

METHAMPHETAMINE USE AND HSV-1 COINFECTION SYNERGISTICALLY ALTER IFN α , IFN γ , AND IL-29 EXPRESSION IN GINGIVAL CREVICULAR FLUID: IMPLICATIONS FOR GINGIVITIS PATHOGENESIS



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Abstract. *Background.* Methamphetamine use compromises both innate and adaptive immune responses, substantially reducing the body's ability to combat pathogens and preserve mucosal integrity. This immunosuppression heightens susceptibility to opportunistic infections such as herpes simplex virus type 1 (HSV-1), promotes viral reactivation, disrupts the balance and diversity of the oral microbiota, and accelerates inflammatory processes within oral tissues. As a result, it exacerbates a wide range of oral health problems, including gingivitis, periodontal disease, dental caries, oral mucosal lesions, and delayed wound healing within the oral cavity. The aim of the study was to investigate the levels of interferon-alpha (IFN α), interferon-gamma (IFN γ), and interleukin-29 (IL-29) in methamphetamine users with or without HSV-1 infection, and to examine their association with the development of gingivitis. *Materials and methods.* This case-control study included 88 male participants aged 20–35 years, categorized into four groups: healthy controls, methamphetamine users, methamphetamine users with HSV-1 infection, and patients with gingivitis. Gingival crevicular fluid (GCF) samples were collected from all participants, and the concentrations of IFN α , IFN γ , and IL-29 were measured using enzyme-linked immunosorbent assay (ELISA). *Results.* IFN α and IFN γ levels were highest in the healthy control group and were significantly reduced in the methamphetamine, methamphetamine with HSV-1, and gingivitis groups ($p < 0.05$). In contrast, IL-29 levels were significantly elevated in gingivitis patients compared to all other groups. Furthermore, methamphetamine users with HSV-1 infection exhibited markedly higher IL-29 concentrations than methamphetamine users without HSV-1 infection. *Conclusion.* Methamphetamine use and HSV-1 infection significantly impair immune cytokine responses, reflected by marked reductions in IFN α and IFN γ levels, alongside elevated IL-29. The pronounced increase in IL-29 was most evident in gingivitis patients, suggesting a potential role for this cytokine in amplifying local inflammatory processes and contributing to periodontal tissue breakdown.

Key words: methamphetamine, HSV-1, gingivitis, interferon, IFN α , IFN γ , IL-29.

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УПОТРЕБЛЕНИЕ МЕТАМФЕТАМИНА И КОИНФЕКЦИЯ ВИРУСОМ ПРОСТОГО ГЕРПЕСА 1 СИНЕРГЕТИЧЕСКИ ИЗМЕНЯЮТ ЭКСПРЕССИЮ $IFN\alpha$, $IFN\gamma$ И IL-29 В ДЕСНЕВОЙ ЖИДКОСТИ: ЗНАЧЕНИЕ ДЛЯ ПАТОГЕНЕЗА ГИНГИВИТА

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Резюме. *Введение.* Употребление метамфетамина подавляет как врожденный, так и адаптивный иммунный ответ, существенно снижая способность организма бороться с патогенами и сохранять целостность слизистых оболочек. Такая иммуносупрессия повышает восприимчивость к оппортунистическим инфекциям, таким как вызванной вирусом простого герпеса 1-го типа (ВПГ-1), способствует его реактивации, нарушает баланс и разнообразие микробиоты полости рта и ускоряет воспалительные процессы в тканях полости рта. В результате усугубляется течение широкого спектра заболеваний полости рта, включая гингивит, пародонтит, кариес зубов, поражения слизистой оболочки полости рта и замедляет заживление ран в полости рта. Целью исследования было изучение уровней интерферона-альфа ($IFN\alpha$), интерферона-гамма ($IFN\gamma$) и интерлейкина-29 (IL-29) у лиц, употребляющих метамфетамин, при инфекции, вызванной вирусом простого герпеса 1 типа (ВПГ-1) или без нее, а также изучить их связь с развитием гингивита. *Материалы и методы.* В исследовании случай-контроль приняли участие 88 мужчин в возрасте от 20 до 35 лет, разделенных на четыре группы: здоровая контрольная группа, лица, употребляющие метамфетамин, с инфекцией ВПГ-1 и пациенты с гингивитом. У всех участников были собраны образцы зубодесневой жидкости (ЗДЖ) для определения концентрации $IFN\alpha$, $IFN\gamma$ и IL-29 с помощью иммуноферментного анализа (ИФА). *Результаты.* Уровни $IFN\alpha$ и $IFN\gamma$ были самыми высокими в группе здоровых людей и значительно снижены в группах лица, употребляющих метамфетамин, с ВПГ-1 и пациентов с гингивитом ($p < 0,05$). Напротив, уровни IL-29 были значительно повышены у пациентов с гингивитом по сравнению со всеми другими группами. Более того, у лиц, употребляющих метамфетамин, с инфекцией ВПГ-1 наблюдалась значительно более высокая концентрация IL-29, чем у лиц, употребляющих метамфетамин, без инфекции ВПГ-1. *Заключение.* Употребление метамфетамина и инфекция ВПГ-1 достоверно ухудшают иммунный цитокиновый ответ, что отражается в выраженном снижении уровня $IFN\alpha$ и $IFN\gamma$ на фоне повышения уровня IL-29. Выраженное повышение уровня IL-29 было наиболее представлено у пациентов с гингивитом, что указывает на потенциальную роль указанного цитокина в усилении местных воспалительных процессов и содействии разрушению тканей пародонта.

Ключевые слова: метамфетамин, ВПГ-1, гингивит, интерферон, $IFN\alpha$, $IFN\gamma$, IL-29.

Introduction

Methamphetamine is a potent central nervous system stimulant chemically classified as a phenethylamine (C₁₀H₁₅N). Chronic use of this substance is associated with severe health consequences, including cardiovascular disease, neurological dysfunction, immune suppression, and significant oral health deterioration [2, 8]. A hallmark condition of long-term methamphetamine abuse is “meth mouth”, characterized by rampant dental decay, xerostomia, periodontal disease, and tooth loss [17]. This condition arises from reduced saliva production, poor oral hygiene, high sugar consumption, and behaviors like bruxism, all of which collectively promote bacterial proliferation and gingival inflammation.

Drug addiction, including methamphetamine use, is a chronic relapsing disorder marked by compulsive drug-seeking behavior and persistent use despite negative consequences [34]. It affects not only the individual but also their family and community. The systemic effects of addiction are wide-ranging, leading to physical and psychological impairments, notably in brain function and immune regulation [16, 26]. Methamphetamine has been shown to suppress immune responses, increasing vulnerability to infec-

tions, including viral pathogens like Herpes Simplex Virus type 1 (HSV-1) [11, 34].

HSV-1, a member of the Herpesviridae family, typically establishes latency in the trigeminal ganglia and periodically reactivates. It is primarily associated with oral infections and can exacerbate periodontal conditions such as gingivitis, especially when coexisting with bacterial plaque accumulation [9]. Clinical signs may intensify in co-infected individuals, presenting with increased gingival erythema, edema, ulceration, and bleeding [11, 28]. The combined impact of meth use and HSV-1 infection may synergistically impair oral immunity, contributing to more severe periodontal manifestations.

Gingivitis, the earliest form of periodontal disease, is a reversible inflammatory condition primarily induced by dental plaque. It is histologically characterized by collagen degradation, inflammatory cell infiltration, and vasodilation [11, 14, 20, 36]. While generally non-destructive in its early stages, untreated gingivitis can progress to periodontitis and systemic inflammatory responses. Bacteria such as *Streptococcus mutans* and *Porphyromonas gingivalis* play central roles in its pathogenesis [1, 21, 37, 38, 43].

The immune response to both viral and bacterial infections involves the production of cytokines and

chemokines, including interferons (IFNs) and interleukin-29 (IL-29), which modulate inflammation and antiviral defense. Type I (IFN α) and Type II (IFN γ) interferons are pivotal in activating macrophages, NK cells, and T-cells, enhancing antigen presentation and immune surveillance [11,37,38]. Though IFNs have clinical utility in cancer immunotherapy, their presence in the oral cavity reflects immune activation against infection more so than oncologic relevance in this context.

IL-29 (a Type III interferon) has emerged as an important immunomodulator in mucosal tissues. It is elevated in gingival crevicular fluid during periodontal inflammation and may be induced by HSV-1 infection. IL-29 has been shown to enhance antiviral responses and is positively correlated with clinical markers such as pocket depth and attachment loss, indicating its involvement in disease progression [11, 37].

This study aimed to evaluate and compare the levels of IFN α , IFN γ , and IL-29 in gingival crevicular fluid among methamphetamine users — with and without HSV-1 infection — alongside patients with plaque-induced gingivitis and healthy individuals.

Materials and methods

Study design. This case-control study was conducted between November 2024 and May 2025, involving 88 male participants aged 20–35 years, recruited from dental clinics and specialized health-care centers. Participants were stratified into four distinct groups: Healthy Controls (n = 25) with no history of systemic or periodontal disease; Methamphetamine Group (n = 22) comprising confirmed meth users without evidence of HSV infection; Meth with HSV Group (n = 21), including meth users with clinical or serological confirmation of HSV-1 infection; and Gingivitis Group (n = 20), consisting of non-drug users diagnosed with gingivitis and negative for HSV. The sample size was determined using the EPITOOLS online calculator, based on a 95% confidence level and an alpha of 0.05.

Ethical approval. All procedures adhered to ethical standards approved by the Scientific Committee of the Basic Science Department, College of Dentistry, University of Baghdad (Ref: 959, Project No: 959824, Date: 24.10.2024). Written informed consent was obtained from all participants.

Included participants

- Males aged 20–35
- Systemically healthy and consistent with group classification
- Free from immunosuppressive therapy

Excluded

- History of systemic illness or autoimmune disorders
- Use of medications affecting immune function
- Substance abuse other than Meth
- Diabetes or other unrelated chronic conditions

Clinical periodontal assessment

A trained periodontist examined all teeth using a standardized protocol.

- Bleeding on Probing (BOP%): Assessed at six sites per tooth using gentle probing.
- Plaque Index (PLI): Quantified the extent and thickness of plaque based on standard scoring criteria.

GCF sampling and calibration. Gingival crevicular fluid (GCF) was collected using PerioPaper strips from four sites on upper first premolars (mesiobuccal, distobuccal, mesiopalatal, distopalatal) between 9:00 AM and 2:30 PM. Strips contaminated with blood/saliva were discarded. GCF volume was quantified using a Periotron 8010 (OraFlow Inc., USA), calibrated via serial dilutions (0.25–1.25 μ L distilled water) to generate a standard curve. Paper strips were immersed in 0.5 mL sterile PBS, centrifuged at 3000 rpm for 10 min, and stored at -20°C until ELISA testing.

Concentration (pg/ μ L) = ELISA result (pg/mL) \times 0.2/GCF volume (μ L)

ELISA analysis of cytokines. ELISA kits sourced from Biotech (Shanghai) were utilized to quantify IFN α (Cat. CK-bio-12065), IFN γ (Cat. CK-bio-12068), and IL-29 (Cat. CK-bio-12121), each based on the double-antibody sandwich principle. In this method, samples and standards were added to wells pre-coated with specific antibodies, followed by the addition of HRP-conjugate reagent to form immune complexes. After incubation and thorough washing to remove unbound components, substrate solutions were introduced to develop a colorimetric reaction, which was stopped with an acid solution. The optical density (OD) was measured at 450 nm using a microplate reader. Cytokine concentrations were determined by comparing sample OD values to standard curves generated through regression analysis, with final results adjusted according to the appropriate dilution factors.

Statistical analysis. Data were analyzed using SPSS version 26. Normality of distribution was assessed using the Shapiro–Wilk test. Descriptive statistics were reported as means \pm standard deviation for normally distributed (parametric) variables. For inferential analysis, one-way ANOVA followed by LSD post hoc tests was applied to compare means among groups. Pearson correlation coefficients were used to examine relationships between cytokine levels parameters. Chi-square tests were applied where appropriate. A p-value < 0.05 was considered statistically significant.

Results

Table 1 illustrates the distribution of age among the four study groups: healthy, methamphetamine users (Meth), methamphetamine users with HSV infection (Meth with HSV), and gingivitis patients. The mean age was highest in the Meth group (26.50 ± 4.52 years), followed by Meth with HSV (25.14 ± 4.39 years), while the lowest mean age was observed in the Gingivitis

group (23.45±1.67 years). The healthy group had a mean age of 23.76±2.19 years. A one-way ANOVA analysis revealed a statistically significant difference in age distribution among the groups (F = 3.672, p = 0.015).

The results showed noticeable variation in IFNα levels across the study groups was shown in Table 2. The healthy group exhibited the highest mean

concentration (193.97±31.61 pg/mL), followed by the Meth with HSV group (182.54±13.17 pg/mL) and the Meth group (165.91±16.80 pg/mL), while the lowest levels were observed in the Gingivitis group (132.63±44.20 pg/mL). One-way ANOVA analysis indicated a statistically significant difference among the groups (p = 0.030).

Table 1. Age (year) distribution among groups

Study groups	N	Mean	Std. Deviation	Std. Error of Mean	F	p-value
Healthy	25	23.76	2.185	0.437	3.672	0.015
Meth	22	26.50	4.522	0.964		
Meth with HSV	21	25.14	4.385	0.957		
Gingivitis	20	23.45	1.669	0.373		
Total	88	24.70	3.572	0.381		

Table 2. Interferon alpha (IFNα) levels in all groups – one-way ANOVA analysis

	Mean	Std. Deviation	Std. Error	F	p-value
Healthy	193.97	31.61	6.32	3.130	0.030
Meth	165.91	16.80	3.58		
Meth with HSV	182.54	13.17	2.86		
Gingivitis	132.63	44.20	9.88		

Table 3. Post hoc Games–Howell multiple comparisons of IFNα levels between study groups

Study groups	Mean Difference	p-value	Sig.
Healthy vs Meth	28.07*	0.002	Sig.
Healthy vs Meth with HSV	11.44	0.979	Non-Sig.
Healthy vs Gingivitis	61.34*	0.000	Sig.
Meth vs Meth with HSV	-16.63	0.938	Non-Sig.
Meth vs Gingivitis	33.28*	0.020	Sig.
Meth with HSV vs Gingivitis	49.91	0.372	Non-Sig.

Table 4. Interferon gamma (IFNγ) levels in all groups – one-way ANOVA analysis

	Mean	Std. Deviation	Std. Error	F	p-value
Healthy	139.22	24.42	4.88	145.168	0.0001
Meth	108.55	13.32	2.84		
Meth with HSV	75.58	8.99	1.96		
Gingivitis	45.87	8.58	1.92		

Table 5. Post hoc Games–Howell multiple comparisons of IFNγ levels between study groups

Study_groups	Mean Difference	p-value	Sig.
Healthy vs Meth	30.67*	0.000	Sig.
Healthy vs Meth with HSV	63.64*	0.000	Sig.
Healthy vs Gingivitis	93.35*	0.000	Sig.
Meth vs Meth with HSV	32.97*	0.000	Sig.
Meth vs Gingivitis	62.68*	0.000	Sig.
Meth with HSV vs Gingivitis	29.71*	0.000	Sig.

Table 6. Interleukin-29 (IL-29) levels in all groups – one-way ANOVA analysis

	Mean	Std. Deviation	Std. Error	F	p-value
Healthy	205.75	21.59	4.32	72.358	0.000
Meth	226.43	4.84	1.03		
Meth with HSV	241.45	4.75	1.04		
Gingivitis	257.14	4.53	1.01		

Table 7. Post hoc Games–Howell multiple comparisons of IL-29 levels between study groups

Study groups	Mean Difference	p-value	Sig.
Healthy vs Meth	-20.68*	0.000	Sig.
Healthy vs Meth with HSV	-35.70*	0.000	Sig.
Healthy vs Gingivitis	-51.39*	0.000	Sig.
Meth vs Meth with HSV	-15.024*	0.000	Sig.
Meth vs Gingivitis	-30.71*	0.000	Sig.
Meth with HSV vs Gingivitis	-15.69*	0.000	Sig.

By using post hoc Games–Howell test, the healthy group had significantly higher IFN α levels than both the Meth group ($p = 0.002$) and the Gingivitis group ($p = 0.000$). Additionally, the Meth group showed a significantly higher level than the Gingivitis group ($p = 0.020$). However, no significant differences were detected between the Meth and Meth with HSV groups, nor between the Meth with HSV and Gingivitis groups, as shown in Table 3.

The results of IFN γ levels comparisons across the study groups was observed in Table 4.

The healthy group had the highest mean IFN γ level (139.22 ± 24.42 pg/mL), followed by the Meth group (108.55 ± 13.32 pg/mL), the Meth with HSV group (75.58 ± 8.99 pg/mL), and the lowest level was recorded in the Gingivitis group (45.87 ± 8.58 pg/mL). One-way ANOVA revealed a highly significant difference among the groups ($p < 0.0001$).

The healthy group had significantly higher IFN γ levels than the Meth ($p = 0.000$), Meth with HSV ($p = 0.000$), and Gingivitis groups ($p = 0.000$). Additionally, the Meth group showed significantly elevated IFN γ levels compared to the Meth with HSV ($p = 0.000$) and Gingivitis groups ($p = 0.000$), while the Meth with HSV group also had significantly higher levels than the Gingivitis group ($p = 0.000$), as shown in Table 5.

The Gingivitis group exhibited the highest mean IL-29 level (257.14 ± 4.53 pg/mL), followed by the Meth with HSV group (241.45 ± 4.75 pg/mL), and the Meth group (226.43 ± 4.84 pg/mL). In contrast, the healthy group showed the lowest IL-29 concentration (205.75 ± 21.59 pg/mL). One-way ANOVA revealed a statistically significant difference among the groups ($p = 0.000$), as demonstrated in Table 6.

The Gingivitis group showed significantly higher IL-29 levels than the Meth with HSV group ($p =$

0.000), the Meth group ($p = 0.000$), and the healthy group ($p = 0.000$). Likewise, the Meth with HSV group exhibited elevated IL-29 levels compared to the Meth group ($p = 0.000$) and the healthy group ($p = 0.000$). The Meth group also demonstrated significantly higher IL-29 levels than the healthy group ($p = 0.000$), as illustrated in Table 7.

Discussion

The present study examined the age distribution across four distinct groups: healthy individuals, methamphetamine users, meth users co-infected with HSV, and patients with gingivitis. The analysis revealed that methamphetamine users were generally older than participants in the other groups. Those with both meth use and HSV infection also tended to be older, though slightly younger than meth users without HSV. In contrast, gingivitis patients and healthy controls were the youngest among all groups. Statistical testing confirmed that the variation in age across these groups was significant.

Methamphetamine users tend to be older than those in healthy and gingivitis-only groups. This is consistent with Shetty et al. (2015) [31] reported that the majority of methamphetamine users are between 18 and 34 years old, with oral health consequences becoming more pronounced with longer duration of use.

Concerning Gingivitis with age groups, in the current study it is more prevalent among younger individuals, particularly adolescents and young adults, these may be due to factors such as poor oral hygiene, hormonal changes, and lifestyle habits. Furthermore, Muqarab et al. (2024) [22] and Alwan (2024) [3] found that the highest prevalence of gingivitis is in the 15–25 year age group, with the frequency decreasing

as age increases, while periodontitis becomes more common in older populations.

Regarding Methamphetamine, HSV infection, and age in this study, Methamphetamine users with HSV infection (meth with HSV) had a mean age between that of meth users and the other groups. This may reflect the cumulative risk behaviors associated with both substance use and viral infection, which tend to manifest in early adulthood and may be linked to longer exposure periods [40].

These findings suggest a trend where older individuals are more likely to be methamphetamine users. However, those in the slightly younger age range appeared more frequently in the group with both meth use and HSV infection. This could point to increased vulnerability to viral infections like HSV among younger meth users. Moreover, the youngest age group showed a higher prevalence of gingivitis, possibly reflecting early-stage gum disease that develops before more severe complications arise.

The investigation of IFN α (interferon-alpha) levels across four groups—healthy controls, methamphetamine users (meth), meth users with HSV infection (meth + HSV), and gingivitis patients—revealed a clear hierarchy. Moreover, the healthy group showed the highest IFN α concentration, followed by the meth + HSV and meth groups, while the gingivitis group had the lowest levels.

These patterns suggest that methamphetamine use impairs the ability of immune cells, including plasmacytoid dendritic cells and antigen-presenting cells, to produce IFN α —even in the presence of viral infection. Indeed, chronic meth exposure has been shown to suppress endogenous IFN α production in macrophages and antigen-presenting cells, weakening critical innate antiviral defenses [18]. The significant drop in IFN α among meth users compared to healthy individuals reflects this immunosuppressive effect, a deficit not substantially worsened by HSV co-infection, which aligns with the lack of significant difference between meth and meth + HSV groups.

Meanwhile, the lowest IFN α levels in the gingivitis group likely reflect the nature of localized, bacterial-driven inflammation. Furthermore, prior studies report that while total IFN α amounts may not differ much between healthy and diseased periodontal sites, the concentration of IFN α is significantly reduced at inflamed sites — possibly due to increased fluid volume diluting cytokines or impaired local production.

Furthermore, it appears that methamphetamine use significantly undermines innate immune signaling through IFN α suppression, even more than local bacterial inflammation associated with gingivitis. Meanwhile, healthy individuals maintain robust IFN α levels, which likely contribute to more effective antiviral surveillance. Moreover, HSV co-infection did not restore IFN α levels among meth users,

suggesting that meth's inhibitory impact on immune cell function outweighs the inflammatory stimulus provided by viral presence.

According to Mathur et al. (1996) [19] and de Menezes et al. (2018) [7] IFN α is crucial for the early immune response, limiting pathogen replication and supporting tissue homeostasis.

Salamanca et al. (2014) [29], Passaro et al. (2015) [24] and Borgmann and Ghorpade (2015) [5] reported that Methamphetamine is known to suppress IFN α production and impair immune responses, making users more susceptible to infections and inflammatory complications, this supported the current finding for IFN α levels were reduced in meth users compared to healthy controls.

Mathur et al. (1996) [14] and shown that IFN α concentrations are significantly lower in diseased gingival sites compared to healthy sites, even when the total amount of IFN α remains similar. This is attributed to increased crevicular fluid volume in disease, which dilutes cytokine concentrations.

The study revealed that healthy individuals had the highest IFN γ levels, followed by meth users, then meth + HSV users, with gingivitis patients showing the lowest levels and each group significantly differing from one another ($p < 0.0001$ overall). Moreover, this aligns with Buno et al. (1998) [6] and Ghallab et al. (2010) [10], who emphasize IFN γ 's key role in mucosal immunity — particularly in activating macrophages and T cells to defend the oral cavity.

The observed decline in IFN γ among meth users supports findings from Potula et al. (2018) and related studies: methamphetamine suppresses Th1 responses, including IFN γ , impairing adaptive immunity and increasing infection risk [25].

Meanwhile, meth users co-infected with HSV showed even lower IFN γ levels. This agrees with Sainz et al. (2002) [27] and Bigley et al. (2014) [4], who found that HSV can dampen IFN γ -mediated immunity. When combined with meth-induced immunosuppression, the decline becomes more pronounced.

Similarly, gingivitis patients recorded the lowest IFN γ , reflecting a shift away from Th1 responses during chronic inflammation. As noted by Sheibak et al. (2022) [30] and Neurath & Kesting (2024) [23], persistent gingival inflammation often diverts immune signaling toward Th2 or regulatory pathways, reducing IFN γ production over time — even though acute or early periodontitis may temporarily elevate IFN γ .

Thus, methamphetamine use significantly suppresses IFN γ , with HSV co-infection further compounding this suppression. Meanwhile, gingivitis without meth use also results in low IFN γ , though via inflammatory rather than immunosuppressive mechanisms. Ultimately, healthy individuals maintain robust IFN γ output, indicative of intact Th1-mediated immunity and effective mucosal defense.

This study demonstrated that IL-29 levels were highest in patients with gingivitis, followed by methamphetamine users with HSV infection, then meth users without HSV, and lowest in healthy controls. These results are consistent with the findings of Shivaprasad and Pradeep (2015) [32] and Tabari et al. (2021) [35], who reported that elevated IL-29 levels in gingivitis reflect a strong local immune response to bacterial plaque and inflammation. They also showed that IL-29 expression is significantly increased in the gingival tissue of patients with chronic and aggressive periodontitis [32, 35].

Methamphetamine users, especially those co-infected with HSV, also showed higher IL-29 levels than healthy individuals. This may be due to the compounding effect of substance-induced immune dysregulation and viral stimulation. Kevil et al. (2019) [13] and Yang et al. (2020) [42] similarly concluded that chronic methamphetamine use is associated with altered cytokine profiles, including increased interferon production, resulting from tissue injury and prolonged immune activation. Furthermore, Zhou et al. (2011) [44] demonstrated that viral infections like HSV-1 can upregulate IL-29, potentially enhancing antiviral defenses in the oral environment. In fact, IL-29 has been shown to inhibit HSV-1 replication in neuronal cells, supporting its direct antiviral properties [44].

Tognarelli et al. (2019) [39] proposed that IL-29 expression may sometimes be suppressed during viral infections due to immune evasion mechanisms, which could explain fluctuating levels depending on infection stage and host factors [39].

IL-29, a type III interferon, is produced by epithelial cells, dendritic cells, and certain leukocytes in response to microbial and viral stimuli [41]. It binds to a specific receptor complex, activating the JAK-STAT signaling pathway and leading to the expression of interferon-stimulated genes, which enhances antiviral defense and regulates inflammatory responses. In gingivitis, the high IL-29 levels may reflect an attempt to control bacterial invasion and prevent tissue damage. In meth users and meth + HSV cases, chronic inflammation and mucosal injury likely stimulate additional IL-29 production as part of the ongoing immune response [32, 35, 44].

IL-29 also exhibits strong antiviral activity by inducing an antiviral state in infected cells, reducing viral replication, and enhancing immune cell surveillance. It modulates the function of T cells, B cells, dendritic cells, and macrophages, helping to shape immune responses and inflammation [12, 15, 41].

Conclusion

This study concludes that methamphetamine consumption, especially when combined with HSV-1 infection, leads to significant suppression of IFN α and IFN γ , indicating a weakened antiviral and immune response. Conversely, IL-29 levels were markedly elevated in gingivitis and further increased in meth users with HSV-1, which may highlight its potential role as a biomarker for inflammation and viral modulation in the oral cavity.

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