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ORIGINAL ARTICLE

Immuno-Role of CCL28 Chemokine and Interleukin-29 in Methamphetamine Users with HSV-1 and Plaque-Induced Gingivitis

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ABSTRACT

Meth mouth is a term for the damage that methamphetamine can do to your teeth and gums. It can also make you more vulnerable to catch infections like herpes simplex virus type 1 (HSV-1). Plaque-induced gingivitis, alongside substance use and viral infection, may modify the levels of local immune mediators, such as CCL28 and interleukin-29 (IL-29). Different things are important for mucosal immunity and protecting against viral infections, although their amounts might change depending on the situation. The study aimed to investigate the immunological roles of CCL28 chemokine and IL-29 in methamphetamine users, both infected and uninfected with HSV-1, as well as in individuals with plaque-induced gingivitis. A case-control study was conducted from November 2024 to May 2025 involving 88 healthy male participants aged 20 to 35 years. The subjects were classified into four categories: healthy controls (n=25), methamphetamine users without HSV-1 (n=22), methamphetamine users with HSV-1 (n=21), and non-drug-using gingivitis patients without HSV-1 (n=20). PerioPaper strips were utilized to obtain samples of gingival crevicular fluid (GCF), which were subsequently analyzed for CCL28 and IL-29 concentrations using ELISA. Bleeding on probing (BOP%) and gingival crevicular fluid (GCF) volume were two clinical metrics. CCL28 levels peaked in healthy persons (420.90 ± 55.86 pg/mL) and decreased gradually in methamphetamine users (380.45 ± 24.80 pg/mL), meth + HSV-1 users (342.56 ± 10.84 pg/mL), and gingivitis patients (306.74 ± 10.34 pg/mL) ($p<0.0001$). IL-29 levels were lowest in healthy controls (205.75 ± 21.59 pg/mL) and highest in methamphetamine users (226.43 ± 4.84 pg/mL), co-infected persons (241.45 ± 4.75 pg/mL), and gingivitis patients (257.14 ± 4.53 pg/mL) ($p<0.0001$).CCL28 and IL-29 levels showed a strong negative correlation in all but the meth-only group. Reduced CCL28 and elevated IL-29 in methamphetamine users and gingivitis patients suggest compromised mucosal defense alongside heightened antiviral signaling. The use of amphetamine plus an HSV-1 infection seem to make these changes in the immune system worse, which could make gum disease worse.

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1- INTRODUCTION

Drug addiction is a long-term illness that makes people want drugs even when they know they are bad for them. It affects not just the person who is addicted, but also their family and community [1]. The health effects of addiction are profound, causing physical and psychological damage across multiple organ systems [2]. Drugs can change how the brain works and how it is built. People who are hooked often have trouble thinking, feel miserable most of the time, and are more likely to get neurological problems. Long-term usage can modify the brain, which can influence how a person makes decisions, controls their impulses, and deals with their feelings. Drugs can also make the immune system weaker, which means that those who use drugs may get sick more often. Drugs like methamphetamine, cocaine, opiates, and alcohol are much more harmful because they are known to weaken the immune system [3]. Methamphetamine, a phenethylamine ($C_{10}H_{15}N$), is a strong stimulant for the central nervous system that can cause a lot of health problems, such as high blood pressure, arrhythmias, and a higher chance of having a heart attack or stroke [4, 5]. Methamphetamine alters the way the brain works and looks, which can lead to problems with thinking, feeling, and a higher risk of neurological illnesses. Long-term drug use also weakens the immune system, which makes it easier for people to get sick [4, 6]. One of the most evident indicators when someone is using meth is that they get "meth mouth [7]. This means a lot of tooth decay, gum disease, and an increased risk of contracting infections. When people use methamphetamine for a long time, they can get a lot of dental problems known as "meth mouth [8]. Because their teeth and gums are diseased, meth mouth patients often lose teeth [9].

Periodontal diseases are infections that affect the tissues that support teeth. They might be as benign as gingivitis, which is inflammation of the gums, or as serious as diseases that can cause tooth loss [10]. Inflammation usually affects gums in gingivitis. If left untreated, it might become periodontitis, which affects tooth base structures [11, 12]. The main cause of gingivitis is the buildup of bacteria on the teeth. Porphyromonas gingivalis and Streptococcus mutans are two important types of bacteria that are linked to cavities [13, 14, 15]. Plaque-induced gingivitis is an inflammatory reaction of the gum tissues caused by the buildup of bacteria at or below the gum line. Managing gingivitis is important for stopping periodontitis, even though it doesn't immediately cause tooth loss [16, 17, 18]. Epidemiological studies show that plaque-induced gingivitis is frequent in people of all ages who have teeth and is thought to be the most common type of periodontal disease [19]. Initial transitions from health to gingivitis may remain clinically undetectable, prompting discussions on clinical limits for differentiating healthy from pathological inflammation. However, as gingivitis gets worse, clinical indications like bleeding while brushing, blood in saliva, puffiness, redness, and bad breath become clear. The intensity of these symptoms differs among individuals and locations inside the oral cavity [20]. Common signs include erythema, edema, bleeding, tenderness, and enlargement [16]. Some things that can cause this are tooth anatomy, restorations, and endodontic problems. Radiographs or probes usually do not demonstrate that supporting structures are missing. Histologically, abnormalities include the elongation of rete ridges, vasculitis, collagen degradation, fibroblast modifications, and an infiltration of immune cells. Research has found various bacterial phylotypes associated with gingivitis; however, further investigations are required to elucidate its microbial community. Gingivitis has not changed at all since it was first classified in 1999. It is still a disease that is caused by plaque on the teeth. Recent studies have investigated the gingival transcriptome concerning inflammation, emphasizing the translation of mRNA into proteins [21]. Important alterations in transcription include interactions between host and bacteria, chemotaxis, phagocytosis, cytokine signaling, T cell activation, angiogenesis, and the immune response of epithelial cells [22].

Herpes simplex virus type 1 (HSV-1) is a major contributor to several oral health issues, including gingival disorders [23, 24, 25]. Evidence indicates that HSV-1 infection may aggravate plaque-induced gingivitis, especially in instances of herpetic gingivostomatitis, where the viral infection occurs concurrently with bacterial plaque buildup [26]. Plaque-induced gingivitis is an inflammatory disorder caused by bacterial biofilm on teeth; however, when worsened by HSV-1, the severity of gingival inflammation may rise. In certain instances, gingivitis may manifest with exacerbated symptoms, including pronounced erythema, edema, and painful ulcerations on the gingiva, with the typical indicators of plaque-induced gingivitis, such as hemorrhage, discomfort, and swelling [24]. When germs or viruses get into the body, it releases cytokines and chemokines that make things swell [23]. If you don't treat gingivitis, it can cause long-term inflammation that damages tissue and is bad for your health in general. Neutrophils are very important for controlling infections during periodontal disorders. They collaborate with macrophages and T-cells, which modulate immune responses. Long-term inflammation caused by periodontal disease can damage tissues and have implications on the whole body that affect health [27]. Methamphetamine changes the way important immune mediators are made, which are important for keeping mucosal immunity strong. This disturbance makes problems like gingivitis worse by making it harder for the immune system to fight against

germs [28]. A significant correlation exists between IL-29 levels and probing pocket depth (PPD), clinical attachment level (CAL), and gingival index. IL-29 increased concomitantly with the escalation of pocket depth and attachment loss. An increased presence of herpesviruses in deeper pockets may elevate IL-29 production [25]. The infection with HSV-1 in the skin elevates the expression of IL-29. When macrophages and dendritic cells are infected with HSV-1, they make more IL-29, which makes the immune response stronger against the virus. IL-29 might be able to help with HSV-1 [29]. Mouth epithelial cells produce CCL28, which attracts immune cells to maintain mucosal immunity. It effectively fights Streptococcus mutans, Staphylococcus aureus, and Candida albicans. CCL28 in salivary glands appears to protect oral health by boosting the innate immune system [30]. This study examined the immunological roles of the chemokine CCL28 and interleukin-29 (IL-29) by measuring their concentrations in gingival crevicular fluid from methamphetamine users, with and without HSV-1 infection, and from patients with plaque-induced gingivitis, using healthy controls for comparison. It focused on how methamphetamine use either alone or alongside HSV-1 infection as well as non-drug-related gingivitis, influences mucosal immune mediators and local defense mechanisms. The study also assessed whether CCL28 and IL-29 levels correlated with clinical measures, including bleeding on probing and GCF volume, to evaluate their potential as biomarkers for tracking disease progression in drug- and virus-associated oral conditions.

2- MATERIALS AND METHODS

2.1 Study Design

The study was designed as a case–control study and included 88 male participants aged between 20 and 35 years, recruited from dental clinics and specialized healthcare centers from November 2024 to May 2025. The subjects were divided into four groups: healthy control group (n = 25) with no history of systemic or periodontal disease, methamphetamine users without HSV infection (n = 22), methamphetamine users with clinical or serological HSV-1 infection (n = 21), and a gingivitis group (n = 20) consisting of non-drug users with gingivitis and negative HSV results. The sample size was calculated using the EPITOOLS online calculator with a 95% confidence level and alpha value of 0.05. All included participants were systemically healthy males and suitable with their group classification and not using immunosuppressive therapy. Participants with history of systemic or autoimmune diseases, diabetes or other chronic illness, use of drugs affecting immune function, or substance abuse other than meth were excluded from the study. Clinical periodontal assessment was done by a trained periodontist, and all teeth were examined using a standard protocol. Bleeding on probing (BOP%) was recorded at six sites per tooth using gentle probing, while the plaque index (PLI) was used to measure the amount and thickness of dental plaque according to standard scoring criteria.

2.2 Ethical Approval

The University of Baghdad College of Dentistry's Basic Science Department Scientific Committee authorized all study ethical requirements (No: 959824, in 24-10-2024). Written consent was required for participation.

2.3 Sampling and Calibration

Gingival crevicular fluid (GCF) was obtained from four upper first premolars (mesiobuccal, distobuccal, mesiopalatal, distopalatal) using PerioPaper strips between 9:00 AM and 2:30 PM. Bloody or salivary strips were disposed of. A standard curve was established by quantifying GCF volume using a Periotron 8010 (OraFlow Inc., USA), calibrated by dilutions of 0.25–1.25 µL of pure water. Immerse paper strips in 0.5 mL of sterile PBS, centrifuge at 3000 rpm for 10 minutes, and preserve at -20°C until ELISA analysis.

"Concentration (pg/µL) = ELISA result (pg/mL)× 0.2 /(GCF) volume (µL)"

2.4 ELISA Analysis of Cytokines

Biotech (Shanghai) ELISA kits employ the double-antibody sandwich technique to quantify CCL28 Chemokine (CK-bio-12527) and IL-29 (CK-bio-12121). This technique generated immune complexes by placing samples and standards in wells coated with specific antibodies and an HRP-conjugate reagent. Following incubation and washing to eliminate any unbound components, substrate solutions were introduced to initiate a colorimetric reaction. After that, they used acid to stop the process. A microplate reader measured the optical density at 450 nm. We measured the cytokine levels by comparing the sample's optical density values to standard curves created using regression analysis, taking into account the effects of dilution.

2.5 Statistical Analysis

We used SPSS 26 to analyze data. The Shapiro-Wilk test verified distribution normality. To demonstrate parametric descriptive statistics with a normal distribution, we used means ± standard deviation. Inferential analysis evaluated group means using LSD post hoc testing and one-way ANOVA. Cytokine level characteristics were correlated using Pearson correlation coefficients. Chi-square analysis was needed. A p-value under 0.05 was significant.

3- RESULTS AND DISCUSSION

Table 1 categorizes the four study groups (healthy individuals, methamphetamine users (Meth), Meth users with HSV, and patients with gingivitis)by age. The mean age was greatest in the Meth group (26.50 ± 4.52), years followed by the Meth with HSV group (25.14 ± 4.39), years, and lowest in the Gingivitis group (23.45 ± 1.67). years The healthy cohort exhibited a mean age of 23.76 ± 2.19 years. A one-way ANOVA revealed a significant age disparity among groups ($F = 3.672$, $p = 0.015$).

Table (1): Age (year) distribution among groups

Study groups	N	Mean	±SD	F	p-value
Healthy	25	23.76	2.185	3.672	0.015
Meth	22	26.50	4.522		
Meth with HSV	21	25.14	4.385		
Gingivitis	20	23.45	1.669		

The mean percentages of bleeding on probing (BOP%) among the four study groups was shown in Table 2 and Figure 1 . The healthy group demonstrated the lowest BOP% (5.52 ± 2.16), while significantly higher values were recorded in the Meth group (24.32 ± 5.47), Meth with HSV group (23.00 ± 6.85), and Gingivitis group (19.30 ± 5.75). Statistical analysis using one-way ANOVA revealed a highly significant difference among the groups ($p < 0.0001$).

Table (2): Bleeding on probing (BOP)% in all groups One-way ANOVA table

BOP%	Mean %	±SD	F	p-value
Healthy	5.52	2.163	64.450	0.0001
Meth	24.32	5.472		
Meth with HSV	23.00	6.848		
Gingivitis	19.30	5.750		

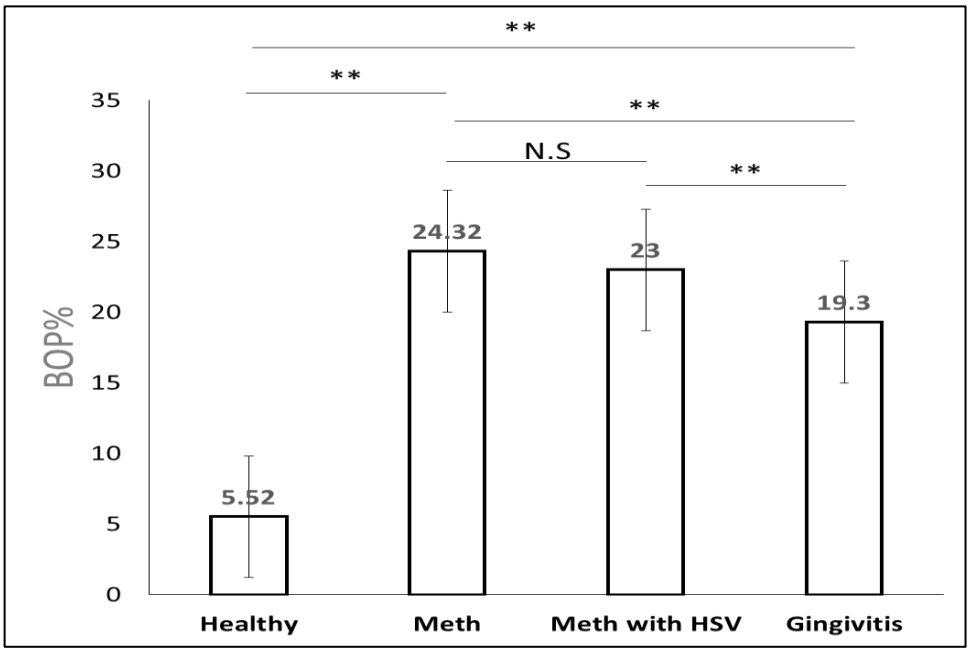

Fig (1): Multiple Comparisons of Bleeding on Probing (BOP%) Between Study Groups

The Meth with HSV group recorded the highest GCF volume (0.4210 ± 0.33885 µL), followed by the Meth group (0.3218 ± 0.26608 µL), while the Gingivitis group and the healthy control group showed lower volumes (0.1665 ± 0.04637 µL and 0.1532 ± 0.05336 µL, respectively). One-way ANOVA revealed a statistically significant difference in GCF volume among the groups ($p < 0.0001$). As recorded in Table 3.

Table (3): GCF volume in all groups Oneway ANOVA table

GCF volume	Mean	±SD	F	p-value
Healthy	0.1532	0.05336	7.824	0.0001
Meth	0.3218	0.26608		
Meth with HSV	0.4210	0.33885		
Gingivitis	0.1665	0.04637		

By using post hoc LSD test for GCF volume revealed several statistically significant differences between the study groups. Notably, the Meth group and Meth with HSV group exhibited significantly higher GCF volumes compared to the healthy group ($p < 0.05$). Similarly, the GCF volume in the Meth with HSV group was significantly greater than that in the Gingivitis group ($p = .000$). A significant difference was also observed between the Meth and Gingivitis groups ($p = .022$). No significant differences were observed between the Meth and Meth with HSV groups, nor between the healthy and Gingivitis groups. As seen in Figure 2.

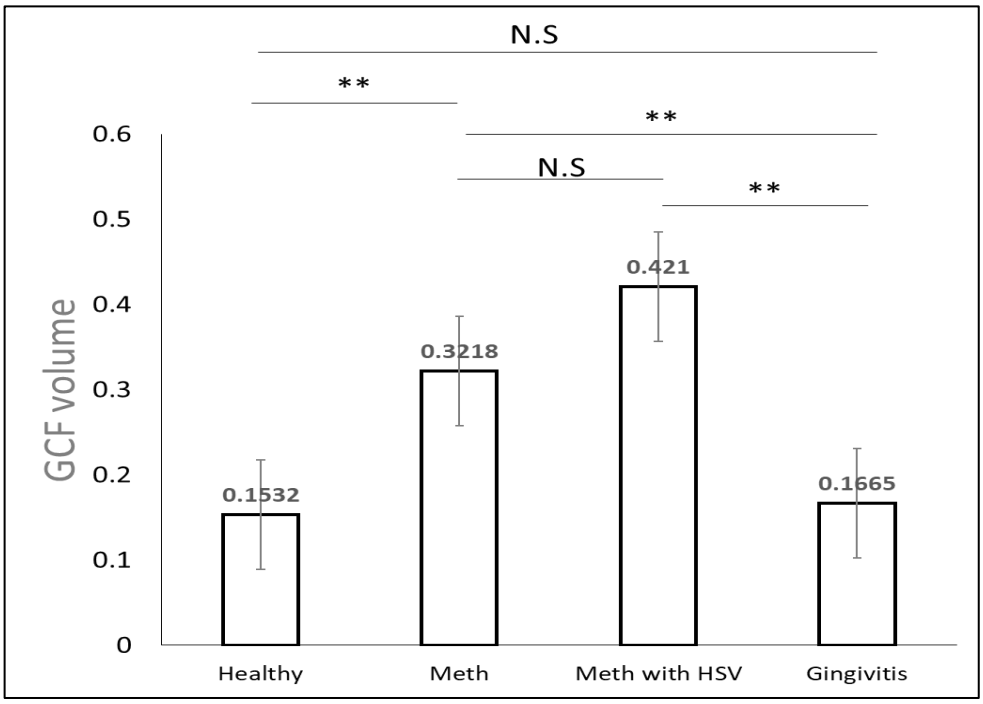

Fig (2): Multiple Comparisons of GCF Volume between Study Groups

Table 4 demonstrates that the Gingivitis group had the lowest average CCL28 level (306.74 ± 10.34 pg/mL), followed by the Meth with HSV group (342.56 ± 10.84) and the Meth group (380.45 ± 24.80). The group that was healthy had the highest mean level (420.90 ± 55.86 pg/mL). The one-way ANOVA indicated substantial differences among groups ($p < 0.0001$).

Table (4): CCL28 Levels in All Groups – One-Way ANOVA Analysis

CCL28 levels	Mean	±SD	F	p-value
Healthy	420.90	55.86	49.123	0.0001
Meth	380.45	24.80		
Meth with HSV	342.56	10.84		
Gingivitis	306.74	10.34		

Gingivitis patients showed significantly lower CCL28 levels than Meth with HSV, Meth, and healthy patients ($p = 0.0001$). Meth with HSV had considerably lower levels than Meth and healthy ($p = .000$). In Figure 3, the Meth group had considerably lower levels than the healthy group ($p = .012$).

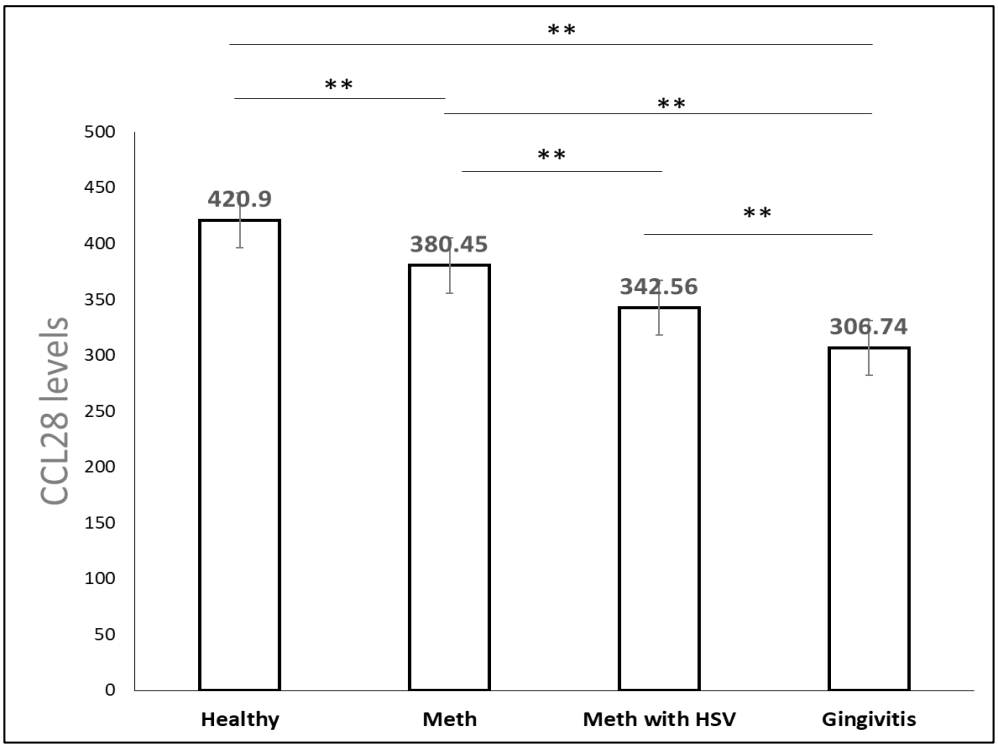

Fig (3): Multiple Comparisons of CCL28 Levels between Study Groups

Gingivitis had the highest average IL-29 level (257.14 ± 4.53), followed by Meth with HSV (241.45 ± 4.75) and Meth (226.43 ± 4.84). The healthy group had the lowest IL-29 levels (205.75 ± 21.59). Table 5 shows that one-way ANOVA showed group differences (p = 0.0001).

Table (5): Interleukin-29 (IL-29) Levels in All Groups – One-Way ANOVA Analysis

IL-29 level	Mean	±SD	F	p-value
Healthy	205.75	21.59	72.36	0.000
Meth	226.43	4.84		
Meth with HSV	241.45	4.75		
Gingivitis	257.14	4.53		

The Gingivitis group had higher IL-29 levels than the Meth with HSV, Meth, and healthy groups (p =0.000). Meth with HSV had higher IL-29 levels than Meth and healthy (p =0.000). The Meth group had significantly higher IL-29 levels than the healthy group (p =0.000). See Figure 4.

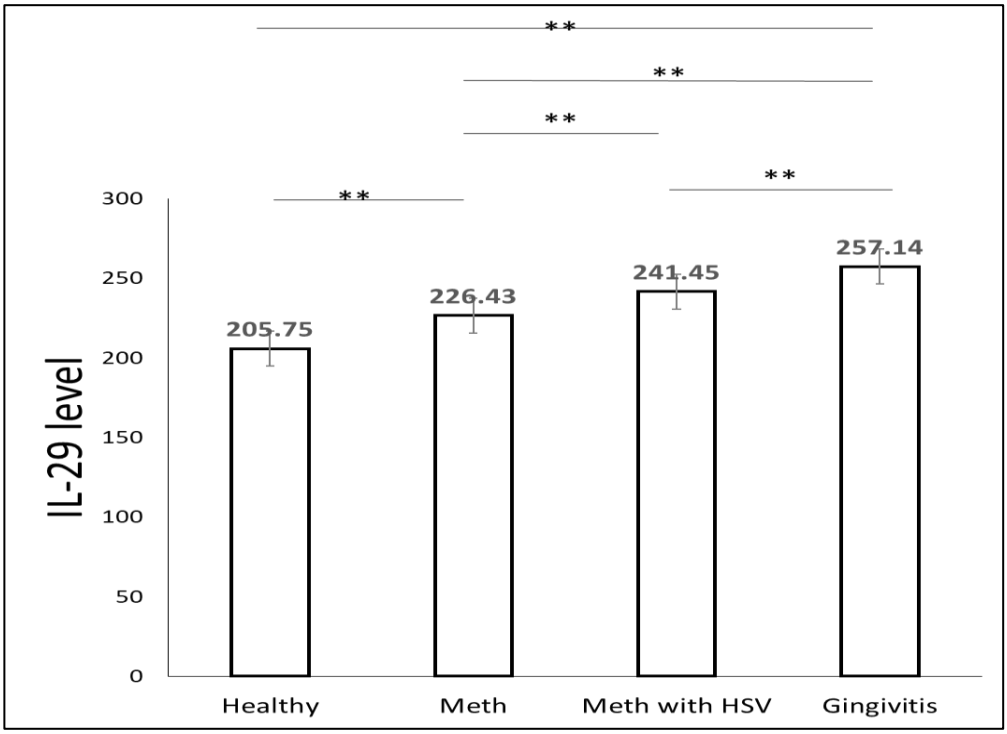

Fig (4): Multiple Comparisons of IL-29 Levels between Study Groups

Table 7 shows how the levels of CCL28 and IL-29 in different research groups are related. The Meth group exhibited a slight negative correlation (r = -0.143, p = 0.525), indicating an absence of a consistent link between the two biomarkers. On the other hand, the Meth + HSV and Gingivitis groups had a perfect positive correlation (r = 1.000, p = 0.000), which means that the levels of CCL28 and IL-29 changed a lot at the same time and were statistically significant.

Table (7): Correlation Coefficient between Biomarkers among the Study Groups

Biomarkers	**Meth**		**Meth with HSV**		**Gingivitis**	
	r	**p. value**	**r**	**p. value**	**r**	**p. value**
IL29 vs CCL28	-.143	.525	1.000**	.000	1.000**	.000

The present study compared mean bleeding on probing (BOP%) in healthy controls, methamphetamine users (Meth), Meth + HSV users, and gingivitis patients. Healthy people had the lowest BOP, while meth addicts had the highest, regardless of HSV. Rommel et al. (2016) indicate that methamphetamine users exhibit elevated levels of BOP and periodontal disease severity in comparison to control subjects, which is ascribed to inadequate oral hygiene, xerostomia, and immunological suppression [31]. Hernández (2016) and Shigeishi et al. (2024) show that having HSV-1 in the mouth is linked to more inflammation in the gums and more blood on probing (BOP), especially in people who already have other risk factors [32, 33].

In this study, individuals using methamphetamine (Meth) and those with herpes simplex virus (Meth + HSV) had significantly elevated levels of gingival crevicular fluid (GCF) compared to individuals with gingivitis and healthy controls. The Meth + HSV group had the most GCF volume overall, which suggests that substance use and viral infection added to the inflammation. According to Subbarao et al. (2019), GCF is an inflammatory exudate made up of serum, tissue breakdown products, and inflammatory mediators that rises following periodontal tissue damage [34]. Moreover, Methamphetamine usage is known to slow down the production of saliva, produce dry mouth, and change the oral microbiota. All of these things can cause gingival inflammation and tissue degeneration [35].

The term "meth mouth" appropriately depicts this severe oral injury, characterized by the deterioration of the gums [36]. The gingivitis group, on the other hand, had substantially lower amounts of GCF, even though their gums were swollen. This is likely due to the fact that gingivitis creates inflammation that may be reversed without harming the tissue, but periodontitis does not. Nonetheless, methamphetamine users, irrespective of HSV presence, exhibited increased GCF output compared to individuals with conventional gingivitis, indicating the direct impact of meth on tissue integrity and inflammatory exudation. The increased GCF in Meth + HSV participants may suggest a synergistic effect: meth-induced gingival degradation fosters an environment favorable to HSV-related inflammatory surges, although direct viral tissue destruction remains inadequately characterized. Nevertheless, Mahmood et al. (2024) and Banks et al. (2024) indicate an increased presence of HHV in inflamed tissues and GCF from pathological locations. supports the notion that HSV, in conjunction with methamphetamine-induced periodontal susceptibility, may enhance inflammatory exudation quantified as GC [37, 38]. Patients with gingivitis had the highest levels of IL-29, followed by methamphetamine users with HSV infection, then those without HSV, and finally healthy controls. Shivaprasad and Pradeep (2015) and Tabari et al. (2021) found that gingivitis patients with high IL-29 levels have a strong local immune response to germs and inflammation. [39, 40]. They also demonstrated that IL-29 expression is markedly elevated in the gingival tissue of individuals with chronic and severe periodontitis [39, 40]. Moreover, Zhou et al. (2011) revealed that viral infections such as HSV-1 might upregulate IL-29, possibly augmenting antiviral responses in the oral milieu. In fact, IL-29 has been proven to stop HSV-1 from replicating in neural cells, which backs up its direct antiviral effects [41]. Shivaprasad and Pradeep (2013) discovered that IL-29 levels do not consistently correlate with the clinical severity of periodontal disease, suggesting significant variability among individuals or the influence of other cytokines [42]. Tognarelli et al. (2019) posited that IL-29 expression could be suppressed during viral infections due to immune evasion mechanisms, potentially clarifying the fluctuations in levels contingent upon the stage of infection and host factors [43].

This research established that CCL28 levels were heightened in healthy persons, substantially reduced in methamphetamine users, more declined in methamphetamine users with HSV infection, and lowest in patients with gingivitis. The reduced CCL28 levels in gingivitis patients corroborate findings by Ertugrul et al. (2013), which indicated compromised mucosal immunity during chronic inflammation. [44]. CCL28 brings IgA-secreting plasma cells and other immune cells to mucosal surfaces. If there aren't enough of these cells, the local defense may be weaker and gingival inflammation may continue [44]. These results align with the studies of Mohan et al. (2017) and Walker et al. (2024), which associated reduced CCL28 with diminished IgA-mediated barrier function and chronic periodontal disease [45, 46]. On the other hand, high levels of CCL28 in healthy people show that the mucosal homeostasis is good and that IgA-secreting cells are being recruited quickly. This is especially important in the mouth, where saliva and epithelial chemokines keep microbes from getting in [47]. People know a lot about this part of CCL28. Mucosal epithelial cells and secretory glands make it. It binds to CCR10 on B and T lymphocytes, which then move to mucosal areas like the salivary glands and oral mucosa [48].

In HSV-infected Meth users, viral modulation likely adds an additional layer of immune suppression. Dhanush-kodi et al. (2023) described that HSV can modulate host chemokine networks, reducing protective signalling and impairing epithelial immune responses [49]. In contrast to gingival inflammation, where chemokine suppression stems from chronic immune exhaustion [50], Meth and HSV may jointly downregulate CCL28 expression through direct damage and immune evasion mechanisms. this may be lead to a compromised mucosal barrier in the oral environment. CCL28 also known as mucosae-associated epithelial chemokine is constitutively expressed in mucosal epithelia and regulates IgA plasma cell and T cell recruitment via CCR10 binding [51, 52]. Wilson & Butcher, (2004) who reported that low CCL28 leads to diminished IgA plasma cell localization, reduced neutrophil chemotaxis, and impaired secretory IgA production [53].

4- CONCLUSION

This study shows distinct immune patterns of CCL28 and IL-29 in methamphetamine users, with or without HSV-1, and in plaque-induced gingivitis. Individuals in good health had the greatest CCL28 levels, which means they had robust mucosal immunity. On the other hand, people with gingivitis had the lowest levels, which means their defense was weak. IL-29 was lowest in healthy controls and greatest in gingivitis, which means that the body was fighting off viruses and inflammation more. Using methamphetamine with HSV-1 made the immune system even more unbalanced, which was shown by lower levels of CCL28 and higher levels of IL-29. This could make gingival inflammation worse. Monitoring these biomarkers in gingival crevicular fluid could help assess mucosal immunity and disease progression in drug- and virus-associated oral conditions.

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