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Research Article

Laminin Levels as a Biomarker for Liver Injury in Methamphetamine Addicts

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Abstract:

Background: Methamphetamine (METH) is a potent synthetic stimulant that significantly impacts the central nervous system and can lead to severe liver damage. Prolonged METH use causes hepatocytes damage and fibrosis, marked by increased laminin deposition, a key component of the extracellular matrix produced by stellate cells during liver injury.

Objectives: This study aimed to investigate the effects of METH abuse on liver function and laminin (LN) levels, correlating these with the duration and concentration of METH use.

Methods: Conducted from January to August 2024, this case-control study involved 75 male participants with METH addiction (6-120 months of use) and 75 healthy controls aged 18-51. Key biomarkers were measured, including serum laminin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), Gamma-Glutamyl Transferase (GGT), albumin and the serum concentration of methamphetamine levels.

Result: The study revealed a significant increase in serum laminin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and Gamma-Glutamyl Transferees. A notable significant decrease in albumin was detected. Additionally, the study demonstrated a positive correlation between LN levels and the duration of drug abuse, as between the concentration of methamphetamine levels with aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, Gamma-Glutamyl Transferees, and albumin, and correlation between methamphetamine of duration with aspartate aminotransferase, alanine aminotransferase, Gamma-Glutamyl Transferees.

Conclusions: The results indicate that METH addiction leads to elevated laminin levels and liver enzyme activity, suggesting progressive liver fibrosis and injury correlating with the duration of substance abuse.

Keywords: Laminin; Liver function; Liver injury; Methamphetamine; Toxicity.

Introduction

Methamphetamine, also known as "ice" or "crystal", is a potent synthetic central nervous system stimulant (1) that is widely abused and often smoked (2), it is absorbed in the lungs and metabolized in the liver to produce metabolites and distributed to various organs, with higher levels accumulating in the lungs, liver, brain, and kidneys (3). Studies have shown high levels of methamphetamine accumulate in the liver but to a lesser extent, in the brain as well as kidneys (4). The hepatotoxicity effects of methamphetamine typically appear within three to 14 days (5), and this leads to liver damage through oxidative stress and inflammation. Prolonged use of methamphetamine may result in hepatic fibrosis (6), cirrhosis, and hepatocellular carcinoma, ultimately resulting in death (7). Hepatic fibrosis is characterized by the excessive deposition of extracellular matrix (ECM), a complex network comprising proteins and polysaccharides. The ECM consists of a Basement Membrane, A thin, sheet-like structure composed mainly of type IV collagen that binds with laminin after liver injury (8). Liver histology is considered the gold standard for evaluating fibrosis. However, it is not always available and may be prone to sampling errors (9). To reduce the need for liver biopsy, serum markers representing extracellular matrix components, such as laminin (LN) (10). Laminin is a non-collagenous glycoprotein synthesized by hepatic stellate cells and deposited at the level of the hepatic basement membrane (11). It serves as a direct and noninvasive marker of hepatic fibrosis, and its concentration is influenced by the severity of liver cell damage and impaired liver function (12). The rise in methamphetamine use in Iraq has become that over 40% of individuals aged 15 to 35, with methamphetamine being notably prevalent.

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This surge necessitates urgent research to understand the underlying causes and effects (13).

The present study aimed to investigate the harmful effects of methamphetamine abuse on liver health based on concentration levels and the duration of methamphetamine addiction. Additionally, it seeks to assess the serum levels of laminin and liver enzymes in addicts.

Patients and Methods

This study was an analytical observational research with a case-control study approach conducted on patients diagnosed by a specialist psychiatric physician in the Medical City Department, Social Rehabilitation Center for Addictions, and the Medico-Legal Institute in Baghdad. It involved 75 methamphetamine addiction. Their age range was between 18-51 years. with duration periods of abuse from 6 to 120 months and different doses of addiction, and matched ages to 75 healthy controls. All of them had the test for viral hepatitis, which was negative. Excluded from this study were alcohol addicts and other drugs as well, patients with liver, heart, and kidney diseases, and Ages less than 18. Research permission was obtained with ethical approval from the Health Research Ethics Committee of the College of Medicine, University of Baghdad, and consent from the hospital and participants. The following biomarkers were measured in the blood: aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, Gamma-Glutamyl Transferees, and albumin. Beckman Coulter used a clinical automation system to measure them. Also, the enzyme-linked immunosorbent assay (ELISA) measured serum laminin levels.

The concentration of methamphetamine levels in serum in this study used the Randox Evidence MultiSTAT Immnoanalyser (Drugs of Abuse (DOA) Toxplex Blood Array). These competitive enzyme immunoassays run on the automated biochip array analyzer. Evidence Multi-STAT is used for the semi-quantitative detection of methamphetamines in human blood with a cut-off of 20 ng/ml.

Statistical analysis

Data analysis was performed with SPSS software version 16.0. Data were presented as Mean ± SEM to compare serum levels based on analysis of (t-test) for each study. Pearson correlation analysis was performed to see if there was a significant association between the parameters. The alpha level for statistical significance was established at a threshold of $p < 0.05$.

Results

The mean value of serum ALT levels was significantly elevated in addicts, with a mean of (44.00± 4.28 U/L) compared to controls with a mean of (19.18± 0.55 U/L; $p < .000001$). Similarly, AST levels were significantly higher among addicts, with a mean of (39.66± 5.07 U/L), whereas the controls exhibited a mean of (17.55± 0.51 U/L; $p =< 0.0001$).

ALP levels also demonstrated a significant increase in the addict's mean (107.26± 4.79 U/L) compared to the control group with a mean of (17.55± 0.51 U/L, $p < .000001$). In addition, GGT levels followed a similar trend, with addicts showing a mean of (80.44± 2.49 U/L) in contrast to controls with a mean of (45.87± 1.48 U/L, $p < .000001$). Moreover, LN levels were significantly higher in addicts, with a mean of (95.32± 5.38 pg/ml), whereas the controls exhibited a mean of (42.56± 1.35, $p =< 0.000001$). Also, Albumin levels were significantly reduced in addicts, with a mean of (4.35± 0.05 g/L) compared to controls, with a mean of (5.46± 0.07 g/L, $p < .000001$) as shown in Table 1, Figure 1.

Table 1 Mean (±SEM) value of parameters of healthy controls and Methamphetamine addicts:

Parameter	Addicts (n=75)	Control (n=75)	*P* value
Age /years	27.28± 0.79	27.99± 0.87	0.546
Duration of addiction/ month	48.08± 3.77	--------	---------
concentration of METH levels (ng/ml)	40.32± 3.57	---------	----------
Laminin pg/ml	95.32± 5.38	42.56± 1.35	< 0.000001*
ALT U/L	44.00± 4.28	19.18± 0.55	< 0.000001*
AST U/L	39.66± 5.07	17.55± 0.51	< 0.0001*
ALP U/L	107.26± 4.79	58.48± 1.99	< 0.000001*
GGT U/L	80.44± 2.49	45.87± 1.48	< 0.000001*
Alb. g/l	4.35± 0.05	5.46± 0.07	< 0.000001*

**: significant at $p < 0.05$*

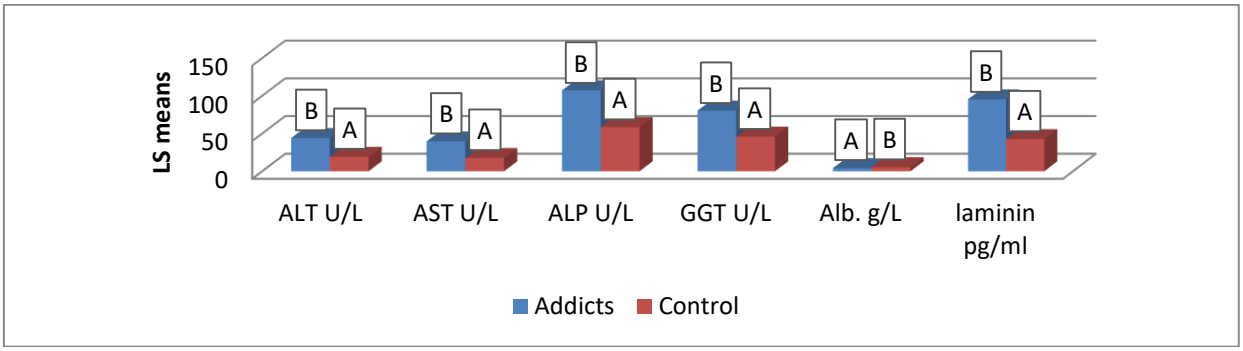

Figure 1. Distribution of all parameters in addicts and controls.

The present study showed that the correlation between the concentration of methamphetamine and laminin is weak and non-significant (r = 0.123, p = 0.2984). Regarding liver function enzymes, a very strong positive correlation exists between the concentration of methamphetamine and ALT, and AST levels (r = 0.744, p < 0.0001), (r = 0.548, p < 0.0001), respectively. ALP exhibited a weaker yet significant positive correlation with methamphetamine abuse (r = 0.289, p = 0.0132), while GGT showed a moderate positive correlation (r = 0.491, p < 0.0001). Also, Albumin exhibited a weak negative correlation with methamphetamine use (r = -0.286, p = 0.0141). Moreover, a strong positive correlation was observed between Laminin (r = 0.556, p < 0.0001) and duration of methamphetamine abuse. Significant correlations were also observed between the duration of methamphetamine use and liver enzymes: ALT (r = 0.373, p = 0.0012), AST (r = 0.391, p = 0.0006), ALP (r = 0.172, p = 0.1468), GGT (r = 0.304, p = 0.0088), albumin (r = -0.11, p = 0.355) as shown in Table 2, Figure 2.

Table 2 Relationships between various biochemical markers with concentration of methamphetamine and the buse duration in addicts:

variable		Concentration of Metham-phetamine ng/ml	Laminin pg/ml	Duration of addiction month
laminin pg/ml	r	0.123	1	
	p	0.2984		
Duration/month	r	0.227	0.556	1
	p	0.0536	<0.0001	
ALT U/L	r	0.744	0.115	0.373
	p	<0.0001	0.3322	0.0012
AST U/L	r	0.548	0.141	0.391
	p	<0.0001	0.2341	0.0006
ALP U/L	r	0.289	0.138	0.172
	p	0.0132	0.2449	0.1468
GGT U/L	r	0.491	0.196	0.304
	p	<0.0001	0.0965	0.0088
Alb. g/L	r	-0.286	0.136	-0.11
	p	0.0141	0.2506	0.355

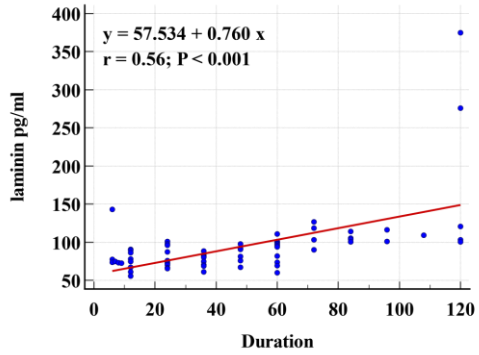

Figure 2: Correlation between Laminin and Duration of methamphetamine abuse in months.

Discussion

The mean age value in the present study was similar between the two groups. The p-value was not statistically significant between the two groups, suggesting that age is not a confounding factor in this study. These findings matched a previous study (3).

The present study's findings showed a significant elevation of serum ALT, AST, GGT, ALP, and GGT levels in addicts compared to healthy controls.

Also, the present study showed a very strong positive correlation between the concentration of methamphetamine and ALT and AST levels; ALP exhibited a weaker yet significant positive correlation with the concentration of methamphetamine abuse, while GGT showed a moderate positive correlation.

Also, Albumin exhibited a weak negative correlation with the concentration of methamphetamine abuse. Significant correlations were also observed between the duration of methamphetamine use and liver enzymes.

These findings were consistent with a previous study, which noted that prolonged abuse impacts liver health. Additionally, levels of serum liver enzymes were higher than the control group (14). Also, agreed with the previous study on rats, which observed that increased doses affect a healthy life (2). So prolonged and high-dose abuse of METH can lead to liver injury by triggering oxidative stress and fibrosis (15). Oxidative stress arises from a state of disequilibrium between the endogenous generation of oxidative stress, antioxidant defenses, and reactive oxygen species(16). Oxidative stress is linked to increased levels of Reactive Oxygen Species (ROS) and depletion of glutathione (GSH) (17), which generates an increase in free radicals (18) That may induce damage to hepatocytes (19) and lead to the release of liver enzymes into the bloodstream, increasing their serum concentrations (20). The injured hepatocytes can directly or indirectly induce hepatic stellate cell (HSC) activation and release cytokines (21), which can produce an extracellular matrix (ECM), leading to fibrosis (22). It was characterized by excessive accumulation of hepatic ECM in the space of Disse (8).

In the present study, Laminin levels were significantly higher in people with addiction compared to controls. Also, a strong positive correlation was observed between Laminin and the duration of methamphetamine abuse. Also, the correlation between Laminin and the concentration of methamphetamine was weak and not significant. This suggests that laminin levels are more reflective of chronic methamphetamine abuse rather than the concentration of METH after continuous liver injury (23).

It has been reported that serum laminin can reflect the activity of liver fibrosis, and previous studies demonstrate that raised serum levels of LN are related to the severity of liver injury and fibrosis in various chronic liver diseases, alcohol abuse, and other drugs (24).

In a previous study similar to the present study, conducted by Akhter et al., rats were administered methamphetamine for eight weeks. The study aimed to investigate oxidative stress and inflammation; histopathological examination revealed an accumulation of inflammatory cells and varying ECM deposition in the liver (25).

A previous study conducted a study on rats used Iranian crack, while another studied cocaine addicts. Both studies found that toxic substances can impair the liver's ability to regenerate, leading to permanent liver damage, fibrosis, and eventually cirrhosis (26) (27). This finding is comparable to the present study's examination of the harmful effects of methamphetamine on liver health.

Limitation

There were some factors and reasons behind the limitations of the study: the small number of methamphetamine abusers that we were able to collect in the study, community customs led to restricted obtaining of other samples, and some patients did not provide their personal information to obtain the sample, which prevented obtaining more samples and information

Conclusion

The study showed that methamphetamine has harmful effects on liver health, which are linked to the concentration of METH levels and the duration of abuse. Elevated LN levels indicate progressive fibrosis associated with ongoing liver injury, showing a positive correlation between LN and the duration of methamphetamine abuse. Also, notable increases in liver enzymes and a positive correlation were found between liver function, methamphetamine concentration, and the duration of methamphetamine abuse.

Authors' declaration:

We confirm that all the Figures in the manuscript are ours. Besides, the authors have signed an ethical consideration approval (Ethical Clearance). The project was approved by the local ethical committee in the Department of Biochemistry, College of Medicine, University of Baghdad according to the guidelines on biomedical research. The license has the code number (215) and is dated July 30, 2024.

Conflicts of Interest: None.

Funding: None

Authors' contributions

Study conception & design: (Shahbaa Waheed Sami, Halla Ghazi Mahmood). Literature search: (Shahbaa Waheed Sami, Halla Ghazi Mahmood). Data acquisition: (Shahbaa Waheed Sami, Halla Ghazi Mahmood). Data analysis & interpretation: (Shahbaa Waheed Sami, Halla Ghazi Mahmood). Manuscript preparation: (Shahbaa Waheed Sami, Halla Ghazi Mahmood). Manuscript editing & review: (Shahbaa Waheed Sami, Halla Ghazi Mahmood).

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مستويات اللامنيين كمؤشرحيوي لاصابة الكبد لدى مدمني الميثامفيتامين

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الخلاصة :

الخلفية: الميثامفيتامين منبه صناعي يؤثر على الجهاز العصبي المركزي .يمكن أن يؤدي الاستخدام المطول للميثامفيتامينالى مستويات عالية من تراكم في الكبد ’مما يؤدي الى أتلاف خلايا الكبد و احداث تليف .

الهدف: تهدف هذه الدراسة الى استكشاف تأثير تعاطي الميثامفتامين على الكبد أعتمادا على مستويات التركيز ومدة التعاطي من خلال تقييم وظائف الكبد ومستويات اللامنين.

الطرق : شملت الدراسة 75 رجلا من مدمنين على الميثامفيتامين كانوا يتعاطون المخدر لمدة 6-120 شهرا وبجرعات مختلفة .بالاضافة الى ذلك ’ كان هنالك 75 من الاشخاص الاصحاء من اعمار متطابقة في مجموعتين (18-51) . قامت الدراسة بقياس المؤشرات الحيوية اللامنين’ اسبارتييت امينو ترانسفيريز ’الانينن امينو ترانسفيريز ’ فوسفايت القاعدي ’جاما كلوتاميل ترانسفيريز والالبومين وتركيزمستويات الميثامفيتامين في المصل.

النتائج : كشفت الدراسة عن زيادة كبيرة في اللامنين’ اسبارتييت امينو ترانسفيريز ’الانينن امينو ترانسفيريز ’ فوسفايت القاعدي ’ وجاما كلوتاميل ترانسفيريزوانخفاض ملحوظ في الالبومين. بالاضافة الى ذلك أظهرت الدراسة وجود ارتباط ايجابي بين مستويات الامنين ومدة تعاطي المخدرات وكذلك بين تركيز الميثامفيتامين ومدة التعاطي مع وظائف الكبد.

الاستنتاجات: أظهرت الدراسة أن الميثامفيتامين له آثار ضارة على صحة الكبد.وتشير مستويات الامنيين المرتفعة الى تليف تدريجي مرتبط باصابة الكبد المستمرة ’ مما يدل على وجود ارتباط ايجابي بين الامنيين ومدة تعاطي الميثامفيتامين وايضا زيادة في وظائف الكبد .

الكلمات المفتاحية : أصابة الكبد; الميثامفيتامين; الامنيين;سمية ;وظائف الكبد.