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Exploring the relationship between adipokines, cytokines, and *Clostridium* bacteria in the pathogenesis of cancrum oris

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Cancrum oris (noma) is a rapidly progressing, necrotizing orofacial infection that primarily affects malnourished children in impoverished regions. It begins as a gingival inflammation and advances to severe tissue destruction, often leading to facial disfigurement and high mortality rates. We investigate the interplay of adipokines, cytokines, and *Clostridium* bacteria in the pathogenesis of cancrum oris to identify their roles in disease progression and potential therapeutic targets. This case-control study (September 1, 2024 – February 1, 2025) at Al-Habboubi Teaching Hospital and Nasiriyah General Hospital included 150 cancrum oris patients (60% males, 40% females) and 75 healthy controls. *Clostridium* spp. were isolated using blood, MacConkey, and anaerobic agar, identified via biochemical tests, and quantified by colony counting. The study analyzed socio-demographic, adipokine, cytokine, bacterial load, hematological, and clinical parameters in cancrum oris patients and healthy controls. Patients had significantly lower socioeconomic status and higher malnutrition rates. Leptin and resistin were elevated, while adiponectin was reduced in patients. Cytokines (TNF-α, IL-6) were higher, while IL-10 was lower. *Clostridium perfringens* was significantly present in patients. Blood tests showed anemia, leukocytosis, and thrombocytosis. Oral ulceration (96%) and pain (89%) were the most severe symptoms. Cancrum oris is strongly associated with altered adipokine and cytokine levels, increased *Clostridium perfringens* load, and significant hematological changes, indicating immune dysregulation and severe infection. Elevated leptin and resistin suggest metabolic imbalance, while reduced adiponectin and IL-10 indicate impaired anti-inflammatory response, contributing to disease severity and tissue necrosis.

Keywords: cancrum oris; adipokines; cytokines; *Clostridium perfringens*; inflammation; metabolic imbalance.

Introduction

Cancrum oris (noma) is a fatal and aggressive infectious disease mainly affecting underprivileged children with poor access to care. It is characterized by the development of necrotizing ulcers that generally originate in the oral cavity and extends to adjacent soft tissues, resulting in considerable facial deformities (Farley et al., 2021). Without rapid medical treatment, the illness can lead to serious, potentially deadly complications. While the exact mechanisms involved in the pathogenesis of cancrum oris remain elusive until today, recent studies have begun to shed light on the complex interplay involved in the role of adipokines, cytokines and recurrent *Clostridium perfringens* infections more than 3–4 weeks prior to the development of cancrum oris (Gebretsadik & de Kiev, 2022; Onu et al., 2023).

Watchtower adipose tissue releases bioactive mediators known as adipokines, that play a role in pathophysiological processes including inflammation, immunity, and metabolism. Specifically, three major adipokines leptin, adiponectin and resistin, have garnered great attention with regard to inflammatory diseases. Leptin was first described as an adipose tissue-derived hormone, which is involved in regulation of appetite and energy homeostasis, however newer information demonstrated that leptin is playing a significant role in inflammation as well as in immune response (Al-Mansoori et al., 2021).

Hyperleptinemia is correlated with excessive production of pro-inflammatory cytokines, which exacerbates tissue injury. However, leptin's role in the inflammatory cascade associated with cancrum oris may promote the evolution of the disease by stimulating the production of pro-inflammatory cytokines and the recruitment of effector cells into the wound bed, thus contributing to tissue destruction (James et al., 2021; Ren et al., 2022).

Another adipokine, adiponectin, is seen as a protective factor because of its anti-inflammatory effects. It plays a role in regulating immune responses by inhibiting the secretion of pro-inflammatory cytokines (e.g., TNF-α and IL-6) and increasing the production of anti-inflammatory molecules (e.g., IL-10). However, regarding cancrum oris, adiponectin may have a dual action, where the protective effects may be obscured by the host reaction of inflammatory response to the aggressive virulence of *C. perfringens* infection and other contributory elements such as malnutrition and immunosystem dysfunction (M'bondoukwé et al., 2022).

The interplay/adiponectin-resistin versus leptin is one of the determinants of the inflammatory milieu and the metabolic path of obese subjects affected by this tragic disease Resistin is another adipokine which has proven to be promising in the holistic inflammation of obesity, and is known to promote secretions of pro-inflammatory cytokines. Individually, resistin can be involved in the inflammatory response in cancrum oris by releasing TNF-α, IL-6 and IL-1β cytokines which play a role in tissue destruction and pathogenesis (Otto et al., 2021). The pro-inflammatory mediators are significant to the pathogenesis of cancrum oris, which induces vascular permeability and leukocyte infiltration and tissue destruction, which are typical of necrotizing infections. Another important participant in the immune response is cytokines, which are important mediators of inflammation, immune effector activities as well as tissue repair. Tumor necrosis factor-alpha (TNF-α), a key pro-inflammatory cytokine is linked to the mechanisms of pathogenesis of a number of infectious and inflammatory diseases such as cancrum oris (Farley et al., 2021).

TNF-α is among the most significant mediators of tissue damage and inflammation, and its significantly elevated concentrations are generated in response to infection and may cause increased tissue necrosis which aggravates the disease. The other essential pro inflammatory cytokine that is also under the same regulation is interleukin-6 (IL-6) that is a part of both innate and adaptive immune reactions. IL-6 is used to stimulate the acute-phase reactions, stimulate the increase of immune cells, and increase the production of other pro-inflammatory cytokines. In fact, IL-6 levels are very high in cancrum oris, which also has a role in systemic inflammatory response, facilitating tissue destruction and spreading the infection (Gezimu et al., 2022). The most common organism involved with necrotizing soft tissue infections, that which is responsible for cancrum oris, is *Clostridium perfringen*s (Adesola et al., 2024). This bacterium secretes various virulent toxins like alpha-toxin, which rapidly lyse tissues through cytolysis, inflammation and impaired perfusion. Sometime during all this coming and going, provisions are taken to manage the inflammatory response, and infection with *C. perfringens* only adds fuel to the inflammatory fire, triggering the release of pro-inflammatory cytokines feeding the systemic sympathetic inflammatory cascade. Bacterial toxins could also further induce the secretion of adipokines (e.g. leptin, resistin, adiponectin), thus aggravating the complexity in the immune response and the damage to the tissue (Bhat et al., 2024; Alasi et al., 2025). A dynamic forest fire is forged between adipokines, cytokines, and *C. perfringens* to generate subcutaneous inflammation and immune response contributing to the pathogenesis of cancrum oris. Excessive inflammatory cytokinocytokines, including TNF-α and IL-6, are also elevated in patients and the altered profile of adipokines, such as increase in leptin and resistin, maintain the inflammation cascade, leading to massive tissue necrosis and severe mutilation (Li et al., 2021). Conversely, the anti-inflammatory effects of adiponectin and IL-10 do not appear sufficient to stanch the acute dysregulated inflammatory response seen in severe polymicrobial infection. In addition, a better understanding of these interactions may ultimately lead to better therapeutic strategies for cancrum oris and similar infections, and also have implications for the management of obesity-mediated inflammatory diseases and bacterial infections in senior populations and immunocompromised patients (Reethega et al., 2021; Fu et al., 2022).

Materials and methods

The human ethics committee gave consent to the protocol of the study. The participants were thoroughly briefed on the aims and methods of the study and informed consent obtained in writing before the research. The confidentiality of participants and their data privacy were scrupulously observed throughout the research according to the principles of ethical research and the Declaration of Helsinki.

This case-control study was conducted from September 1, 2024, to February 1, 2025, at Al-Habboubi Teaching Hospital and Nasiriyah General Hospital. The sample population consisted of 150 patients with cancrum oris (60% males, 40% females) who were examined by specialist physicians as well as a control group of 75 healthy participants (40 males and 35 females). Participants had to have newly diagnosed cancrum oris and be between the age of 5 and 18 years with the inclusion criteria and exclusion criteria; those with autoimmune disease, recent antibiotic use, or systemic infections. Informed consent was obtained, and ethical approval acquired prior to blood collection. ELISA kits were used to measure leptin (ng/mL), adiponectin (µg/mL), resistin (ng/mL), TNF-α (pg/mL), IL-6 (pg/mL), and IL-10 (pg/mL) as per the instructions of the manufacturer (Biotechne, USA). The parameters of complete blood count (CBC) such as hemoglobin (g/dL), white blood cells ($x10^3/\mu L$) and platelets ($x10^3/\mu L$) were evaluated by Sysmex (Germany) automated analyzer. The isolation of bacteria was conducted on necrotic tissue samples based on blood agar, MacConkey agar and anaerobic agar in suitable conditions at 37 °C, 24–48 hours in aerobic and anaerobic conditions. The identification of *Clostridium* species was performed by gram staining, biochemical tests (catalase, oxidase and lecithinase tests) and anaerobic growth patterns. The bacterial load (CFU/g) was determined by serial dilution and spread plating, followed by colony counting. Data were analyzed to evaluate the correlation between adipokines, cytokines, bacterial presence, and disease severity.

Statistical analysis is often used to analyze quantitative data, and provides methods for data description, simple inference for continuous and categorical data. The procedure involves the collection of data leading to test of the relationship between two statistical data sets. In this study, all data are presented as frequency and percentage. We used SPSS (version 26) and the dependent t-test (two-tailed) and independent t-test (two-tailed) for variables that had a normally distributed distribution. For variables that did not have a normally distributed distribution, we used the Mann-Whitney U test, the Wilcoxon test, and the Chi-square test. P < 0.05 was seen as statistically significant.

Results

The results shown in Table 1 showed the analysis of the socio-demographic characteristics of the study participants, where the mean age ± standard deviation in the group of patients with cancrom auris was (10.5 ± 4.1) compared to the healthy group (11.0 ± 3.5) without statistically significant differences (P = 0.38). As for the distribution by gender, the percentage of males in the group of patients was 60% and females 40%, compared to the healthy group in which the percentage of males and females was equal (50%), without statistical differences (P = 0.24). As for the socio-economic status, it showed statistically significant differences in favor of the group with low social status (P = 0.01). Finally, a significant increase in malnutrition rates was observed among cancrom oris patients (42%) compared to the healthy group (15%), with strong statistical significance (P < 0.001).

Table 1
Sociodemographic characteristics
between cancrum oris patients and healthy controls

Characteristic	Cancrum oris group (n = 150)	Healthy control group (n = 75)	P-value
Age (mean ± SD)	10.5 ± 4.1	11.0 ± 3.5	0.38
Male, %	60	50	0.24
Female, %	40	50	0.24
Socioeconomic status, %	low	low	0.01
Malnutrition, %	42	15	< 0.001

The results displayed in Table 2 showed the levels of adipokines in the two groups of cancrom oris patients and healthy controls. The mean level of leptin in the patient group was (24.1 ± 5.9 ng/mL) compared to the healthy group (15.3 ± 4.1 ng/mL), with a statistically significant difference (P < 0.001). For the adiponectin level, the mean was lower in the patient group (6.5 ± 1.8 µg/mL), compared to the healthy group (9.8 ± 2.3 µg/mL) with statistically significant differences (P < 0.001). The resistin level was significantly higher in the patient group (17.2 ± 4.4 ng/mL) than the control group (10.2 ± 3.1 ng/mL) (P < 0.001).

Table 2
Comparative analysis of leptin, adiponectin, and resistin
in cancrum oris and control groups

Adipokine	Cancrum oris group (n = 150)	Healthy control group (n = 75)	P-value
Leptin, ng/mL	24.1 ± 5.9	15.3 ± 4.1	< 0.001
Adiponectin, µg/mL	6.5 ± 1.8	9.8 ± 2.3	< 0.001
Resistin, ng/mL	17.2 ± 4.4	10.2 ± 3.1	< 0.001

Cytokine levels in both the group with cancrum oris and healthy controls are presented in the Table 3 results. In the patient group, the mean level of tumor necrosis factor alpha (TNF-α) was 35.6 ± 8.2 pg/mL and in the healthy group 18.2 ± 5.3 pg/mL, and the difference was statistically significant (P < 0.001) Interleukin-6 (IL-6) level was also found to be significantly higher in the patient group (20.4 ± 6.3 pg/mL) compared to the healthy group (9.7 ± 2.5 pg/mL, P < 0.001). Interleukin-10 (IL-10) was significantly decreased in the patient group (7.8 ± 2.1 pg/mL) compared to the healthy group (10.2 ± 2.7 pg/mL, P = 0.03). These findings mirror the alterations in cytokine levels accompanying cancrom oris disease.

The results shown in Table 4 demonstrated the assessment of the bacterial load of *C. perfringens* in the cancrum oris group of patients and healthy controls. The pathogenic load of *C. perfringens* was observed in the patient group was statistically significant higher ($3.2 \times 10^5 \pm 1.5 \times 10^4$ CFU/g); no load was detected in the healthy control group (P < 0.001). Moreover, total bacterial load was ($2.9 \times 10^6 \pm 1.3 \times 10^5$ CFU/g) in the patient group while it was ($1.2 \times 10^3 \pm 0.4 \times 10^2$ CFU/g) in the healthy control group, which was highly statistically significant (P < 0.001). These data illustrate the magnitude of the increased bacterial burden caused by cancrum oris.

Table 3
Comparison of TNF-α, IL-6, and IL-10 levels in cancrum oris and control groups

Cytokine	Cancrum oris group (n = 150)	Healthy control group (n = 75)	P-value
TNF-α, pg/mL	35.6 ± 8.2	18.2 ± 5.3	< 0.001
IL-6, pg/mL	20.4 ± 6.3	9.7 ± 2.5	< 0.001
IL-10, pg/mL	7.8 ± 2.1	10.2 ± 2.7	0.03

Table 4
Quantitative analysis of *Clostridium perfringens* and total bacterial load

Bacteria	Cancrum oris group (n = 150)	Healthy control group (n = 75)	P-value
C. perfringens	$3.2 \times 10^5 \pm 1.5 \times 10^4$	undetected	< 0.001
Bacterial load, CFU/g	$2.9 \times 10^6 \pm 1.3 \times 10^5$	$1.2 \times 10^3 \pm 0.4 \times 10^2$	< 0.001

Table 5 compares the blood parameters of the cancrom oris patients and the healthy controls. The mean hemoglobin levels were significantly lower in the patient group (10.2 ± 2.1 g/dL) than in the healthy group (12.5 ± 1.3 g/dL, P < 0.001) respectively. Furthermore, the white blood cell count correlated positively with the patient group ($12.6 \pm 3.8 \times 10^3$/μL) vs. the healthy group($6.8 \pm 2.3 \times 10^3$/μL, P < 0.001). The platelet count was higher in the patient group ($320 \pm 70 \times 10^3$/μL) than in the healthy group ($270 \pm 58 \times 10^3$/μL), with a statistically significant difference (P = 0.04). These findings are consistent with the profound changes in hematological values seen in cancromegaly.

Table 5
Comparison of hemoglobin, white blood cells, and platelet counts in cancrum oris and control groups

Hematological parameter	Cancrum oris group (n = 150)	Healthy control group (n = 75)	P-value
Hemoglobin, g/dL	10.2 ± 2.1	12.5 ± 1.3	< 0.001
White blood cell, $\times 10^3$/μL	12.6 ± 3.8	6.8 ± 2.3	< 0.001
Platelets, $\times 10^3$/μL	320 ± 70	270 ± 58	0.04

Patient clinical symptoms for the cancrum oris patients are depicted in Table 6. The most frequently reported symptom was oral ulceration (96%) which was the most severe (7.1 ± 1.3). Next was swelling of the face with 85% incidence and moderate severity (6.4 ± 1.0). Fever was observed in seventy-two percent with a mean severity of (5.2 ± 0.9). Mouth pain was recorded in 89% with a mean severity of (7.6 ± 1.2). These results show that oral ulceration and pain in the mouth were the most serious and common symptoms among the patients.

Table 6
Frequency and severity of key symptoms

Symptom	Cancrum oris group (n = 150), %	Frequency, %	Severity (mean ± SD)
Oral Ulceration	96	high	7.1 ± 1.3
Swelling (Face)	85	moderate	6.4 ± 1.0
Fever	72	moderate	5.2 ± 0.9
Pain in Mouth	89	high	7.6 ± 1.2

Discussion

The findings of this study as far as the significant association of malnutrition, low socioeconomic status, and cancrum oris are concerned are concurrent with several studies which point to the pathogenesis of the disease by virtue of the above-mentioned factors. For example, Chukwuma et al. (2021) and Bala et al. (2024) demonstrated that there is a strong association between low socioeconomic status and increased cases of cancrum oris because of limited access to nutrition and health care, thus increasing the risk for serious infections such as those of *C. perfringens* (Chukwuma et al., 2021; Bala et al., 2024). Furthermore, the high percentage of malnutrition in the cancrum oris group in the current study (42%) also supports the results of Adeniyi et al. (2019), who connected malnutrition with greater susceptibility to infections. The only variation found was in the sense of the variables, illustrated by age and sex (Adeniyi & Awosan, 2019). Although no significant differences in age or sex could be identified between the cancrum oris and healthy controls groups in this study, studies such as O'Brien et al. (2019) reported a male predominance, which may be related to differences in environmental exposure or immune response (O'Brien, 2019).

As for age, a few studies suggest that the disease tends to affect younger children, particularly those under the age of 10, whose immune systems are still developing. This discrepancy may be due to different age groups in different studies (Braun et al., 2020). Dominic et al. (2022) highlighted a slight predominance of males and did not reveal any gender differences, supporting previous findings that malnutrition and other health-related aspects may characterize risk of the disease better than gender alone. Although there are some contradictory data present in the literature, the general trends demonstrated in the current study correlate well with already established knowledge regarding the significance of socioeconomic factors, particularly malnutrition, in the pathogenesis of cancrum oris, therefore reinforcing the importance of health care and nutritional intervention in this population (Dominic et al., 2022).

The data in Table 2 have shown a highly statistical significance (P < 0.001) between the levels of leptin, adiponectin and resistin measured in cancrum oris patients as compared with controls (healthy subjects). The cancrum oris group had higher levels of leptin (24.1 ± 5.9 ng/mL) and resistin (17.2 ± 4.4 ng/mL) than the healthy control group (15.3 ± 4.1, and 10.2 ± 3.1 ng/mL). In contrast, the cancrum oris group exhibited lower levels of adiponectin (6.5 ± 1.8 μg/mL) than the control group (9.8 ± 2.3 μg/mL). Our findings are in line with multiple studies that have investigated the role of adipokines in other infectious diseases since they play an important role in immune responses and inflammation. The elevated leptin concentration in the cancrum oris group may correlate with the inflammatory process of the disease. Previous studies have shown normal to elevated concentrations of leptin in the serum during systemic inflammation and infection, suggesting that leptin could play a role in the pathogenesis of cancrum oris. Lower levels of adiponectin in the cancrum oris group are in agreement with another study Siffeti et al. (2021), which showed lower levels of adiponectin in individuals suffering from chronic inflammatory disease. Adiponectin has anti-inflammatory, and insulin-sensitizing effects, and its decrease is thought to further aggravate the host susceptibility to infection and impaired repair seen in cancrum oris patients, most especially those who are malnourished (Siffeti et al., 2021). As for resistin, the present results found by us of elevated levels in cancrum oris group were consistent with the results of Zameer et al. (2024) which raised awareness on the role resistin plays in inflammation and its link to infectious pathologies. Resistin is believed to promote both inflammatory and insulin resistance properties; additionally, the increased levels of this compound observed in cancrum oris could patients suggest a systemic inflammatory response or an underlying metabolic altered state (Sambreen et al., 2024).

Levels of inflammatory cytokines TNF-α, IL-6 and IL-10 were significantly different in the cancrum oris group as compared with the healthy control group (Table 3). Cancrum oris patients had significantly higher TNF-α and IL-6 concentrations: cancrum oris TNF-α 35.6 ± 8.2 vs 18.2 ± 5.3 pg/mL; cancrum oris IL-6 20.4 ± 6.3 vs 9.7 ± 2.5 pg/mL (P < 0.05). IL-10 levels were also reduced in the cancrum oris group (7.8 ± 2.1) vs control group (10.2 ± 2.7 pg/mL, P = 0.03). Such results align with the current literature, which indicates a more robust inflammatory response in infectious and chronic inflammatory conditions such as cancrum oris. TNF-a, one of the main pro-inflammatory cytokines, is involved in various inflammation and immune reactions. The higher levels of TNF-α in the cancrum oris group can be foreseen by the results of earlier studies such as Karched et al. (2022), who have reported high levels of TNF-α in patients and are worth noting along with the destruction of the tissues which occur with infectious diseases. TNF-α a major contribution to cancrum oris pathogenesis. The TNF-8 can mediate local inflammation and tissue damage (Karched et al., 2022). There is a correlation of the cancrum oris group and IL-6 levels against levels, which are higher than the levels reported in a study by Otto et al. (2021), which indicated that IL-6 is up-regulated by infections and other inflammatory diseases. One of such pleiotropic cytokines that seem to be relevant in both innate and adaptative immunity, as well as an increase in the level of IL-6, may be associated with the systemic inflammatory response in cancrum oris, particularly, considering the significant tissue damage and the infection involved (Otto et al., 2021). By contrast, although IL-10 levels were not necessarily drastically reduced, lower levels of IL-10 in the cancrum oris group suggest an impaired anti-inflammatory response. IL-10 is a potent anti-inflammatory cytokine that normally modulates the immune response and prevents overinflammation. For example, in cancrum oris, IL-10 levels are diminished, which can lead to dampened control of the inflammation response, continuing the cycle of chronic inflammation and tissue destruction.

The findings found in this study emphasize the complex relationship between pro-inflammatory and anti-inflammatory cytokines in cancrum oris patients. Increased levels of TNF-α and IL-6 indicate a continuing inflammatory response whereas the reduced level of IL-10 suggests a failure of the regulatory response to dampen this inflammation. These results confirm the theory of cancrum oris being mediated through an aberrant immune response with chronic inflammation furthering tissue damage and disease progression.

The levels of TNF-α and IL-6 seen in cancrum oris patients are similar to those found in the literature describing other infectious / inflammatory processes, including periodontal infections and diabetic wounds which also demonstrate increased levels of both of these cytokines. The contrast of high IL-10 levels in chronic inflammatory conditions to other studies may relate to the lower levels of IL-10 found in cancrum oris patients as compared to more common chronic inflammatory diseases, which suggests that these regulatory mechanisms are disrupted in cancrum oris or other chronic diseases (Phillips et al., 2005).

In conclusion, more directed cytokines (TNF-α and IL-6) relative to anti-inflammatory cytokines (IL-10) in pathological tissue, as shown in Table 3, may play an important role in cancrum oris pathogenesis. Also, elevated pro-inflammatory cytokines possibly contribute to tissue destruction and chronic infection, whereas decreased anti-inflammatory response may impair the resolution of inflammation events and promote chronic progression of disease. However, more work will be needed to characterize these cytokine dynamics and their influence on cancrum oris therapeutics. Table 4 shows significantly higher presence and load of *C. perfringens* in the cancrum oris group compared to the healthy control group. *Clostridium perfringens* was isolated at a concentration of $3.2 \times 10^5 \pm 1.5 \times 10^4$ CFU/g in the cancrum oris group and not detected in the healthy control group ($P < 0.001$). Furthermore, total bacterial load was significantly higher in the cancrum oris group (average $2.9 \times 10^6 \pm 1.3 \times 10^5$ CFU/g) than in the healthy control subjects ($1.2 \times 10^3 \pm 0.4 \times 10^2$ CFU/g, $P < 0.001$). These results highlight the possible association of *C. perfringens* in the pathogenesis of cancrum oris, which is a severe, necrotizing disease that primarily involves the soft tissues of the mouth and face. *Clostridium perfringens* is a famous human pathogen, which causes gas gangrene and other destructive infections of tissues and is of significant interest in terms of the analysis of the context of this infection. Such results show a much greater bacterial load and reveal the presence of *C. perfringens* in the cancrum oris group, which demonstrates that the bacteria might contribute to the active process of tissue lesion and exacerbate the disease. The results of those findings are consistent with the literature, one study finding that the levels of *C. perfringens* were high in the tissues involved in infection, the vast majority of which were severe and gangrenous (Schaller, 2009).

The high bacterial load in cancrum oris paients is similar to the results of other studies, which have previously tested the microbial profile of oral and perioral infections such as necrotizing fasciitis or periodontal diseases, in which the high bacterial burden is associated with the severity of the infection and the degree of tissue necrosis. *Clostridium perfringens* is especially dangerous as it is one of the most widespread causative agents in the anaerobic environment because it is able to produce a variety of toxins, such as alpha-toxin, which leads to extensive tissue necrosis and exacerbations of the inflammatory process, which clinically manifests as cancrum oris. This does not disagree with the findings of research done by Finegold et al. (1985), where similar measurements of bacteria load in tissue associated infections were taken (Finegold et al., 1985).

The microbiome of the healthy control group, where *C. perfringens* was not detected, on the other hand, exhibits a much different microbial composition which is normally characterized by a balanced microbiota present in healthy subjects. The fact that the total number of bacteria in the control group ($1.2 \times 10^3 \pm 0.4 \times 10^2$ CFU/g) was significantly lower supports the idea that the high concentration of bacteria is directly related to progression of the disease in the cancrum oris group (Silva et al., 2011). The results reveal the significance of *C. perfringens* in the pathogenesis of cancrum oris and that its observation and higher counts are associated with the intensity of the infection. The findings also suggest that bacterial load is a determinant factor in the tissue destruction which is characteristic of the disease. The comparison of bacterial load in the cancrum oris and control groups was found to not only indicate the microbial etiology of the disease but also indicate that controlling infections was an important therapeutic target. In addition, such findings compare with the research that has been conducted on *C. perfringens* in the context of other infectious diseases that supports its role in the aetiology of the disease and in imposing a high bacterial burden as an adjunctive causative factor of the aggressive manifestation of cancrum oris. *Clostridium perfringens* produces extremely potent toxins to make the process of tissue destruction easier, and controlling its growth and load could be one of the necessary measures to alleviate the severity of the disease and achieve better results (Grobusch et al., 2024).

Our findings suggest, therefore, that both *C. perfringens* and high bacterial load are key players in the pathogenesis of cancrum oris. In conclusion, targeting the microbial burden, which involves designing strategies to counteract pathogenic bacterial species like *C. perfringens*, could emerge as the most promising therapeutic strategy to contain the inflammatory response and tissue damage, paving the way for future exploratory studies (Schneiderman & Grossman, 2022). As shown in Table 6, oral ulceration, facial swelling, fever, and oral pain were commonly and severely observed. Oral ulceration was the most common (96%) and severe (7.1 ± 1.3), and pain in the mouth (89%) was reported with a severity of 7.6 ± 1.2. These results are consistent with other studies (Taori et al. (2024)) which documented high rates of oral ulceration and oral pain in patients with cancrum oris. Our study shows that fevers (72%) were less frequent and moderate, while Todorov et al. (2015) reported higher fever incidence (above 80%) than we did in cancrum oris patients, which might imply that fever is a product of the severity of the infections or the immune response of the individual. In this study, the relatively high severity of such symptoms as oral pain and ulceration is indicative of the debilitating nature of cancrum oris, and the evidence provided by other studies has a high statistical power in indicating that one of the most debilitating effects of the given condition relates to the quality of life of the patient. The frequency and severity of symptoms in this review and other studies can be explained by the sample size, geographical diversities and development of the disease (Todorov et al., 2015).

Conclusion

Cancrum oris is closely associated with dysregulation of the immune system, metabolic imbalance and bacterial infection. The massive rise in the concentration of leptin and resistin and the fall in adiponectin indicate an imbalanced metabolic-inflammatory axis. High TNF-α and IL-6 are signs of an increased inflammatory condition whereas low IL-10 is a sign of poor regulation against inflammation. *Clostridium perfringens* load is high, implying the presence of bacteria in the disease progression. Additional signs of systemic inflammation, such as anemia and leukocytosis, are hematological changes, which lead to tissue necrosis and the general severity of the disease.

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