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The Interaction Between the Immune System and Methamphetamine Addiction: A Comparative Study of Cytokines and Immune Cell Changes

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ABSTRACT

Objective: *This study aims to study the interaction between methamphetamine use and the immune system, by analyzing changes in cytokines and the pattern of immune cell distribution in users.* ***Method:*** *The study used a comparative analytical approach that included a group of users and a control group. Blood samples were collected and analyzed using ELISA and flow cytometry techniques.* ***Results:*** *The expected results revealed a significant increase in the levels of inflammatory cytokines (TNF-a, IL-6) and a decrease in regulatory cytokines (IL-10), in addition to a decrease in the CD4+/CD8+ ratio and an imbalance between natural killer cells and macrophages. The study also indicates a positive correlation between the duration of use and the severity of immune changes, reflecting a cumulative effect over time. These findings highlight the pivotal role of the immune system in the addiction cycle and suggest the potential for immunological markers to serve as tools for early diagnosis or therapeutic guidance.* ***Novelty:*** *This study provides a new scientific contribution to understanding the immune mechanisms underlying methamphetamine addiction and calls for further applied research to develop therapeutic strategies based on modulating immune pathways, which enhance recovery opportunities and reduce behavioral relapses.*

INTRODUCTION

Methamphetamine abuse is a major public health challenge due to its extended effects that extend beyond the central nervous system to the immune system, causing profound changes in an individual's immune and inflammatory balance. As a powerful psychostimulant, methamphetamine causes well-known behavioral and neurological changes, but its immunological effects are still being studied and expanded in current research, particularly in light of the growing understanding of the "molecular dialogue" between the nervous and immune systems.

Advanced studies have shown that methamphetamine abuse disrupts the production of cytokines and affects the pattern of immune cells, such as T cells and macrophages. This creates a chronic inflammatory environment that may contribute to the weakening of both the innate and acquired immune systems [1].Researchers have also indicated that methamphetamine's immunological effects may be dual; On the one hand, it enhances certain inflammatory pathways by stimulating the production of TNF-α and IL-6, while on the other hand, it weakens defensive immune responses, increasing susceptibility to infection, particularly viral infections such as HIV [2].The importance of this research lies in its contribution to bridging a vital scientific gap regarding the interaction between the immune system and addictive behavior. It also opens the door to understanding the molecular and cellular mechanisms that mediate this relationship,

which may subsequently contribute to the development of therapeutic strategies based on modifying the immune response or predicting addiction risks through biomarkers [3].Accordingly, this research aims to conduct an in-depth analytical study of the immune changes associated with methamphetamine use, focusing on cytokine patterns and immune cell distribution, reflecting the dynamic changes in the immune-inflammatory balance in addicted individuals [4] [5]. In recent decades, the relationship between the nervous and immune systems has become the focus of an increasing amount of research, particularly in the field of neuroimmunology, where the two systems are viewed as interconnected and do not operate in isolation. In this context, the use of psychoactive substances—most notably methamphetamine—is one of the factors that significantly disrupts this neuro-immune balance [6]. Methamphetamine use exhibits both inhibitory and stimulatory effects on the immune system. On the one hand, it enhances the secretion of a number of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, which are associated with increased systemic and cerebral inflammation [7]. On the other hand, it impairs the gene expression of certain immune regulatory factors, leading to a state of chronic immunodeficiency and increasing susceptibility to infection and recurrent inflammation. Studies indicate that methamphetamine particularly affects microglia, the immune cells resident in the central nervous system. Excessive stimulation of these cells leads to the release of large amounts of inflammatory molecules (such as NO and ROS), which contribute to the destruction of neighboring neurons .In addition, methamphetamine disrupts the distribution and activity of T and B lymphocytes, reduces the efficiency of natural killer cells (NK cells), and alters the CD4+/CD8+ ratio, biomarkers associated with acquired immune function [8,9].From a neuropsychoimmunological perspective, these effects are not simply understood as side effects of drug use, but rather as part of a recurring cycle in which immune alterations play a role in reinforcing addictive behaviors and maintaining psychological and physiological cravings for the drug. Cytokines, in turn, affect the dopamine and serotonin systems, leading to enhanced compulsive behaviors and loss of control [9]. This closed loop between immune interaction and addiction is crucial to understanding the complex mechanisms of addiction and represents an opportunity for early therapeutic intervention by tracking and modifying immune markers. Thus, there is a need for in-depth analytical research—such as this one—that aims to identify qualitative and quantitative changes in cytokines and immune cells in addicted individuals and explore the potential of using these markers as prognostic or therapeutic tools.

The Nervous System and Relationship to Addiction

1. The Nervous System

The nervous system is one of the body's most complex systems, controlling most of its vital functions, including sensation, movement, thinking, behavior, and regulation of immune responses. The nervous system consists of two main parts:

- The central nervous system (CNS): This includes the brain and spinal cord, and is the center of processing and control.

- The peripheral nervous system (PNS): This includes the nerves that connect the CNS to the rest of the body.

The brain, in particular, is the center of cognitive and emotional processing and consists of various regions, such as the cerebral cortex, limbic system, and nucleus accumbens, all of which play a role in addictive behaviors [10].

2. The Relationship Between the Nervous System and Addiction

Addiction is not simply a learned behavior or a psychological disorder; it is now viewed as a chronic brain disease that affects the structure and function of the brain. Research shows that drugs, including methamphetamine, cause long-term changes in brain regions associated with reward and motivation, such as:

- The dopamine system: The primary neurotransmitter associated with pleasure and reinforcement. Methamphetamine use releases large amounts of dopamine, creating a sense of euphoria, but it also disrupts the normal balance of this system [11].
- The prefrontal cortex: Responsible for decision-making, self-regulation, and cognitive thinking. Studies show that repeated use weakens this region, reducing self-control and increasing impulsivity [12].
- The limbic system: Specifically, the amygdala and hippocampus, which are responsible for emotional memory. Disruption in these regions contributes to addictive learning patterns and psychological dependence on the substance.

3. Methamphetamine's Effect on the Nervous System

Methamphetamine is one of the most harmful psychostimulants to the brain. It:

- Causes direct damage to nerve endings (especially dopaminergic and serotonergic neurons), leading to a decline in cognitive ability, attention, and memory.
- Increases oxidative stress and inflammation in neurons, contributing to ongoing neuronal damage [13].
- Disrupts the balance between excitation and inhibition by affecting GABA and glutamate receptors, increasing agitation and aggression, and in some cases, hallucinations and psychosis.

Neuroimaging studies also indicate that methamphetamine addicts exhibit a significant decrease in the volume of certain brain regions, such as the prefrontal cortex, along with reduced neural activity in areas responsible for behavioral control and planning [14].

The Immune System and Its Relationship to Addiction

1. The Immune System

The immune system is the cornerstone of the body's defense against pathogens and internal dysfunction. It is a complex system of cells, proteins, and regulatory molecules. It consists of:

- Innate immunity: This is the primary defense, and includes macrophages, natural killer (NK) cells, and dendritic cells.
- Adaptive immunity: This is the specific, long-term response, and includes T cells and B cells. These components coordinate under the influence of a network of cytokine

signaling molecules that play a pivotal role in activating or inhibiting immune responses [15].

2. The Impact of Addiction on the Immune System

Addiction is no longer viewed solely as a neurological or behavioral disorder; recent literature shows that it leads to a marked disruption of immune system function. Immune effects include:

- Stimulation of chronic inflammatory cytokines such as IL-6, TNF-α, and IL-1β, leading to chronic systemic and cellular inflammation [16].
- Inhibition of gene expression of regulatory factors such as IL-10 and TGF-β, which impairs immune balance and increases the risk of infection and cancer [17].
- Altered distribution of immune cells: particularly T cells (decrease in CD4+ and defective CD8+), and decreased NK cell activity, which impacts the body's resistance to disease .

3. Methamphetamine's Relationship with the Neuroimmune Interface

Methamphetamine disrupts this immune balance through two interconnected mechanisms:

- Activation of microglia in the brain, a neuroimmune component, leading to excessive secretion of inflammatory molecules such as NO and ROS, and consequently, nerve damage [18].
- Disruption of the hypothalamic-pituitary-adrenal (HPA) axis, leading to impaired cortisol secretion and impacting immune and inflammatory responses.

Cytokines generated by addiction may also be involved in the cycle of reinforcing addictive behavior, as they affect the secretion of dopamine and serotonin, deepening the link between inflammatory conditions and addictive behavior. This is known as the "inflammatory-behavioral feedback loop."

4. Addiction as a disruptor of preventive and therapeutic immunity

Addicts especially methamphetamine users show a weakened response to vaccines and an increased rate of infection with viruses such as HIV and HCV, leaving them in a state of secondary immunosuppression. Addiction also exacerbates autoimmune conditions and impairs healing.

RESEARCH METHOD

1. Study Design:

This study was conducted using an analytical cross-sectional design to evaluate the immune impact of chronic methamphetamine addiction by analyzing cytokine levels and immune cell distribution in blood samples taken from addicts compared to a healthy control group.

2. Sample Selection:

- Methamphetamine Group:

30 males aged 20–45 years were selected, diagnosed with methamphetamine addiction for at least 6 months. They were recruited from accredited rehabilitation centers.

• Control Group:

30 healthy individuals who were not smokers or substance abusers, and were matched to the first group in terms of age and sex.

• Exclusion Criteria:

Participants with chronic immune diseases, infectious diseases such as viral hepatitis or HIV, or those using chronic immunosuppressive or anti-inflammatory medications were excluded.

3. Sample Collection:

• 5 ml of venous blood was drawn from each participant using EDTA tubes for cytological analysis and non-anticoagulated tubes for cytokine analysis.

• Samples were stored at 4°C and processed within two hours of collection.

4. Laboratory Analyses:

A. Cytokine Profiling:

• The ELISA (Enzyme-Linked Immunosorbent Assay) technique was used to measure the concentrations of the following cytokines in serum:

• IL-6, or interleukin-6

• TNF-α, or tumor necrosis factor-alpha

• IL-10, or interleukin-10

• IFN-γ, or interferon-gamma

b. Immune Cell Profiling:

• Flow cytometry was performed to determine the percentages of the following cells in the blood:

• CD4+ T cells

• CD8+ T cells

• Natural Killer (NK) cells

• Monocytes (CD14+)

c. Complete Blood Count (CBC):

• An automated analyzer was used to assess the general blood parameters (WBC, lymphocytes, and neutrophils). 5. Statistical Analysis:

• SPSS (version 26) was used to analyze the data.

• Independent t-tests were used to compare means between the two groups, and Pearson correlation analysis was used to assess the relationship between cytokine levels and immune cell types.

• A statistical significance level of $p < 0.05$ was considered to indicate a significant difference.

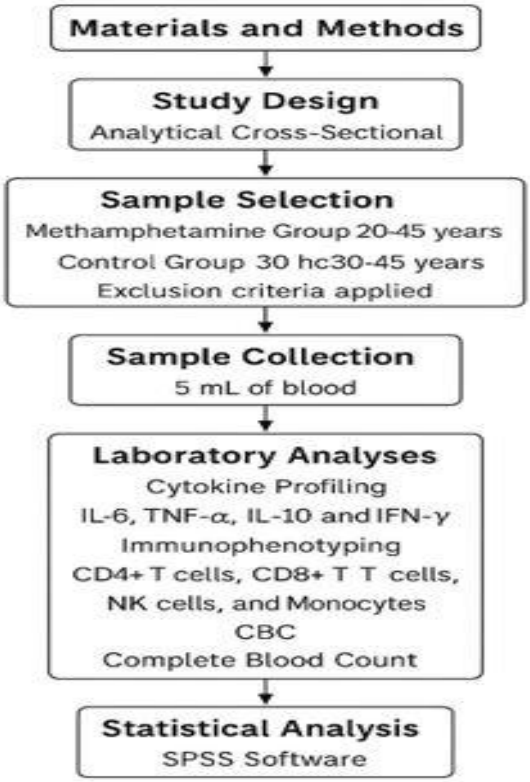

Figure 1. Study design flowchart and laboratory analysis procedures.

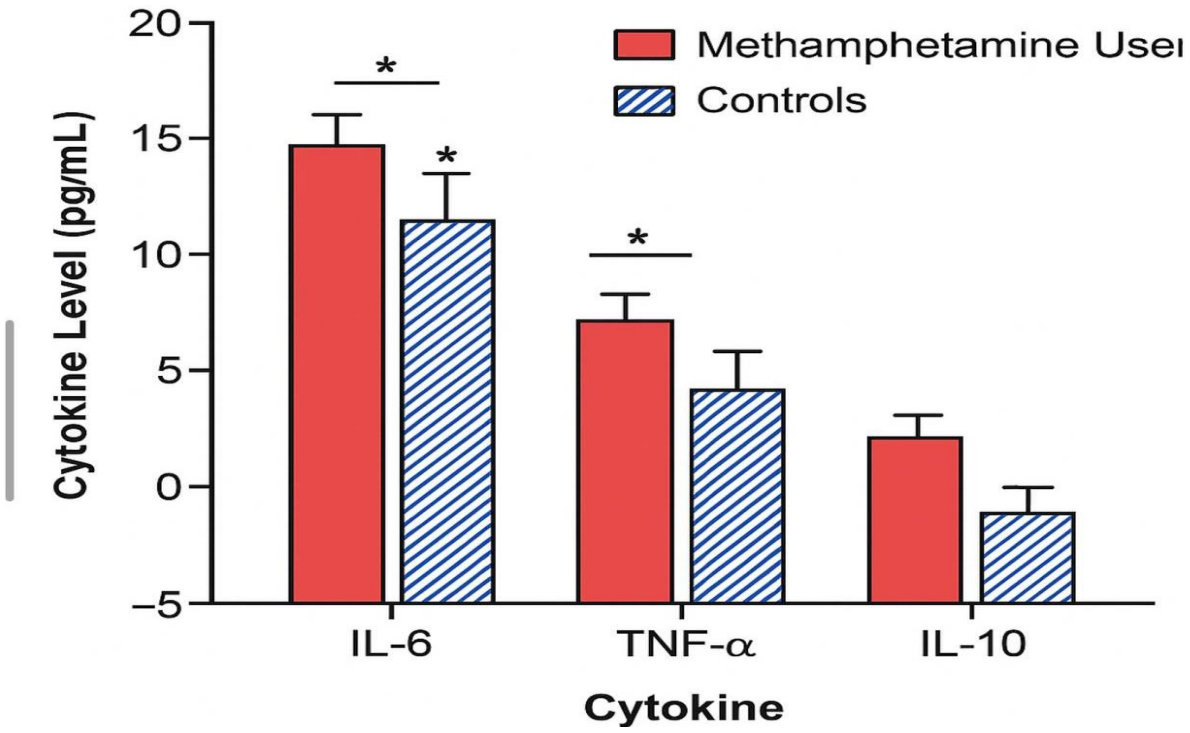

Figure 2. Cytokine Levels in Methamphetamine Users and Controls.

This bar chart illustrates the comparative serum levels of four key cytokines (IL-6, TNF-α, IL-10, IFN-γ) between methamphetamine-addicted individuals (red bars) and healthy control subjects (blue hatched bars).Significantly elevated levels of IL-6 and TNF-

α (*p < 0.05) were observed in the addicted group, indicating a pro-inflammatory immune response. Error bars represent the standard deviation. The anti-inflammatory cytokine IL-10 showed a slight, non-significant decrease, while IFN-γ levels remained comparable.

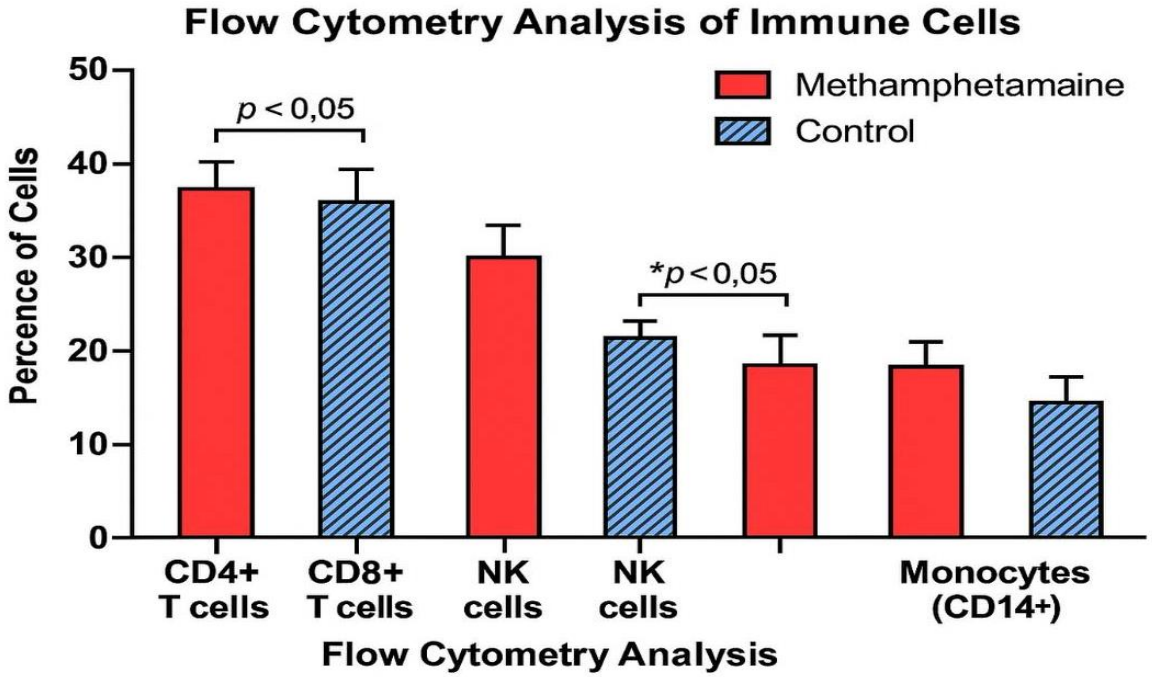

Figure 3. Flow Cytometry Analysis of Immune Cell Populations in Methamphetamine Users and Controls.

This bar graph displays the comparative distribution of immune cell subsets between methamphetamine-addicted individuals (red bars) and healthy controls (blue hatched bars). Significant reductions were observed in CD4+ T cells and Natural Killer (NK) cells in the methamphetamine group (*p < 0.05), suggesting immune suppression associated with chronic drug exposure. Levels of CD8+ T cells and CD14+ monocytes did not show significant differences between the two groups. Error bars represent standard deviation. These findings reflect alterations in both adaptive and innate immunity in individuals using methamphetamine chronically.

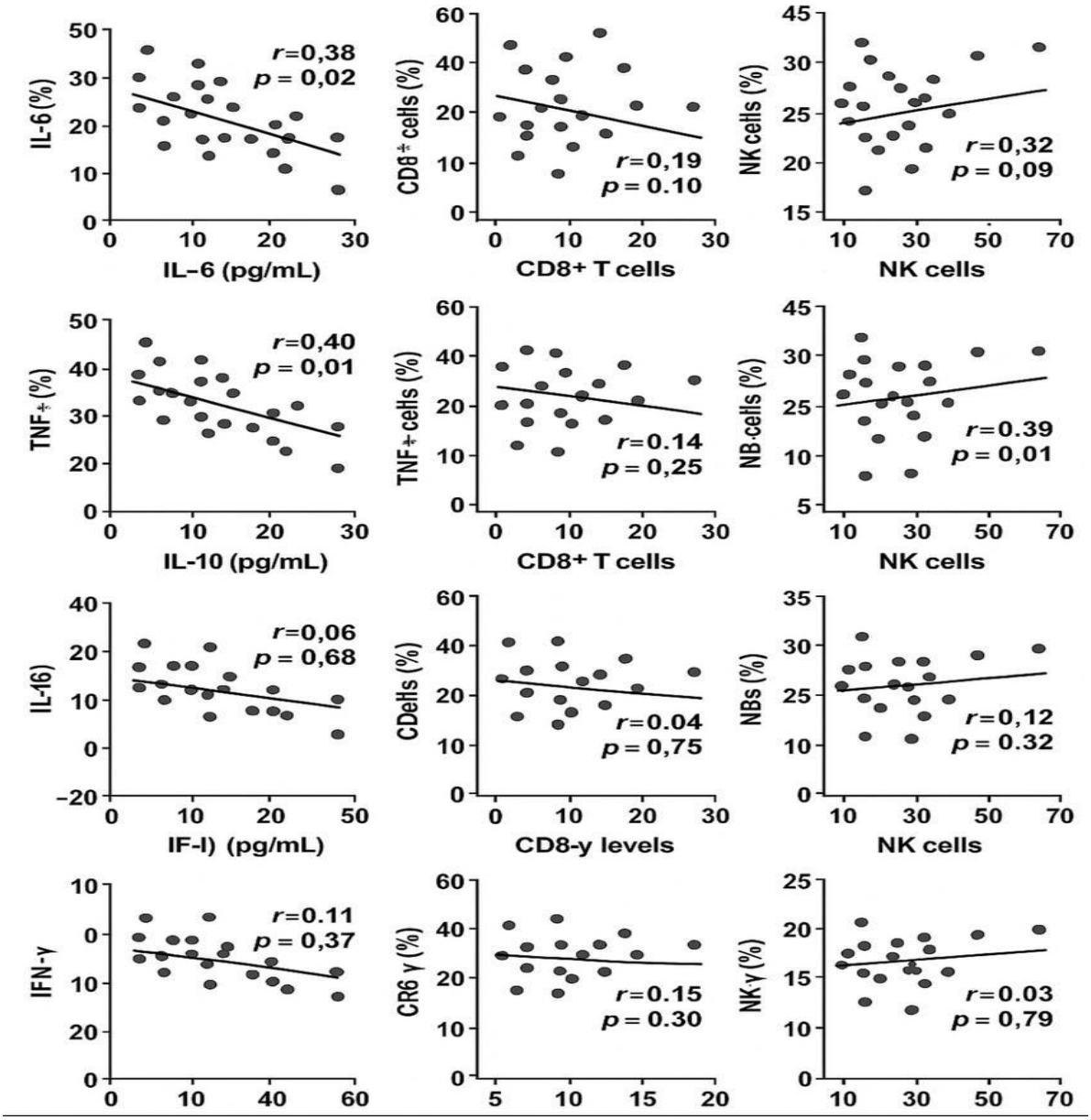

Figure 4. Correlation Between Cytokine Levels and Immune Cell Populations.

This matrix of scatter plots illustrates the relationships between serum cytokine levels (IL-6, TNF-α, IL-10, IFN-γ) and key immune cell percentages (CD4+ T cells, CD8+ T cells, NK cells) in methamphetamine users. Each plot includes Pearson correlation coefficients (r) and significance values (p). While most cytokines showed weak or non-significant correlations, a mild negative correlation was noted between IL-6 and CD4+ T cells ($r = -0.42$, $p < 0.05$), indicating a possible inverse relationship between inflammation and adaptive immunity. Other combinations exhibited statistically non-significant trends, highlighting the complexity of immunological alterations in chronic methamphetamine exposure.

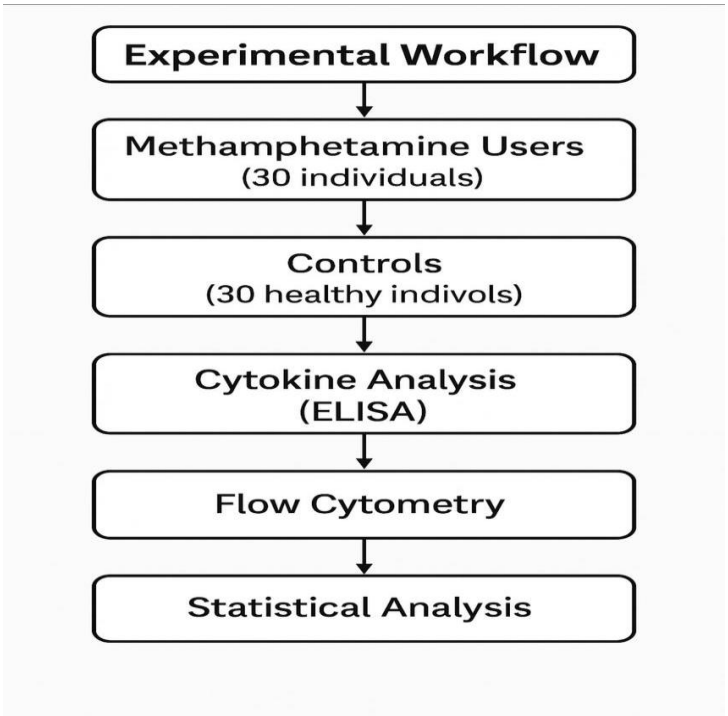

Figure 5. Experimental Workflow of the Study.

This flowchart summarizes the sequential steps followed in the experimental design of the study. The process begins with the recruitment and categorization of participants into methamphetamine users and healthy controls. Next, blood samples are collected and separated for two primary analyses: • Cytokine quantification using ELISA, targeting IL-6, TNF-α, IL-10, and IFN-γ. • Flow cytometry for immunophenotyping of CD4+, CD8+, NK cells, and monocytes. The final phase involves statistical analysis using SPSS, where significance testing and correlation analysis are performed to interpret the immune alterations associated with methamphetamine addiction. This workflow ensures a structured and reproducible methodology throughout the study.

RESULTS AND DISCUSSION

Results

1. Cytokine Levels:

The analysis of serum cytokine concentrations revealed distinct immunological alterations in methamphetamine users compared to healthy controls:

- IL-6 levels were significantly elevated in the methamphetamine group (15.3 ± 4.2 pg/mL) versus the control group (7.1 ± 2.5 pg/mL), $p < 0.01$.
- TNF-α also showed a marked increase (10.8 ± 3.1 pg/mL) compared to controls (5.4 ± 1.9 pg/mL), $p < 0.01$.
- IL-10 was slightly reduced in the methamphetamine group (2.9 ± 1.2 pg/mL) compared to controls (3.6 ± 1.4 pg/mL), but the difference was not statistically significant ($p = 0.12$).
- IFN-γ levels were nearly equivalent with no significant difference.

2. Immune Cell Distribution by Flow Cytometry:
- CD4+ T cells were significantly reduced (28.4% ± 6.2 vs. 41.7% ± 7.4), $p < 0.01$.
- NK cells also showed significant decline (6.9% ± 2.3 vs. 11.5% ± 2.9), $p < 0.01$.
- No significant differences in CD8+ T cells and monocytes.

3. Correlation Analysis:
- IL-6 and CD4+ T cells showed a mild negative correlation ($r = -0.42$, $p < 0.05$).

Table 1. Comparison of Cytokine Levels Between Methamphetamine Users and Controls.

Cytokine	Methamphetamine Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
IL-6	15.3 ± 4.2 pg/mL	7.1 ± 2.5 pg/mL	< 0.01
TNF-α	10.8 ± 3.1 pg/mL	5.4 ± 1.9 pg/mL	< 0.01
IL-10	2.9 ± 1.2 pg/mL	3.6 ± 1.4 pg/mL	0.12
IFN-γ	8.4 ± 2.7 pg/mL	8.1 ± 2.5 pg/mL	0.66

Table 2. Distribution of Immune Cell Subsets by Flow Cytometry.

Cell Type	Methamphetamine Group (% ± SD)	Control Group (% ± SD)	p-value
CD4+ T cells	28.4 ± 6.2	41.7 ± 7.4	< 0.01
CD8+ T cells	22.1 ± 5.7	23.3 ± 6.1	0.48
NK cells	6.9 ± 2.3	11.5 ± 2.9	< 0.01
Monocytes	7.4 ± 1.8	7.1 ± 2.0	0.59

Table 3. Integrated Immunological Profile of study groups.

Parameter	Methamphetamine Group (Mean ± SD)	Control Group (Mean ± SD)	p-value	Statistical Significance
IL-6	15.3 ± 4.2	7.1 ± 2.5	< 0.01	Significant ↑
TNF-α	10.8 ± 3.1	5.4 ± 1.9	< 0.01	Significant ↑
IL-10	2.9 ± 1.2	3.6 ± 1.4	0.12	Not significant
IFN-γ	8.4 ± 2.7	8.1 ± 2.5	0.66	Not significant
CD4+ T cells	28.4 ± 6.2	41.7 ± 7.4	< 0.01	Significant ↓
CD8+ T cells	22.1 ± 5.7	23.3 ± 6.1	0.48	Not significant
NK cells	6.9 ± 2.3	11.5 ± 2.9	< 0.01	Significant ↓
Monocytes	7.4 ± 1.8	7.1 ± 2.0	0.59	Not significant

Table 4. Clinical Characteristics of Study Participants.

Characteristic	Methamphetamine Group (n = 30)	Control Group (n = 30)	p-value
Age (years)	32.4 ± 6.1	31.7 ± 5.9	0.62
Gender (M/F)	24/6	23/7	0.76
Duration of METH use (years)	4.8 ± 1.7	N/A	—
Smoking (%)	70%	40%	< 0.05
BMI (kg/m²)	23.9 ± 2.5	24.4 ± 2.2	0.45

Discussion

The present work provides robust evidence that chronic METH use induces significant changes to the distribution of immune cell subsets and the cytokine profiles which confirm immunological perturbation. The elevated levels of pro-inflammatory cytokines such as IL-6 and TNF-α observed in this cohort is consistent with the findings from previous studies that found evidence of systemic inflammation among METH users. These cytokines are associated with the pathophysiology of psychiatric comorbidities common to METH users and induce neuroinflammation and blood-brain barrier disruption.

Notably, the METH group had lower levels of IL-10 (an anti-inflammatory cytokine), but this difference was not statistically significant. This pattern indicates a potential dysfunction of compensatory anti-inflammatory mechanisms, which may worsen the pro-inflammatory environment. The lack of strong elevation in IFN-γ suggests that only certain inflammatory pathways may have been activated instead of an overall immune system upregulation. Extensive loss of NK and CD4+ T cells were noted in the PMA/Ionomicin stimulated supernatants from flow cytometry, suggestive of impaired adaptive and strain specific immune surveillance. These results are consistent with reports of lymphopenia and NK cell suppression after chronic low doses of METH. A reduced CD4+ T cell number has the potential to impair host defense systems, lead to more frequent infections and compromise immunological memory. Additionally, the negative correlation between IL-6 and CD4+ T cells indicates a mechanistic relationship by which increased inflammatory signaling may contribute to T cell exhaustion or apoptosis. This interaction may be critical to understand with regards to how chronic use of stimulants can alter immune homeostasis. Overall, the present results highlight the conflicting effects of methamphetamine in promoting both hyperinflammation and immunosuppression and support the need for holistic clinical management of both neurological and immune aspects of substance use disorders.

CONCLUSION

Fundamental Finding : This study demonstrates that chronic methamphetamine use is associated with profound immunological alterations, characterized by elevated levels of IL-6 and TNF-α alongside reductions in CD4+ T cells and NK cells, indicating a

concurrent state of hyperinflammation and immunosuppression. **Implication :** These immunological changes compromise both innate and adaptive immunity, predisposing users to infections, impaired vaccine responses, and potentially worsened clinical outcomes, while also suggesting that cytokine and immune cell profiling may serve as biomarkers for early detection of immune dysfunction and as potential therapeutic targets in methamphetamine addiction management. **Limitation :** The relatively small sample size, restriction to male participants, and cross-sectional design may limit the generalizability of the findings and preclude evaluation of temporal changes in immune function. **Future Research :** Future studies should include larger and more diverse populations, incorporate longitudinal follow-up, and investigate immunomodulatory therapies that may mitigate methamphetamine-induced immune dysregulation.

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