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Exploring the connection between canker lesions and inflammatory cytokines: Implications for treatment and diagnosis

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Canker lesions are painful ulcerations affecting the oral mucosa, often linked to immune dysregulation. The aim of the study is investigate the relationship between canker lesions and inflammatory cytokines, exploring their potential role in disease progression. This study, conducted at Al-Habboubi Teaching Hospital and Nasiriyah General Hospital, enrolled 200 participants: 75 with diabetes, 75 without diabetes, and 50 healthy controls. Inclusion criteria included adults aged 40–60 years, while exclusion criteria excluded those with autoimmune diseases, immunosuppressive therapy, pregnancy, or recent infections. Blood samples were collected and processed for cytokine analysis (IL-6, TNF-α, IL-10, CRP, adiponectin) using ELISA and metabolic parameters (FBS, cholesterol, triglycerides) using spectrophotometry. Informed consent was obtained from all participants, and ethical approval was granted. The results showed no significant differences in age and gender between diabetic and non-diabetic individuals, while BMI was higher in diabetic patients. IL-6 and TNF-α levels were significantly elevated, whereas IL-10 was lower in diabetics compared to other groups. Diabetics also had higher amounts of CRP and fasting blood sugars, but lower levels of adiponectin. The amounts of total cholesterol, triglycerides, and LDL-C were higher in people with diabetes, while the levels of HDL-C were lower. The differences between diabetic and non-diabetic individuals were significant for all parameters, highlighting the inflammatory and metabolic effects associated with diabetes. Diabetic patients showed increased IL-6, TNF-α, CRP, glucose, and lipid levels, with decreased IL-10 and adiponectin, indicating chronic inflammation and metabolic dysregulation. Elevated pro-inflammatory markers contribute to insulin resistance, while lower adiponectin affects lipid metabolism, increasing cardiovascular risk in diabetes.

Keywords: canker lesions; inflammatory cytokines; oral ulcers; immune response; diagnosis; treatment strategies.

Introduction

Canker lesions, or aphthous ulcers, are common, painful, inflammatory conditions affecting the oral mucosa. These lesions typically appear as shallow, round or oval ulcers with a white or yellow center and a red border. While they are usually self-limiting, their recurrence and discomfort can significantly impair quality of life. The precise mechanisms underlying their onset and recurrence remain unclear; however, recent studies highlight the central role of inflammatory cytokines in their pathogenesis (Sekar, 2023).

This study is among the first to explore the relationship between canker lesions and inflammatory biomarkers such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-10 (IL-10), C-reactive protein (CRP), and adiponectin. These molecules are implicated in the development, severity, and recurrence of aphthous ulcers and may serve as diagnostic markers or therapeutic targets (Balakhane., 2024). Cytokines are small proteins secreted in response to infection, injury, or other immune triggers, playing critical roles in inflammation and immune regulation (Gasmi Benahmed et al., 2021; Rivera et al., 2021). In canker lesions, several key cytokines including IL-6, TNF-α, and IL-10 are involved in the local immune response. Additional markers like CRP and adiponectin may also reflect systemic and mucosal inflammatory activity (Smith & Mintline., 2023).

IL-6 is a multifunctional cytokine involved in immune regulation and the acute-phase response. Elevated IL-6 levels in the blood or tissues indicate active inflammation and have been associated with pain severity in canker lesion patients, making IL-6 a potential biomarker for disease monitoring and treatment planning (Inchingolo et al., 2024; Anwar et al., 2025). Clinically, IL-6 is measured in pg/mL, and its elevated levels in aphthous ulcer cases suggest its importance in mucosal inflammation (Prayoga et al., 2024). TNF-α, another key cytokine, is primarily produced by macrophages and dendritic cells in response to infection or tissue damage. It promotes the expression of other inflammatory mediators and is significantly elevated in patients with canker lesions, contributing to tissue destruction and chronic inflammation (Jang et al., 2021; Romanowska-Próchnicka et al., 2021; Abbas et al., 2025). Measurement of TNF-α in pg/mL may correlate with ulcer size, pain, and duration, and anti-TNF-α therapies may be beneficial in severe or recurrent cases (Mahdi et al., 2024). IL-10, an anti-inflammatory cytokine secreted by T and B lymphocytes and macro-phages, helps suppress excessive inflammation by downregulating IL-6 and TNF-α. Adequate IL-10 levels promote healing, while reduced expression may lead to persistent inflammation and delayed recovery (Mirlekar, 2022; Casu et al., 2025). Increased IL-10 in response to inflammation may represent a regulatory mechanism attempting to resolve the lesion. However, imbalance between high pro-inflammatory cytokines and low IL-10 may exacerbate disease severity.

CRP, synthesized in the liver during systemic inflammation, is widely used to assess inflammatory status. Though usually reported in mg/L, elevated CRP in recurrent ulcer patients may indicate more severe systemic inflammatory responses (van der Houwen et al., 2024). Adiponectin, a protein with anti-inflammatory properties, is inversely related to various inflammatory and autoimmune diseases. Lower adiponectin levels in patients with canker lesions may suggest a heightened inflammatory state, predisposing individuals to ulcer formation or recurrence. This study aims to analyze the involvement of inflammatory cytokines and biomarkers in the pathogenesis of canker lesions and assess their potential as indicators of disease severity, immune modulation, and therapeutic intervention.

Materials and methods

The study was approved by the ethics committee at the Thi-Qar Health Directorate, Al-Habboubi Teaching Hospital, under committee code 387, on January 1, 2024. All participants were fully informed about the study and provided written consent to participate. They were also assured that their personal information would remain confidential.

This study was conducted between January 1, 2024, and March 10, 2025, at Al-Habboubi Teaching Hospital and Nasiriyah General Hospital. A total of 200 participants were enrolled, divided into three groups: 75 people with diabetes, 75 people without diabetes, and 50 healthy controls. Inclusion criteria included adults aged 40–60 years, patients diagnosed with diabetes for at least one year (for the diabetic group), patients without diabetes but with other metabolic disorders (for the non-diabetic group), and healthy individuals without any chronic diseases (for the control group). Exclusion criteria included patients with autoimmune diseases or chronic inflammatory conditions, individuals on immunosuppressive therapy, pregnant or lactating women, and patients with a history of recent infections or acute illnesses. Blood samples were collected from all participants following standard venipuncture techniques under sterile conditions. After collection, the samples were processed by centrifugation to separate the serum, which was then stored at –80 °C for further analysis. Cytokine and inflammatory marker analysis included the measurement of serum levels of IL-6, TNF-α, IL-10, CRP, and adiponectin using ELISA kits (Bio-Techne, USA), following the manufacturer's recommendations. Metabolic parameters, including fasting blood sugar (FBS), total cholesterol, triglycerides, HDL-C, and LDL-C, were assessed using a spectrophotometer according to standard laboratory protocols. Participants were diagnosed by specialist doctors based on clinical evaluation and laboratory tests to ensure accurate group classification. Prior to sample collection, written informed consent was obtained from all participants, and ethical approval was granted by the relevant institutional review board. Researchers involved in the study also provided consent for the collection and use of the samples for the purposes of this investigation.

Statistical analysis is used to describe data and draw conclusions from both continuous and categorical variables. The study data are presented as percentages and frequencies. For normally distributed variables, we used the dependent and independent t-tests (two-tailed). For non-normally distributed variables, we applied the Mann-Whitney U test, Wilcoxon test, and Chi-square test. A significance level of $p < 0.05$ was considered statistically significant.

Results

Comparison of demographic and anthropometric characteristics among diabetic patients, non-diabetic patients, and healthy controls. The results shown in Table 1 indicate no statistically significant differences in the mean age and sex distribution between the three study groups (diabetics, non-diabetics, and healthy individuals), as the P values for all comparisons were > 0.05, indicating the homogeneity of the samples in terms of age and sex. On the other hand, the results showed clear significant differences in the mean body mass index (BMI), with diabetic patients recording the highest value compared to non-diabetics (P = 0.02) and healthy individuals (P < 0.001). A significant difference was also observed between non-diabetics and healthy individuals (P = 0.003). These results indicate a strong association between increased BMI and the development of diabetes, reinforcing the hypothesis that obesity is associated with an increased risk of developing type 2 diabetes.

Table 1
Distribution of age, gender, and body mass index across the three study groups

Variable	Patients with diabetes (n = 75)	Patients without diabetes (n = 75)	Healthy controls (n = 50)	P-value (diabetes vs. controls)	P-value (non-diabetes vs. controls)	P-value (diabetes vs. non-diabetes)
Age, years	50.2 ± 4.1	49.8 ± 3.9	48.5 ± 3.5	0.07	0.12	0.45
Gender (male/female)	40/35 (53.3%/46.7%)	38/37 (50.7%/49.3%)	26/24 (52%/48%)	0.80	0.85	0.72
BMI, kg/m²	30.5 ± 2.8	28.9 ± 2.5	26.4 ± 2.2	<0.001	0.003	0.02

Comparative analysis of pro- and anti-inflammatory cytokine levels in diabetic patients, non-diabetic patients, and healthy controls. The results shown in Table 2 indicate highly statistically significant differences in the levels of the three cytokines (IL-6, TNF-α, and IL-10) between the study groups. Diabetic patients showed significantly higher levels of IL-6 and TNF-α compared to both non-diabetic patients and healthy individuals (P < 0.001), indicating a state of chronic inflammation. In contrast, levels of IL-10, an anti-inflammatory cytokine, were significantly lower in diabetic patients compared to the other two groups (P < 0.001), reflecting a weakened anti-inflammatory immune response. The non-diabetic patients group also showed higher levels of IL-6 and TNF-α and lower levels of IL-10 compared to healthy controls (p < 0.001 for all comparisons), which may indicate the presence of early inflammatory changes associated with prediabetes or metabolic disorders. These findings reflect the important role of inflammatory cytokines in the development of type 2 diabetes and support their use as potential biomarkers for the early detection of metabolic disorders.

Table 2
Serum levels of IL-6, TNF-α, and IL-10 (pg/mL) among study groups

Cytokine	Patients with diabetes	Patients without diabetes	Healthy controls	P-value (diabetes vs. controls)	P-value (non-diabetes vs. controls)	P-value (diabetes vs. non-diabetes)
IL-6	12.5 ± 3.2	9.2 ± 2.8	5.4 ± 1.9	<0.001	<0.001	<0.001
TNF-α	18.3 ± 4.6	14.7 ± 3.9	9.1 ± 2.2	<0.001	<0.001	<0.001
IL-10	3.9 ± 1.1	5.2 ± 1.5	7.8 ± 1.9	<0.001	<0.001	<0.001

Biochemical marker profiles in diabetic patients, non-diabetic patients, and healthy controls. The results presented in Table 3 showed highly statistically significant differences in the levels of fasting blood glucose (FBG), C-reactive protein (CRP), and adiponectin between the three groups. Diabetic patients had the highest mean fasting blood glucose level (156.8 ± 22.3 mg/dL) compared to non-diabetics (98.6 ± 10.2 mg/dL) and healthy controls (92.5 ± 9.8 mg/dL), with significant differences (P < 0.001). A significant increase in CRP levels was also observed in diabetic patients (9.2 ± 2.1 mg/L) compared to the other two groups, reflecting the presence of a chronic inflammatory state associated with diabetes. In contrast, levels of adiponectin, a protein with anti-inflammatory and insulin-sensitizing properties, were significantly lower in the diabetic group (6.8 ± 2.4 ng/mL) compared to the non-diabetic group (10.1 ± 2.8 ng/mL) and healthy controls (13.5 ± 3.1 ng/mL). The non-diabetic group also showed significant differences compared to the healthy controls in all three indicators, suggesting early metabolic and inflammatory changes that may precede the onset of overt diabetes, emphasizing the importance of these indicators as tools for assessing risk and predicting disease progression.

Comparison of serum lipid profiles among diabetic patients, non-diabetic patients, and healthy controls. The results shown in Table 4 indicate clear significant differences in lipid levels between the three study groups. Diabetic patients showed significantly higher mean total cholesterol (210.5 ± 28.6 mg/dL), triglycerides (178.3 ± 35.4 mg/dL), and LDL-C (136.7 ± 22.9 mg/dL) compared to non-diabetics and

healthy controls, with a significantly lower HDL-C level (38.2 ± 6.5 mg/dL). All differences were statistically significant ($P < 0.001$). The non-diabetic group showed a similar but less severe pattern, with higher total cholesterol, triglycerides, and LDL-C levels and lower HDL-C levels compared to healthy controls, with significant differences ranging from $P < 0.001$ to $P = 0.02$. These findings suggest that lipid metabolism disorders are more pronounced in diabetic patients, reflecting what is known as diabetes-associated dyslipidemia. The observed differences in the non-diabetic group also suggest the possibility of early metabolic abnormalities or prediabetes, reinforcing the importance of monitoring lipid markers as risk factors for cardiovascular and metabolic diseases.

Table 3
Levels of fasting blood glucose, C-reactive protein, and adiponectin across study groups

Parameter	Patients with diabetes	Patients without diabetes	Healthy controls	P-value (diabetes vs. controls)	P-value (non-diabetes vs. controls)	P-value (diabetes vs. non-diabetes)
Fasting blood glucose, mg/dL	156.8 ± 22.3	98.6 ± 10.2	92.5 ± 9.8	<0.001	0.01	<0.001
CRP, mg/L	9.2 ± 2.1	6.5 ± 1.8	2.9 ± 1.0	<0.001	<0.001	<0.001
Adiponectin, ng/mL	6.8 ± 2.4	10.1 ± 2.8	13.5 ± 3.1	<0.001	<0.001	<0.001

Table 4
Levels of total cholesterol, triglycerides, HDL-C, and LDL-C (mg/dL) in study groups

Lipid parameter	Patients with diabetes	Patients without diabetes	Healthy controls	P-value (diabetes vs. controls)	P-value (non-diabetes vs. controls)	P-value (diabetes vs. non-diabetes)
Total cholesterol	210.5 ± 28.6	189.4 ± 25.2	175.8 ± 20.9	<0.001	0.02	<0.001
Triglycerides	178.3 ± 35.4	152.6 ± 31.8	120.7 ± 25.5	<0.001	<0.001	<0.001
HDL-C	38.2 ± 6.5	44.1 ± 7.3	52.3 ± 8.1	<0.001	<0.001	<0.001
LDL-C	136.7 ± 22.9	119.4 ± 19.7	105.2 ± 18.4	<0.001	<0.001	<0.001

Discussion

The analysis of Table 1 reveals that there are no statistically significant differences in age and gender among diabetic patients, non-diabetic patients, and healthy controls ($P > 0.05$). This finding aligns with prior research indicating that type 2 diabetes mellitus (T2DM) affects individuals across a wide age range and both genders without significant bias. However, the body mass index (BMI) was significantly higher in diabetic patients compared to both non-diabetic individuals ($P = 0.02$) and healthy controls ($P < 0.001$), suggesting a strong correlation between obesity and diabetes. These findings are consistent with studies that have demonstrated obesity as a major risk factor for T2DM development (Cazzolla et al., 2021). However, other studies suggest that the relationship between BMI and diabetes may be confounded by additional metabolic, genetic, and lifestyle factors. For example, differences in physical activity levels, dietary patterns, and genetic predispositions could influence how BMI contributes to diabetes risk, with some populations showing weaker associations when these factors are controlled (Darjani et al., 2021).

As shown in Table 2, the inflammatory cytokines IL-6 and TNF-α were significantly elevated in diabetic patients compared to healthy controls ($P < 0.001$), while IL-10, an anti-inflammatory cytokine, was significantly lower ($P < 0.001$). These results are in line with earlier research linking chronic low-grade inflammation with the pathogenesis of T2DM, where increased IL-6 and TNF-α levels promote insulin resistance and β-cell dysfunction (Majeed et al., 2020; Ou et al., 2023). Conversely, reduced IL-10 levels reflect impaired anti-inflammatory signaling, which exacerbates metabolic inflammation and further contributes to the progression of diabetes (Hamad et al., 2024; Casu et al., 2025). Although most studies confirm the inflammatory nature of diabetes, some discrepancies, especially regarding IL-10 levels, have been attributed to variability in study population characteristics, disease duration, and cytokine measurement techniques. In some studies, IL-10 levels were found to be unchanged or even elevated, possibly due to compensatory mechanisms, use of anti-inflammatory medications, or differences in the inflammatory phase of the disease (Adejumo et al., 2023; Bernardoni et al., 2024).

Table 2 also shows that non-diabetic patients, potentially in a prediabetic state, had significantly higher IL-6 and TNF-α levels than healthy controls ($P < 0.001$ for both), and significantly lower IL-10 levels ($P < 0.001$). These findings highlight the presence of systemic inflammation even before overt hyperglycemia develops, supporting the idea that inflammatory dysregulation precedes T2DM and could serve as an early biomarker. The elevation of pro-inflammatory cytokines in these individuals suggests that they may be undergoing early metabolic disturbances and insulin resistance, which could evolve into full-blown diabetes over time (Toader et al., 2021). The diminished IL-10 levels in this group also suggest reduced anti-inflammatory capacity, contributing to chronic low-grade inflammation associated with metabolic syndrome (Wu et al., 2018). While IL-6 elevation is commonly reported, some studies show minimal changes in non-diabetic individuals, possibly due to differences in BMI, lifestyle, or genetic predisposition, and some suggest that elevation becomes more prominent only with progression to overt diabetes (Zaid & Al Ramahi, 2019).

According to Table 3, fasting blood glucose (FBG), C-reactive protein (CRP), and adiponectin levels differed significantly across the study groups. Diabetic patients had significantly higher FBG levels than both non-diabetic patients and healthy controls ($P < 0.001$), consistent with diagnostic criteria and indicative of impaired glucose metabolism and insulin resistance. Elevated FBG levels in diabetic patients are a hallmark of β-cell dysfunction and the reduced ability of insulin to regulate glucose uptake, which characterizes T2DM pathophysiology (Panknin et al., 2023). CRP levels were also markedly elevated in diabetic patients ($P < 0.001$), reinforcing the link between systemic inflammation and insulin resistance as well as cardiovascular risk (Panknin et al., 2023). Conversely, adiponectin levels were significantly lower in diabetic patients ($P < 0.001$), echoing evidence of its anti-inflammatory and insulin-sensitizing roles. Reduced adiponectin is associated with increased adiposity, inflammation, and impaired insulin sensitivity, contributing to the chronic metabolic dysfunction seen in T2DM (Das et al., 2024). However, some variability in adiponectin findings across studies is attributed to differences in BMI, genetic background, and adiponectin isoforms (Di Cianni et al., 2024).

In non-diabetic patients, elevated CRP and reduced adiponectin levels compared to healthy individuals ($P < 0.001$ for both) were also observed (Table 3). These patterns support the concept that metabolic derangements linked to inflammation occur before the clinical onset of diabetes. Adiponectin deficiency in this group suggests early insulin resistance and heightened inflammatory responses, aligned with findings on prediabetes and metabolic syndrome. Moreover, the higher CRP levels in this group compared to healthy individuals support findings associating systemic inflammation with early metabolic disturbances and increased risk of glycemic dysregulation (Mena et al., 2023; Lateef et al., 2024). Adiponectin, in particular, plays a vital role in modulating insulin sensitivity, and its decline in non-diabetics may reflect the body's compromised ability to maintain glucose homeostasis (Al-Snafi, 2022; Kaihena et al., 2024). Despite inconsistencies in CRP and adiponectin levels among studies, the current results strengthen their potential as early biomarkers of metabolic dysfunction and predictors of diabetes risk.

Table 4 presents the lipid profile comparison. Diabetic patients exhibited higher levels of total cholesterol, triglycerides, and LDL-C,

and lower HDL-C compared to healthy controls ($P < 0.001$ for all). These alterations, commonly referred to as diabetic dyslipidemia, result from insulin resistance-driven hepatic VLDL overproduction and defective HDL metabolism, contributing to increased cardiovascular risk. Elevated triglycerides and LDL-C levels in diabetics are indicative of disrupted lipid clearance mechanisms and enhanced lipogenesis in the liver due to insulin resistance (Banel & Hu, 2009; Bilgili et al., 2013). Variability in lipid profiles among diabetics may stem from medication use (e.g., statins), dietary habits, genetic predisposition, or comorbid conditions such as obesity or metabolic syndrome. Furthermore, differences in physical activity and glycemic control can also influence the lipid profiles in diabetic individuals, resulting in interstudy differences (Maurya et al., 2009; Mohammad et al., 2024).

In non-diabetic individuals, lipid abnormalities were less pronounced but still significant compared to healthy controls (Table 4), including higher total cholesterol, triglycerides, and LDL-C, and lower HDL-C (P-values ranging from < 0.001 to 0.02). These findings suggest a latent metabolic disturbance possibly linked to prediabetes or insulin resistance. Elevated triglycerides and LDL-C in this group reflect early alterations in lipid metabolism, consistent with previous studies associating such changes with metabolic syndrome and cardiovascular risk. The reduction in HDL-C in non-diabetics compared to healthy individuals may also signify impaired cholesterol efflux and lipid transport, early features of metabolic dysregulation (Norman & Townsend, 2001; Taher & Radhi, 2024). Additionally, these lipid abnormalities further support the hypothesis that dyslipidemia can precede overt diabetes and may serve as a marker for assessing the risk of future cardiovascular events in at-risk populations. The observed trends are consistent with mechanisms of altered lipoprotein metabolism due to insulin resistance, particularly in hepatic lipid processing and HDL catabolism (Linawati et al., 2022).

Conclusion

Diabetic patients exhibited elevated IL-6, TNF-α, and CRP levels, alongside increased glucose and lipid profiles, while IL-10 and adiponectin were significantly reduced. These findings suggest a chronic inflammatory state contributing to insulin resistance through cytokine-mediated disruption of insulin signaling. Elevated TNF-α and IL-6 impair glucose uptake, while reduced IL-10 fails to counteract inflammation. Low adiponectin levels negatively impact lipid metabolism, promoting dyslipidemia and increasing cardiovascular risk. This imbalance highlights the role of inflammation in diabetes progression.

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