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WNT-Inducible Signaling Pathway Protein 1 (WISP-1) and Malondialdehyde Level in Methamphetamine Users and Its Effects on the Kidneys

Shatha Hamed Jwaid [1*], Huda Farhan Ahmed [2], Shahbaa Waheed [3]

[1*] College of Health and Medical Technologies, Middle Technical University, Baghdad, Iraq.
E-mail: shathahamed143@gmail.com

[2] College of Health and Medical Technologies, Middle Technical University, Baghdad, Iraq.
E-mail: hudafarhan@mtu.edu.iq

[3] Medico-legal Institute, India. Email: chemist.shahbaaa@gmail.com

Abstract

Methamphetamine is an extremely addictive stimulant of the central nervous system. It makes a person more alert and physically active, but also causes a rapid heart rate, violent behaviour, high blood pressure, and hallucinations. Methamphetamine is metabolised by the liver and excreted by the kidneys, causing inflammation and may lead to fibrosis in both kidneys. Both WNT-inducible signaling pathway protein 1 (WISP-1), which is engaged in fibrotic processes in a variety of organ systems, and malondialdehyde (MDA), which is an indicator of oxidative stress in kidney tissue and is measured in blood, assesses damage caused by oxidative reactions, have been studied. In this research, we aim to inspect the impact of different concentrations and durations of methamphetamine use on kidney toxicity and fibrosis, and the correlation between the level of methamphetamine use and the biomarkers WISP-1 and MDA as new potential biomarkers. 75 men with methamphetamine addiction and misusing the drug for more than 6 months up to upto120 months at varying dosages participated in this case-control study. Furthermore, 75 healthy controls with ages ranging from 18 to 51 were part of groups at the Social Rehabilitation Centre for Addictions, Medico-legal Institute, and Medical City Department in Baghdad from February to July 2021. The study measured biomarkers, including WISP-1 and MDA levels, by Enzyme-linked Immunosorbent assay. Urea, creatinine and albumin by the Beckman Coulter automation system, Glomerular filtration rate (GFR) estimated mathematically. Serum concentration of methamphetamine levels by Randox Evidence MultiSTAT Immnoanalyser (Drugs of Abuse (DOA) Toxplex Blood Array). The result shown there was a significant difference [P-value<0.001] in serum urea, creatinine, albumin and GFR. It also a positive correlation between kidney test and the concentration of methamphetamine uses the *duration* of abuse. The correlation was positive between WISP-1 and MDA levels in this study. Methamphetamine is harmful to renal health, according to the study. Elevated WISP-1 and MDA levels imply progressive fibrosis with ongoing damage to the kidney, showing a positive correlation with duration of addiction and methamphetamine concentration levels.

Keywords:

Kidney dysfunction and fibrosis, methamphetamine addicts, WNT, WISP-1, malondialdehyde, GFR.

Corresponding Author: Shatha Hamed Jwaid, E-mail: shathahamed143@gmail.com

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Introduction

Methamphetamine is a highly addictive psychostimulant that produces euphoria and insomnia at the same time and is best known as a recreational drug (Devi & Priya, 2024). It can be taken orally, injected intravenously, inhaled intranasal, or smoked as a hydrochloride salt that contributes to oxidative stress, reactive oxygen species, aging, necrosis, and apoptosis (Weng et al., 2020). One effect of methamphetamine is the stimulation of endothelin-1, the most potent renal vasoconstrictor. Increased production of endothelin-1 reduces renal blood flow, which reduces glomerular filtration rate (GFR), leading to an increase in blood pressure in the kidneys (Kohan et al., 2011; Suji & Kumar, 2022). Methamphetamine's effects on the kidneys are divided into three categories: nephrotoxicity, vascular consequences, and rhabdomyolysis (Godrati et al., 2020). Serum markers, or WISP-1 “MCNC4/ELM-1” (Chiang et al., 2015), this protein is associated with renal fibrosis and is commonly associated with inflammation and oxidative stress and can serve as an invasiveness biomarker for patients with chronic kidney disease (Zhong et al., 2017) Malondialdehyde (MDA) is the most significant indicator of lipid peroxidation and oxidative stress (Suresh et al., 2010). It is a valuable marker for evaluating oxidative damage by degrading key chain reactions that lead to the creation of diverse active compounds, leading to cell damage (Singh et al.,2014). Levels rise with the advancement of renal dysfunction, especially in patients undergoing dialysis (Peti et al., 2011). Concomitant with the progression of fibrosis and progressive acute renal failure, both serum markers representing WISP1 and MDA increase. This study aims to inspect the negative impact of methamphetamine addiction on renal dysfunction and fibrosis based on the study of both the concentration and duration of methamphetamine addiction (Rothwell & Cruz, 2025). In addition to the study of WISP1 and MDA, a new biomarker that can predict renal dysfunction and fibrosis in addicts.

Materials and Methods

This study carries on patients diagnosed by a psychiatrist in three centres in Baghdad, including the Social Rehabilitation Centre for Addictions, the Medical City Department, and the Medico-legal Institute, from February to July 2024. Permission for the study was acquired with ethical approval from Baghdad Medical College No. 215/EC/KEPK/FK-UNDIP/III/2024. The study included 75 methamphetamine addiction men their age range was between 18-51 years, with the duration of abuse for 6-120 months, with different doses of addiction and 75 healthy individuals as a control group.

Blood samples (10 ml) were collected by venipuncture using sterile disposable syringes. Each sample was divided into two parts and put in a gel tube, then centrifuged to separate and collect serum for biochemical tests. The concentration of methamphetamine levels in serum in this study was measured using the Randox Evidence MultiSTAT Immnoanalyser (Drugs of Abuse (DOA) Toxplex Blood Array). These competitive enzyme immunoassays run on the automated biochip array analyser. Evidence MultiSTAT is used for the semi-quantitative detection of methamphetamines in human blood with a cut-off of 20 ng/ml. Sandwich enzyme-linked immunosorbent assay was used to measure serum WISP-1 and malondialdehyde levels. Urea, creatinine and albumin were quantified in this investigation using the Beckman Coulter as a clinical automation system to measure them. GFR was estimated using the MDRD GFR equation, which was based on creatinine and patient characteristics like age and gender.

Statistical Analysis

Descriptive data analysis methods, such as percentages, mean, and standard deviation, were carried out. In our study, the independent T-test, receiver operating characteristic (ROC) curve, and Pearson's correlation test were used too. The significance threshold of < 0.05 was considered significant. The SPSS 24 program was used to examine current data.

Results and Discussions

This study involved 75 men with methamphetamine addiction and 75 healthy men as controls. The results indicated that serum albumin levels were significantly lower in addicts (4.35±0.05 g/L) than in controls (5.46±0.07 g/L) (p <.0001). Uera, creatinine and GFR show a mean of (4.88±1.58 mg/dl), (88.26±10.5 mg/dl), (105.37±13.7 mg/dl) compared to controls with a mean of (3.83±0.67 mg/dl), (68.72±4.8 mg/dl) (125.12±7.4 mg/dl) with p < .0001. The biomarker WISP-1 levels were significantly higher in addicts, with a mean of (531.34±109.51 ng/ml), where the controls exhibited a mean of (25.05±8.28ng/ml). Similarly, MDA levels were significantly higher in addicts, with a mean of (291.10±95.11ng/ml), whereas the controls exhibited a mean of (67.21±5.23 ng/ml).

Table 1. Study group distribution based on age, duration of addiction, concentration of METH and kidney biomarker test

Parameters	Addicts METH (n=75)	Controls (n=75)	P value
Age	27.28± 0.79	27.99± 0.87	0.546
Duration period	48.08± 3.77	--------	---------
Concentration of METH levels	40.32± 3.57	---------	----------
Alb.(g/l)	4.35± 0.05	5.46± 0.07	< 0.0001*
urea (mg/dl)	4.88±1.58	3.83±0.67	< 0.0001*
creatinine(mg/dl)	88.26±10.5	68.72±4.8	< 0.0001*
GFR	105.37±13.7	125.12±7.4	< 0.0001*
WISP-1(ng/ml)	531.34±109.51	25.05±8.28	< 0.0001*
MDA(ng/ml)	291.10±95.11	67.21±5.23	< 0.0001*

In Table 2, the correlation is positive, strong to moderate between the concentration and duration of methamphetamine use with WISP-1 and MAD levels. There is a positive association with methamphetamine and a negative association with duration of use for albumin level. A positive association was also found between urea and creatinine and duration of use. Furthermore, there is a negative relationship between glomerular filtration rate and duration of use, which is statistically significant.

Table 2. Association between methamphetamine concentration levels and duration of use in addicts with various biochemical markers

	Methamphetamine		Duration	
	Pearson Correlation	P-value	Pearson Correlation	P-value
WISP-1 (ng/ml)	0.62	0.001	0.530	0.031
MDA (ng/ml)	0.42	0.024	0.391	0.021
Alb. g/L	0.289	0.013	-0.343	0.023
Urea(mg/dl)	0.481	0.050	0.358	0.001
Creatinine(mg/dl)	0.432	0.010	0.551	0.041
eGFR	-0.552	0.020	0.432	0.432

WISP-1 and MAD were significantly positively correlated with urea and creatinine, while it was significantly negatively correlated with GFR, as shown in Table 3.

Table 3: Correlations between WISP-1 and MDA and kidney function test

	WISP-1		MDA	
	Pearson Correlation	P-value	Pearson Correlation	P-value
Alb. (g/L)	0.131	0.398	0.178	0.248
Uera(mg/dl)	0. 481	0.050	0.594	0.024
Creatinine (mg/dl)	0.546	0.045	0.459	0.030
GFR	- 0.687	0.02	-0.63	0.037

According to the ROC curve of the level between the addicted groups and the control group, shown in Table 3 and Figure 1. The cutoff value for WISP-1was 164.25 with 100% sensitivity and 100% specificity, area under the curve (AUC) of 0.95 was highly significant (P<0.0001), The cutoff value for MAD was 89.00 with 95% sensitivity and 100% specificity, AUC of 0.99 was highly significant (P<0.0001).

Table 3. ROC curve for GDF-15 (receiver operating characteristic curve test)

Markers	**AUC**	**p-value**	**Cut-off Point**	**Sensitivity**	**Specificity**
WISP-1 (ng/ml)	0.95	<0.0001	164.25	100%	100%
MDA (ng/ml)	0.99	<0.0001	89.00	95%	100%

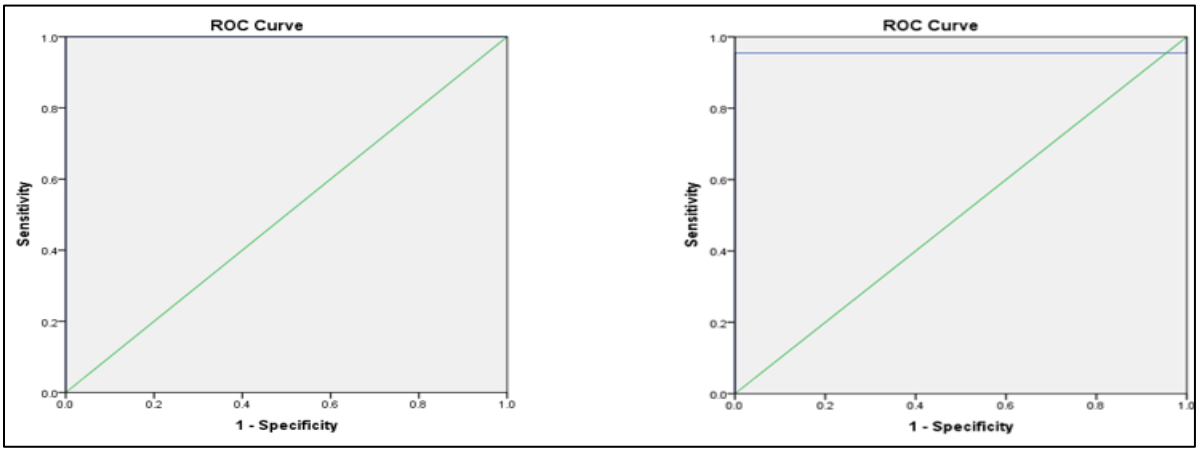

Figure 1. ROC curve for GDF-15 (receiver operating characteristic curve test)

This study showed no statistical significance between the addicted group and the control group concerning age, indicating that age is not an important factor. The current results showed a significant increase in the level of blood urea, serum creatinine, and glomerular filtration rate levels in addicted men compared to healthy controls (Castillo & Al-Mansouri, 2025; Shetty & Kapoor, 2024; Malhotra & Joshi, 2025) and a decrease in albumin levels when comparing addicted individuals with healthy controls in as shown in Table 1. Amphetamines are toxic to muscles and cause rhabdomyolysis, which causes vascular obstruction and tubular deterioration due to myoglobin deposition (Gupta et al., 2018). Acute kidney injury or renal failure results from the released myoglobin's damage to the kidneys and a reduction of their filtration capacity. As muscle cells are destroyed, the plasma level of free myoglobin increases, and then is filtered by the kidneys. Following methamphetamine usage, several processes are believed to be involved, including oxidative stress, reactive oxygen species, aging, apoptosis, and necrosis. The statistically significant increase in creatinine with duration of use suggests that long-term methamphetamine use may cause metabolic derangements, leading to toxic effects of methamphetamine on kidney dysfunction. Some research has shown that methamphetamine increases serum creatinine levels in kidney transplant recipients, one year after

transplantation from addicted donors (Habibollahi et al., 2020). The kidney is affected much more than any other organ. The glomerular filtration rate with the length of chronic methamphetamine use affects its filtration efficiency, and the increased production of endothelin 1 causes a decrease in both the renal blood flow level and GFR and leading to renal hypertension (Rahimi et al., 2018). Also shows the correlation is significant and positive between the concentration of methamphetamine and the duration of its use, and the WISP1 level and MAD level. According to this study, WISP1 may play a part in stimulating renal fibroblast activity, mostly during inflammation. One harmful feature of kidney damage is inflammation, which is linked to the onset of renal fibrosis and can result in decreased kidney function. The result is consistent with another study (Wang et al., 2022), which showed the importance of proximal tubular epithelial cells in the WISP1-mediated inflammatory response. These cells are prevalent in the kidney and can produce cytokines that can attract and activate macrophages. MDA is a crucial biomarker that shows lipid peroxidation (Suresh et al., 2010). MDA is one of numerous aldehydes produced by lipid oxidation that are reliable markers of tissue damage and nephrotoxicity. Malondialdehyde can effectively identify graft malfunction before blood creatinine does, and it is a dependable diagnostic biomarker of first graft injury. Additionally, the strategy of employing MDA as a safety biomarker when employing potentially nephrotoxic drugs and as a trigger to start and track immunosuppressive treatments seems encouraging. Our findings concur with the study by Sebnem et al (Muñoz et al., 2004)

Conclusion

Study of WISP1 and MDA as a novel biomarker that can predict kidney dysfunction and fibrosis in addicts. The study found that methamphetamine intoxication is coupled with a significant rise in the risk of kidney dysfunction, with the possibility of organ failure.

Author Contributions

All Authors contributed equally.

Conflict of Interest

The authors declared that no conflict of interest.

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