abdominal pain, diarrhea and this may put doctors at alert and distinguish them from hidradenitis suppurativa [1]. These differences can significantly inform surgical and medical decision-making.

Diagnostic imaging modalities such as magnetic resonance imaging (MRI) and ultrasonography (US) play a critical role in differentiating hidradenitis suppurativa (HS) from Crohn's disease (CD), particularly in patients presenting with perianal disease [1]. In a comparative study evaluating pelvic MRI features, Monnier *et al*. (2017) analyzed 23 patients with HS and 46 with CD, all of whom had anoperineal involvement. The findings revealed that certain radiologic patterns could assist in distinguishing the two conditions. Specifically, patients with HS more frequently demonstrated bilateral lesions, an absence of rectal wall thickening, and a lack of characteristic perianal involvement typically seen in CD [28]. Histologically, fistulas in Crohn's disease exhibit a central fissure that branches and traverses through the lamina propria and muscularis mucosae, extending profoundly into the underlying tissue [29]. Furthermore, biopsy of the affected part showing granulomatous inflammation on histopathology strongly supports a diagnosis of CD [26]. Although the histological characteristics of HS tunnels might differ, generally, an extended cavity in the dermis or subcutis surrounded by unevenly thick squamous epithelium is frequently observed [30]. Understanding these microscopic differences is vital for appropriate diagnosis, especially when standard clinical tools yield inconclusive results.

3.3. What Is the Impact on Disease Burden and Quality of Life?

The co-occurrence of hidradenitis suppurativa (HS) and perianal Crohn's disease (pCD) compounds disease burden by intensifying clinical symptoms, reducing therapeutic responsiveness, and worsening patient quality of life. Clinically, patients often present with overlapping symptoms such as abscesses, draining sinus tracts, perianal pain, erythema, pruritus, bleeding, and purulent discharge; features that pose significant diagnostic and management challenges [31]. Although both HS and pCD may respond to anti-TNF-alpha therapies, their concurrent manifestation can signal a more severe inflammatory phenotype. Kamal *et al*. (2016) in a retrospective review of 15 patients with both conditions, reported greater colonic involvement and more severe Crohn's disease activity in this subgroup [9]. This suggests that HS may not merely coexist with CD but may amplify its clinical expression.

Further evidence of intensified disease severity is seen in treatment outcomes. Zhang *et al*. (2021) noted that therapeutic management became more complex

when HS and CD co-occurred, highlighting a need for aggressive, multidisciplinary approaches [1]. Consistent with these findings, Dumont *et al*. (2020) demonstrated that patients with both HS and pCD not only required more anti-TNF agents but were also at increased risk of permanent stoma formation [32]. The need for intensified biologic therapy despite poor outcomes emphasizes the synergistic impact of co-morbid HS and pCD on disease progression. These observations imply a unique inflammatory burden that current treatment modalities may be ill-equipped to address fully.

Beyond physical symptoms, HS significantly disrupts social and emotional well-being. Pain, malodour, and recurrent lesions interfere with daily functioning, work, and relationships. Zouboulis *et al*. (2015) emphasized the role of discomfort, pruritus, and suppuration in shaping the lived experiences of HS patients, often leaving them socially isolated [6]. Pain, in particular, has been repeatedly identified as the most distressing symptom. Nielsen *et al*. (2020) described this pain as burning, shooting, and incapacitating; qualities that impact nearly all affected areas [33]. Matusiak (2020) reported that over 95% of HS patients experience pain, especially around inflamed nodules or abscesses, a symptom strongly correlated with reduced quality of life [34]. Molina-Leyva *et al*. (2020) and Matusiak *et al*. (2018) found pain prevalence rates of 65.2% and 77.5%, respectively [35] [36], reinforcing the idea that pain is not only widespread but deeply influential in shaping psychological and functional outcomes.

Pain's effect extends into psychological and behavioral domains. Matusiak *et al*. (2018) found that pain had a more significant influence on quality of life than lesion location or frequency. Supporting this, two studies linked HS-related pain to worsened psychological functioning, particularly in mental health domains such as self-esteem and social interaction [37] [38]. Interestingly, while Frings *et al*. (2019) found that pain primarily exacerbated anxiety and not depression, Kaaz *et al*. (2019) associated HS-related pain with poor sleep quality [39] [40]. These findings underscore how persistent physical discomfort can infiltrate multiple aspects of patients' lives, from mood to rest, making holistic pain management an essential element of care.

Moreover, HS-related structural damage, including scarring and tunneling, presents additional barriers to personal hygiene. A study noted that these lesions often promote bacterial overgrowth, increasing the severity of malodour and discharge. Over time, patients may underestimate their body odor due to olfactory habituation, even as their social circles continue to be affected [41]. Two additional studies reported that this mismatch can result in strained personal and professional relationships, fostering social withdrawal and emotional distress [38] [42]. These secondary effects highlight the need for comprehensive symptom control beyond inflammation alone to meaningfully improve quality of life.

As HS progresses, its impact becomes more pronounced. Ingram *et al*. (2022) reported that worsening disease severity correlated with poorer scores on the Dermatology Life Quality Index (DLQI) and the Hidradenitis Suppurativa Quality of

Life (HiSQOL) tool [43]. Patients frequently identified appearance, self-confidence, and intimate relationships as the most adversely affected domains. These findings are consistent with studies that detailed the stigma, embarrassment, and emotional toll experienced by HS patients [44] [45]. The chronic, visible nature of the disease often leads to persistent fear of judgment, reducing both social participation and psychological well-being.

Expanding on the effect of perianal Crohn's disease on quality of life, another study found that pain from perianal fistulas significantly interfered with mobility, productivity, and daily routines [2]. Participants in their study described needing to adapt their lifestyles, often through behavioral modifications like carrying extra clothing or scheduling frequent restroom use to manage the burden of fistula discharge. This theme was buttressed in the study by Jiang *et al.* (2023) where patients with cutaneous perianal fistulas (CPF) reported worse health-related quality of life than those without CD, based on standardized patient-reported outcomes [46]. Notably, patients also described heightened feelings of self-consciousness and frustration due to the unpredictable nature of discharge, often leading to a hypervigilant approach to personal hygiene [2]. Over time, such adjustments may evolve into ritualistic behaviors that reflect deeper emotional coping mechanisms. The co-occurrence of hidradenitis suppurativa and perianal Crohn's disease amplifies symptom severity, complicates disease management, and erodes quality of life through a multidimensional burden. Patients face not only intensified clinical symptoms but also compounded psychological, social, and functional challenges. Understanding this interaction is vital for informing integrated care strategies that prioritize both symptom relief and overall patient well-being.

4. Genetic Susceptibility and Shared Immunologic Pathways

4.1. Role of NOD2/CARD15 and Other Genetic Mutations

Variants in caspase recruitment domain-containing protein 15 (CARD15, also known as nucleotide-binding oligomerization domain-containing protein 2, NOD2) are linked to complex and familial forms of Crohn's disease (CD). A Finnish cohort study found the 1007fs variant was more frequent in familial CD than in sporadic cases and was associated with ileal involvement, stricturing or penetrating behavior, and higher surgical rates [14]. This frameshift mutation leads to premature termination of the CARD15 protein and reduced nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation in response to lipopolysaccharide. Transcriptomic analysis has identified two CD immunopathotypes: one with increased interleukin-1 beta (IL-1β) and macrophage markers associated with granuloma formation, and another dominated by cluster of differentiation 8 positive (CD8+) T-cell infiltration and cytotoxicity [47]. The IL-1β-dominant group showed reduced response to anti-tumor necrosis factor (anti-TNF) therapy, illustrating how immune signatures may inform treatment strategies, though this study did not directly assess CARD15 status. In hidradenitis suppurativa (HS), pathogenic mutations in gamma-secretase complex genes such as nicastrin (NCSTN)

have been identified in familial cases, impairing Notch signaling and promoting follicular occlusion, epithelial cyst formation, and sustained inflammation, including IL-1β and TNF-α upregulation [15]. A genome-wide association study (GWAS) also identified HS risk variants near SRY-box transcription factor 9 (SOX9) and Krüppel-like factor 5 (KLF5), genes involved in epithelial regulation and inflammation [48]. Although direct genetic overlap with CARD15 in CD has not been confirmed, the convergence of IL-1β and TNF-driven pathways suggests shared molecular vulnerabilities between CD and HS, with potential implications for personalized therapeutic approaches. Beyond genetics, Crohn's disease and hidradenitis suppurativa share immune dysregulation, clinical manifestations, and therapeutic challenges, as outlined in **Table 1**.

Table 1. Comparison of Crohn's disease (CD) and hidradenitis suppurativa (HS) across genetics, immune pathways, symptoms, and treatments.

Domain	Crohn's disease (CD)	Hidradenitis suppurativa (HS)
Genetics	Variants in CARD15 (NOD2); HLA genes linked	Mutations in NCSTN; risk regions near SOX9, KLF5
Key immune pathways	Impaired NF-κB activation, IL-1β, TNF-α pathways	Disrupted Notch signaling, IL-1β, TNF-α pathways
Typical symptoms	Abdominal pain, diarrhea, weight loss, perianal disease	Painful nodules, abscesses, draining sinuses, scarring
Disease distribution	Ileum, colon, perianal region	Axillae, groin, inflammatory regions
Standard treatments	Corticosteroids, immunomodulators, anti-TNF biologics	Antibiotics, intralesional steroids, anti-TNF biologics, surgery
Treatment challenges	Strictures, fistulas, biologic non-response in IL-1β-high subtypes	High recurrence, treatment resistance, chronicity in familial cases

4.2. Contribution of HLA Alleles and Family History to Disease Risk

Familial clustering of Crohn's disease (CD) and hidradenitis suppurativa (HS) underscores the importance of inherited genetic factors in shaping disease severity and distribution. In CD, the 1007fs caspase recruitment domain-containing protein 15 (CARD15, also known as nucleotide-binding oligomerization domain-containing protein 2, NOD2) variant was nearly three times more common in familial cases than in sporadic forms and was strongly linked with ileal location and complications in a population-based Finnish study [14]. This association suggests that familial CD may reflect a distinct genetic profile predisposing patients to more aggressive disease. In HS, family history has also been shown to predict clinical outcomes, with familial HS defining a subset characterized by increased disease burden and chronicity. Garg *et al.* (2018) analyzed insurance claims data and demonstrated that patients with HS had significantly elevated odds of being diagnosed with CD or ulcerative colitis (UC), highlighting an epidemiologic overlap

between these conditions [7]. Certain human leukocyte antigen (HLA) class II alleles, particularly HLA-DRB1 and HLA-DQ, have been associated with CD, especially in early-onset and familial cases, due to their role in shaping antigen presentation and T-cell activation [49]. While no HLA loci have been definitively linked to HS, rare co-occurrence with HLA-B27–associated spondyloarthritis suggests potential shared immune mechanisms [50]. A recent genome-wide association study (GWAS) identified new susceptibility loci for HS unrelated to the HLA region, including a noncoding region near SRY-box transcription factor 9 (SOX9), though their functional implications remain under investigation [48]. Together, these findings affirm that both CD and HS feature heritable risk components influencing disease onset, extent, and treatment response.

4.3. Functional Implications of Genetic Susceptibility Factors

The genetic factors underlying Crohn's disease (CD) and hidradenitis suppurativa (HS) appear to exert their effects through disruption of epithelial barrier function and immune regulation. In CD, the 1007fs variant of CARD15 leads to diminished cellular detection of bacterial components and impaired NF-κB signaling, compromising mucosal defense and promoting chronic inflammation in the ileum and perianal regions [14]. Baer (2023) found that IL-1β-associated immunopathotypes in CD biopsies correlated with macrophage infiltration, granuloma formation, and poor response to biologics. This subgroup demonstrated increased expression of pro-inflammatory cytokines and chemokines, suggesting that transcriptional profiles could serve as predictive tools for treatment selection [47]. In HS, mutations in NCSTN and related γ-secretase genes disrupt Notch signaling, leading to follicular plugging, rupture, and activation of innate immunity. Vossen *et al*. (2018) reported elevated local levels of IL-1β and TNF-α in HS lesions, indicating a pro-inflammatory loop similar to that observed in CD. This immune profile has functional consequences, including neutrophil recruitment and abscess formation. Additionally, Caparrós *et al*. (2021) demonstrated that in CD, microbial dysbiosis and epithelial barrier failure promote bacterial translocation, further stimulating immune responses and fibrosis [51]. Collectively, these studies illustrate that genetic mutations in both CD and HS impair epithelial homeostasis and increase susceptibility to uncontrolled inflammation. Importantly, these disruptions may contribute to more severe or treatment-resistant disease in some patients.

5. Inflammatory Pathways and Microbiome Disruption

Crohn's disease (CD) and hidradenitis suppurativa (HS) share several inflammatory pathways that contribute to their chronic nature. One of the most well-known cytokines in both conditions is tumor necrosis factor alpha (TNF-α). Elevated levels of TNF-α have been detected in the intestinal mucosa of patients with CD as well as in the lesioned skin of individuals with HS [1]. This cytokine promotes leukocyte recruitment and persistent immune activation, potentially explaining

the overlapping clinical features observed in both diseases. One cross-sectional analysis found that patients with CD were more likely to develop HS than those without CD [8]. This supports the idea that shared inflammatory drivers like TNF-α may be responsible for both conditions. Clinical improvement has been demonstrated with TNF-α inhibitors such as infliximab and adalimumab in both CD and HS [11]. The role of these inhibitors in delaying the implications of these diseases show that these cytokines have a crucial role in pathogenesis and emphasize the potential for shared treatment methods.

In addition to TNF-α, the interleukin-23 and interleukin-17 (IL-23/IL-17) axis has demonstrated to be an important contributor to chronic inflammation within gastrointestinal and dermatologic settings. IL-23 supports the survival and expansion of Th17 cells, which are responsible for producing IL-17 [52]. This is important as IL-17 is associated with neutrophil recruitment. In CD, increased levels of IL-23 and IL-17 have ultimately been correlated with more aggressive disease phenotypes [53]. This relationship exemplifies the feedback mechanism between these two cytokines, and the necessity for further examination into their implications. Similar upregulation has also been documented in HS lesions. For instance, IL-17-producing T cells are frequently present [12]. These findings suggest that therapies targeting the IL-23/IL-17 axis may offer dual benefit in patients affected by both conditions. Additional cytokines such as interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) further amplify inflammatory signaling. IL-1β is primarily produced by activated macrophages and has been implicated in early lesion formation in HS and epithelial injury in CD [54]. This suggests that IL-1β may act as an early signal in chronic inflammation and helps prepare for subsequent immune activation in both diseases. IL-6 plays a role in the differentiation of Th17 cells and supports chronic inflammation in both the gut and the skin [55]. By promoting Th17-mediated responses, IL-6 may maintain the inflammatory cycle started by other cytokines. These cytokine pathways form a unique profile that helps explain the co-occurrence of CD and HS.

Microbiome compositions can influence disease expression. In CD, patients frequently demonstrate reduced diversity of gut commensal bacteria. *Faecalibacterium prausnitzii* is a butyrate-producing species with known anti-inflammatory properties, and it is often depleted in CD [56]. Its depletion is associated with increased mucosal inflammation and impaired epithelial barrier function. Additionally, there is often an overrepresentation of pro-inflammatory bacteria, such as certain strains of *Escherichia coli* [57]. The combination of these factors worsens intestinal immune activation and epithelial disruption. Similar patterns of microbial imbalance are observed in HS. Lesional skin exhibits shifts in microbial communities, including increased abundance of *Staphylococcus aureus* and anaerobic Gram-negative organisms [58]. These changes are thought to promote chronic inflammation through mechanisms such as biofilm formation and immune evasion. These characteristics due to changes in microbiome suggest a possible overlap in microbial triggers between the gut and skin.

Recent studies support the role of the gut-skin axis in inflammatory responses across these organ systems. Both the gut and skin contain unique environments that communicate through metabolites, cytokines, and neuroendocrine pathways. Dysbiosis can lead to increased intestinal permeability. This can lead to the translocation of bacterial endotoxins such as lipopolysaccharides into circulation [59]. These circulating microbial products can activate immune cells in distant tissues, including the skin, contributing to inflammation seen in HS and other follicular occlusion disorders. Shared cytokine pathways highlight the sharing nature of immune activation in both conditions. Additionally, reduced production of short chain fatty acids (SCFAs) may worsen cutaneous inflammation [60]. This is attributed to the fact that SCFAs help maintain regulatory T cell function and skin barrier homeostasis. These interconnected mechanisms highlight the clinical relevance of the gut-skin axis in mediating chronic inflammation and may help explain the overlapping features observed in patients with both perianal CD and HS.

The overlapping features of dysbiosis in CD and HS may offer a therapeutic window in targeting the microbiome. Although the gut and skin harbor distinct microbiomes, both conditions are marked by a loss of microbial diversity and an increase in pro-inflammatory organisms. In CD, this includes a well-documented reduction in *Faecalibacterium prausnitzii* and an overgrowth of *Escherichia coli* [61]. These differences are associated with impaired gut barrier function and increased immune activation. In HS, lesional skin often shows increased colonization by *Staphylococcus aureus* and anaerobic Gram-negative bacteria [62]. Despite the anatomical differences, these microbial changes appear to activate similar inflammatory pathways. These pathways include TNF-α and the IL-17/IL-23 axis. The overlap suggests that modifying the microbiome could help manage both diseases. In CD, treatments such as fecal microbiota transplantation, probiotics, and dietary interventions have shown some success in reducing inflammation by restoring microbial balance [63]. While evidence in HS remains limited, early findings indicate that similar strategies may help reduce cutaneous inflammation. Improving microbial diversity and restoring balance may also support barrier function and reduce systemic immune activation. For patients with both CD and HS, modulation of the microbiome may offer an effective strategy.

6. Epithelial-Mesenchymal Transition: A Common Fibrotic Pathway

6.1. Contributions to Fistula Formation in Crohn's Disease

The epithelial-mesenchymal transition (EMT) describes a biologic process whereby an epithelial cell undergoes biochemical changes that renders a mesenchymal cell phenotype. This transition is facilitated by the loss of epithelial markers E-cadherin and catenins. Epithelial cells, which are normally anchored to the basement membrane, begin to adopt migratory capacity, increased resistance to apoptosis, invasiveness, and an increased production of the extracellular matrix components [64]. Thus, the role of EMT has largely been recognized in embryogeneis and or-

gan-specific tissue differentiation. However, these cellular pathways have also been recognized in tissue repair and pathological stresses. EMT is then categorized into 3 types: type 1 in embryogenesis and organ development, type 2 in fibrosis and tissue remodeling, and type 3 in tumor growth and proliferation [65]. EMT is associated with chronic inflammation and it has been proposed to play a role in fistula formation, a complication of Crohn's disease (CD). When intestinal epithelial cells are triggered to undergo EMT, they convert into transitional cells (TC) and line at CD fistulas [29]. Since these cells are only present in CD patients, the EMT must play a critical role in CD pathogenesis. Fistula formation is further complicated by bacterial involvement, which triggers endogenous induction of EMT [66]. Muramyl dipeptide (MDP), a bacterial cell wall component, has been demonstrated to trigger expression of TGF-β, SNAIL1, and IL-13 in fistulas [67]. These transcription factors have also been shown to enhance the EMT response.

6.2. Implications in Hidradenitis Suppurativa Disease Pathogenesis

Hidradenitis suppurativa (HS) is a chronic inflammatory disease characterized by immune system dysfunction and inflammation of sweat glands across the body. Although the pathogenesis of HS is not fully understood, important associations have been identified that suggest EMT plays a key role. Flora *et al*. (2023) found altered gene expression of SNAI2 and altered protein expression of ZEB1, TWIST1, Snail/Slug, E-Cadherin and N-Cadherin in HS lesional tissue [68]. These aforementioned transcription factors are upregulated during EMT, suggesting an upregulation of pro-inflammatory fibroblasts after epithelial differentiation. Furthermore, studies have found that hepatocyte growth factor (HGF), which is overexpressed by HF fibroblasts, is a trigger for the activation of EMT-associated pathways and genes [69]. HS tunnel lesions have also been found to contain HGF-induced genes [70]. This stimulation of the EMT pathway in patients with HS highlights the importance of EMT in disease pathogenesis. Similar to CD, we observe the migration of differentiated epithelium to inflammatory pathways, leading to chronic lesion formation. These cell processes are then further propagated by the release of inflammatory cytokines and transcription factors.

6.3. Potential Treatments and Therapeautic Targets

Due to the established relationship between the epithelial-mesenchymal transition and inflammatory cell processes in diseases like hidradenitis suppurutiva and Crohn's diesease, it has been identified as a potential target for clinical therapy. The majority of studies targeting EMT for therapeutic treatment have been centered about the slowing of tumorigenesis. Unfortunately, EMT has been found to resist various forms of treatment, including chemotherapy and radiotherapy, through avoidance of apoptosis and increased drug efflux [71] [72]. Still, three main strategies have been identified for EMT therapy: blocking upstream signaling pathways of tumorignesis (e.g. TGF-β), targeting EMT transcription factors,

and targeting mesenchymal cells or outer stroma [73]. One study looked at resveratrol, a natural polyphenol compound that reverses EMT by targeting the hedgehog/Gli-1 signaling pathway. Via inhibiting Gli-1, resveratrol downregulates Snail and N-cadherin expression, while restoring E-cadherin expression [74]. This change reverses some of the biochemical alterations that epithelium undergo during EMT, rendering the cells less active.

Several studies have identified potential therapeutic targets for hidradenitis suppurutiva. Flora *et al*. (2023) found that fostamatinib, a spleen tyrosine kinase inhibitor, significantly reduced fibrosis, inflammatory, and EMT-associated genes and pathways in hidradenitis suppurativa after 4 weeks of therapy. These changes were attributed to downregulation of pathways associated with chronic inflammatory response, TGF-β, and fibroblast proliferation. For CD, infliximab, an anti-TNF agent, has been indicated for use in fistulizing disease [75]. Moreover, a global consensus was reached in 2014 that established anti-TNF therapy in conjunctoin with thiopurine for superior healing and closure of fistulas as compared to monotherapy alone [76]. Another therapeutic invertion for CD is targeting of the TGF-β pathway. A systematic review by Bettenworth and Rieder (2014) found that the anti-TGF agents fresolimumab and avotermin were successful in reducing the deleterious effects to other organs of the body, such as the kidney, lung, and skin. Jiang, Shen, & Ran (2018) also proposes the blocking of β6-integrin for the treatment of CD, a downstream molecule controlled by TGF-β, however, this intervention still requires further research. Although there are potential drugs that show promise for the inhibition or reversal of EMT, further research is required into the therapeutic benefit for patients with HS and CD [77].

7. Management Strategies and Future Directions

Management of patients with both perianal Crohn's disease and follicular occlusion disorders demands coordinated multidisciplinary care. Dermatologists, gastroenterologists, colorectal surgeons, radiologists, and wound care specialists each bring vital expertise to address the multifactorial nature of these diseases [78]. Diagnostic accuracy improves significantly with integrated care. Both HS and pCD can present with perianal abscesses and draining sinuses, leading to diagnostic confusion (Griffiths *et al*., 2024). In collaborative settings, gastroenterologists may detect signs of systemic disease, while dermatologists can distinguish HS-specific lesion distribution and morphology [28]. Imaging modalities like pelvic MRI further assist in differentiating between CD fistulas and HS tunnels, as CD tends to involve the rectal wall, whereas HS is more superficial and bilateral [28].

Surgical intervention is often necessary in both diseases, particularly for abscess drainage and fistula management. Colorectal surgeons play a critical role in managing perianal sepsis and placing setons, while dermatologic surgeons may perform unroofing or wide excision of HS tunnels [32]. Proper timing of surgery during immunological quiescence—achieved through biologic therapy—requires close collaboration between medical and surgical teams [3]. Biologic therapy is

central to management. TNF-α inhibitors such as infliximab and adalimumab have demonstrated efficacy in both pCD and HS, though treatment must be individualized (Martínez *et al*., 2001; Yamanaka, 2024). Multidisciplinary teams can better monitor response to treatment and adjust regimens when standard therapies fail [1]. Emerging biologics targeting IL-17, IL-23, and IL-36 pathways may offer new therapeutic avenues [78]. Wound care specialists are vital for managing chronic non-healing wounds resulting from sinus tracts or post-surgical excisions. Negative-pressure wound therapy, antimicrobial dressings, and patient education can reduce recurrence and promote healing [41]. In conclusion, multidisciplinary collaboration enables earlier diagnosis, more precise treatment planning, and improved long-term outcomes. Given the overlapping pathophysiology and therapeutic needs of pCD and FODs, integrated care models should become the standard for managing this dual disease burden.

An important therapeutic target for managing patients with HS or pCD is inhibition of TNF-α, which has greatly reduced incidence [1]. Inhibiting TNF-α blocks several pro-inflammatory processes including production of cytokines (IL-1, IL-6, and IL-8), adhesion molecules, and acute phase reactants, all of which contribute to the destructive nature of these diseases [79]. For patients with HS, adalimumab is currently the preferred anti-TNF agent [80]. For patients with pCD, infliximab is the first-line anti-TNF agent, but adalimumab has been shown to be efficacious as well [3]. Unfortunately, even with targeted anti-TNF therapies, some patients with HS or pCD do not improve, which has led to the exploration of other biologics for treatment. Several target molecules are under investigation for future HS treatment such as IL-17, IL-23, and IL-36, as they play a significant role in the perceived pathogenesis [78]. Likewise, studies exploring future management options for pCD are underway, with promising results seen with treatments targeting IL-12 and IL-23, as well as $\alpha 4\beta 7$ integrin [3]. Despite the large body of existing literature on the treatment of HS and pCD as individual entities, there has yet to be a standardized treatment option for patients who harbor both diseases simultaneously. There is increasing evidence that the anti-TNF agent, infliximab, is the preferred choice for managing HS and pCD together [1]. When both conditions co-exist, multimodal treatment options should be discussed between a gastroenterologist, dermatologist, and surgeon, to optimize medical or surgical management to improve patient outcomes. Further research on this complex interplay of HS and pCD is needed to elucidate the optimal treatment plan for patients.

Although significant strides have been made in understanding perianal Crohn's disease (pCD) and follicular occlusion disorders (FODs) independently, the intersection of these two chronic inflammatory conditions remains largely underexplored. The co-occurrence of pCD—particularly its fistulizing phenotype—and hidradenitis suppurativa (HS), the most severe form of FODs, presents a complex clinical challenge. Yet, despite mounting evidence supporting shared inflammatory pathways, there is a paucity of high-quality research specifically addressing

patients with both conditions. Several critical gaps in knowledge must be addressed to improve patient outcomes and guide evidence-based care.

Limitations of Current Literature

Most existing studies investigating the association between pCD and HS are retrospective in design, derived from single-center experiences or claims-based databases with limited granularity. These studies often suffer from small sample sizes, heterogeneous diagnostic criteria, and lack of control groups, which restricts the ability to generalize findings or draw firm causal conclusions [9] [32]. Furthermore, the overlap in clinical presentation—particularly in the perianal region—can lead to misclassification and underdiagnosis, contributing to the underrepresentation of dual disease in both dermatology and gastroenterology literature [1].

There is also a lack of standardized disease severity scoring systems for coexisting pCD and HS. Tools such as the Hidradenitis Suppurativa Clinical Response (HiSCR) or the Perianal Disease Activity Index (PDAI) are not designed to assess the burden of dual disease, further complicating efforts to monitor disease progression or evaluate treatment response.

The Need for Natural History and Biomarker-Driven Studies

A major unmet need lies in characterizing the natural history of patients with coexisting HS and perianal CD. Longitudinal cohort studies are essential to determine whether patients with one disease are at increased risk of developing the other, whether co-occurrence portends a more aggressive phenotype, and how treatment outcomes differ compared to isolated disease.

Moreover, there is an urgent need to identify and validate predictive biomarkers that can inform early diagnosis, stratify patients by disease risk or severity, and guide therapeutic selection. Genetic markers such as NOD2/CARD15 mutations in Crohn's disease and NCSTN or PSENEN mutations in HS suggest shared pathogenic underpinnings [14] [15]. Cytokine profiling—particularly involving TNF-α, IL-1β, IL-17, and IL-23—has also revealed promising targets that may serve as both biomarkers and therapeutic endpoints [11]. Similarly, alterations in the gut-skin microbiome axis present a frontier for exploration, with dysbiosis playing a role in perpetuating inflammation across both organ systems [58].

Addressing Therapeutic Ambiguity

Despite anecdotal evidence supporting the use of anti-TNF therapies like infliximab and adalimumab in both pCD and HS, no clinical guidelines currently exist for the management of dual disease. There is limited understanding of when to initiate treatment, which agents to prioritize, and how to adjust therapy when one disease improves while the other persists. This therapeutic ambiguity places patients at risk for suboptimal outcomes and may delay timely escalation of care.

Prospective clinical trials specifically designed to evaluate patients with overlapping disease are critically needed. These studies should investigate not only the efficacy of biologics targeting TNF-α, IL-17, and IL-23, but also the role of combination therapy, timing of surgical intervention, and adjunctive wound care strategies. Furthermore, inclusion of patient-reported outcomes will be vital

to assess the multidimensional impact of these diseases on quality of life.

Unlocking the Promise of Personalized Medicine

Precision medicine holds transformative potential in addressing the complexities of coexisting HS and pCD. Advances in transcriptomic profiling have already delineated immunologic subtypes of Crohn's disease, with implications for therapeutic responsiveness and long-term prognosis [47]. Applying similar multi-omics strategies to HS may reveal immune signatures that identify patients at risk for more severe or treatment-resistant disease. The integration of genetic, epigenetic, microbial, and clinical data—leveraged through artificial intelligence—could facilitate personalized treatment algorithms that dynamically adapt to a patient's evolving disease profile. Moreover, personalized approaches could help predict adverse reactions, optimize medication dosing, and reduce healthcare costs by avoiding ineffective therapies. Future research should focus on validating these models in real-world populations and developing accessible tools for their implementation in routine clinical practice.

8. Conclusion

The intersection of perianal fistulizing Crohn's disease (pCD) and follicular occlusion disorders (FODs), such as hidradenitis suppurativa (HS), represents a clinically significant yet under-recognized inflammatory overlap with profound implications for patient outcomes. These conditions share converging pathogenic mechanisms, including genetic susceptibility, immune dysregulation, epithelial barrier dysfunction, and microbial imbalance. Despite these observations, current clinical frameworks lack standardized tools for diagnosing and managing this dual disease phenotype. Therapeutic ambiguity, absence of validated biomarkers, and a scarcity of prospective studies hinder the development of evidence-based treatment algorithms. Future research must prioritize interdisciplinary collaboration and precision-based approaches to address these knowledge gaps. Large-scale, prospective studies that integrate genetic, immunologic, and microbiome data are essential to understand the natural history of coexisting disease and guide targeted therapeutic interventions. The recognition of pCD and FODs as intersecting components of a broader inflammatory spectrum demands a paradigm shift in how these diseases are studied and treated.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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