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ABSTRACT

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ASSESSMENT OF DNA OXIDATIVE DAMAGE IN INDIVIDUALS WITH METHAMPHETAMINE ADDICTION

Introduction. Methamphetamine abuse has many detrimental effects on the central nervous system. An important aspect of methamphetamine addiction is oxidative stress, characterized by an imbalance between antioxidants and oxidants, leading to disruptions in redox signaling and molecular damage. The present study was conducted to assess genomic damage in addicted males to predict their potential cancer risk.

Methods. The study involved 42 Iraqi male patients aged 16 to 46 years, diagnosed with methamphetamine addiction. The control group consisted of 24 healthy volunteers. Buccal and urine samples, as well as personal information, were obtained from all the participants. Genomic damage was evaluated by measuring micronuclei and binucleated cells in exfoliated buccal mucosa using the buccal micronucleus cytome assay. Also, urinary concentrations of 8-hydroxy-2′-deoxyguanosine (8-OHdG), a biomarker of DNA oxidative damage, were determined using an enzyme-linked immunosorbent assay.

Results and Discussion: The study compared patients (mean age 25.12 ± 6.73) and controls (23.92 ± 6.55, $p < 0.05$). Controls had higher body mass index (BMI) (20.85 ± 2.22 vs. 19.88 ± 2.3, $p < 0.001$). Patients showed elevated 8-OHdG level (1132.53 ± 3103.98 ng/ml), positively correlating with age ($r = 0.442$) and BMI ($r = 0.391$, $p < 0.01$). Micronucleus and binucleated cell frequencies were significantly higher in patients ($p < 0.001$). The patient group exhibited a higher concentration of 8-OHdG compared to the control group (6.334 ± 2.952 ng/ml). The current study offers original findings on the effect of methamphetamine abuse on genomic instability. This directs a higher frequency of chromosomal abnormalities mitotic distraction among methamphetamine users, supporting the link between methamphetamine abuse and elevated genomic instability which is an identified risk factor for the development of cancer.

Keywords: addiction, methamphetamine, 8-Hydroxydeoxyguanosine, DNA oxidation.

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ABBREVIATIONS

CNS– central nervous system (CNS)
8-OHdG – 8-hydroxydeoxyguanosine
DNA – deoxyribonucleic acid
BMCyt – buccal micronucleus cytome
BMI – body mass index
MN – micronucleus
ROS – reactive oxygen species
BER – base excision repair
NER – nucleotide excision repair

INTRODUCTION

An addictive disorder is a chronically reversible brain disease that progresses with time. It is a disease that results from facultative drug use that leads to irresistible, drug-seeking behaviors that can affect the individual's ability to function in society [1]. Methamphetamine abuse has many detrimental effects on the central nervous system (CNS). An important aspect of methamphetamine addiction is oxidative stress, characterized by an imbalance between antioxidants and oxidants, leading to disrupted redox signaling and molecular damage. To develop effective treatment plans for methamphetamine addiction, it is essential to identify the oxidative stress process [2]. One of the adverse effects of oxidative stress is damage to genetic material, including the formation of 8-hydroxydeoxyguanosine (8-OHdG), a well-known biomarker of oxidative stress. This damage can result in mutations that may lead to cancer. Therefore, it is important to moderate oxidative stress and prevent damage to deoxyribonucleic acid (DNA) [3]. The presence of 8-oxoG lesions in DNA can lead to mutations, genomic instability, and disrupted cellular functions if not properly repaired. Previous research indicates that exposure to methamphetamine can increase oxidative DNA damage in various tissues, including fetal tissues, the brain, and the liver. To counteract this damage, DNA repair mechanisms, such as the base excision repair pathway, are initiated [4, 5].

The micronuclei assay in human or animal cells has been identified as one of the typical cytogenetic biomarkers utilized *in vivo* or *ex vivo* genetic toxicological studies. In humans, micronuclei can be readily assessed in erythrocytes and primary mitogen-stimulated lymphocytes. Additionally, numerous studies have measured the frequency of micronuclei in exfoliated epithelial cells, including oral, urothelial, and nasal cells [6, 7]. In the buccal micronucleus cytome (BMCyt) assay, buccal cells are classified into normal and abnormal groups based on their nuclear characteristics. The presence of micronuclei and nuclear buds indicates genomic damage, while features such as condensed chromatin, karyorrhexis, pyknosis, karyolysis, and anucleated cells are markers of cell death. Cytogenetic failure is evidenced by the presence of binucleated [7]. In the early 1980s, Stich and colleagues applied the micronuclei assay in buccal cells to prove that a high frequency of micronuclei in buccal cells was a predictive factor for oral cancer in smokers. Since then, numerous biomonitoring studies using the cytome assay in buccal mucosa cells have investigated the impact of various factors, including environmental and occupational exposures, radiotherapy, chemoprevention, vitamin supplementation trials, and lifestyle choices [8].

AIM OF THE STUDY

The present study aimed to evaluate genomic damage in addicted males to predict potential cancer risk. Genomic damage was assessed by measuring micronuclei and binucleated cells in exfoliated buccal mucosa using the BMCyt assay. Additionally, urinary levels of 8-OHdG were measured as a biomarker of DNA oxidative damage.

MATERIALS AND METHODS

Subjects

Forty-two male Iraqi patients, diagnosed with methamphetamine addiction by a psychiatric professional, participated in the current study. These patients were admitted to Al-Ataa Hospital for Addiction Treatment in Baghdad, Iraq, and ranged in

age from 16 to 46 years. The control group consisted of 24 healthy volunteers.

Sample and data collection

Buccal and urine samples were obtained only after participants provided informed consent and upon approval from the Ethics Committee in the College of Science, Mustansiriyah University, Baghdad, Iraq. All urine samples were collected using polypropylene tubes, aliquoted, and kept at 80°C immediately. Also, information, such as age, marital status, smoking habit, alcohol consumption, diagnostic X-rays, chemical exposure during the occupation, family history of cancer, and medical and residential history, was rigorously collected using a comprehensive questionnaire. The body mass index (BMI) was meticulously evaluated using the formula: weight (in kilograms) divided by the square of height (in meters) (kg/m^2) [9].

Determination of 8-OHdG concentration

The 8-OHdG concentration in human urine was determined using an enzyme-linked immunosorbent assay (ELISA) kit provided by My Biosource, Canada. The measurement procedure was performed following the kit manufacturer's instructions (Catalogue: MBS764814, MyBioSource) and based on the principles outlined by Tolbert *et al*. [10] and Sarto *et al*. [11].

Buccal micronucleus cytome assay

Buccal cells were collected from all participants for the BMCyt assay. Initially, each individual was instructed to rinse their mouths thoroughly with tap water to remove any excess debris. Exfoliated buccal epithelial cells were then collected from the cheeks using a sterile soft toothbrush and spread onto clean glass slides. For each subject, double slides of buccal cells were prepared. Exfoliated buccal cells were examined using a light microscope (Kruss, Germin).

RESULTS

Table 1 shows the characteristics of the study participants (the patient and control groups). There are significant age differences between the groups, with a mean age of 25.119 ± 6.73 years in the patient group and 23.917 ± 6.554 years in the control group ($p < 0.05$). Body mass index values were significantly different between the control and patient groups ($p < 0.001$), with the control group showing higher values (20.85 ± 2.22) compared to the patient group (19.877 ± 2.3). The patient group exhibited a higher concentration of 8-OHdG (1132.531 ± 3103.981 ng/ml) compared to the control group. The statistical analysis showed a significant positive association between levels of 8-OHdG and age ($r = 0.442$, $p < 0.01$) in the patient group. There was also a moderate correlation between the level of 8-OHdG and BMI ($r = 0.391$, $p < 0.01$).

Table 1. Characteristics of study population

Parameter	Patient (n = 42)	Control (n = 24)
Age (years)	25.119 ± 6.73**	23.917 ± 6.554
Body mass index (kg/m^2)	19.877 ± 2.3**	20.850 ± 2.22
8-hydroxydeoxyguanosine (ng/Ml)	1132.531 ± 3103.98**	6.334 ± 2.952

*Values are presented as mean ± standard deviation; * – $p < 0.05$; ** – $p < 0.001$*

The frequency of the micronucleus (MN) in the epithelial cells of the patients was significantly higher than in the control group ($p < 0.001$), as shown in Table 2. The mean value of the MN in the patient group was (27.89 ± 11.78), while the mean value of MN in the control group was (9.33 ± 4.49). Moreover, the number of binucleated cells in the patient group was 3.92 ± 1.23, which was significantly different ($p = 0.05$) compared to the frequency of binucleated cells in the control group (4.67 ± 4.23).

Table 2. Micronuclei and binucleated cells in buccal cells of patients and controls

Nuclear characteristics	Patient (n = 42)	Control (n = 24)
Micronuclei	27.89 ± 11.78	9.33 ± 4.49**
Binucleated cells	3.92 ± 1.23	4.67 ± 4.23*

*Values are presented as mean ± standard deviation; *: $p < 0.05$; **: $p < 0.001$*

DISCUSSION

To the best of our knowledge, the current study is the first to explore the correlation between genomic instability and methamphetamine abuse in Iraq. Methamphetamine was evaluated for its potential genotoxic properties by measuring its 8-OHdG

concentration. The findings of this study indicated that addicted males had elevated levels of 8-OHdG. Several key processes contribute to DNA oxidation by methamphetamine. First, methamphetamine and its metabolites can induce reactive oxygen species (ROS), such as hydrogen peroxide and superoxide anion, through several mechanisms, including cytochrome P450-mediated metabolism and mitochondrial dysfunction. These ROS can bind with DNA bases, leading to oxidative damage [12, 13]. Increased ROS production overwhelms cellular antioxidant defense mechanisms, resulting in oxidative stress. The consequence of this imbalance between ROS generation and antioxidant capacity is the promotion of DNA oxidation, particularly damaging nitrogenous bases such as guanine, leading to the formation of 8-oxo-dG. Studies have shown that methamphetamine treatment leads to oxidized purines in FPG-sensitive DNA sites and oxidized pyrimidines in ENDO III-sensitive DNA sites. As a result of these lesion-specific enzymes, oxidized DNA bases are targeted and cleaved directly, providing direct evidence of DNA oxidation by methamphetamine [14]. The oxidative DNA damage caused by methamphetamine can trigger DNA repair pathways, including base excision repair (BER) and nucleotide excision repair (NER), to eliminate and replace damaged DNA. However, chronic or excessive exposure to methamphetamine can overload these repair mechanisms, leading to persistent DNA damage and potentially increasing the risk of mutagenesis. This may ultimately contribute to carcinogenesis and other adverse health effects associated with methamphetamine [15, 16].

Methamphetamine addiction leads to elevated levels of dopamine, which results in rewarding effects. Dopamine auto-oxidizes rapidly and produces free radicals, including hydrogen peroxide, hydroxyl radicals, superoxide, and quinones. Moreover, additional dopamine is converted through monoamine oxidase into dihydroxyphenyl acetic acid with hydrogen peroxide as a by-product. Further progression of oxidative damage occurs when hydrogen peroxide interacts with metal ions to create highly reactive hydroxyl radicals. Methamphetamine exposure also elevates both synaptic and circulating catecholamine levels, which may partly explain the increase in oxidative stress. Diet and cell death have minimal effects on extracellular levels [17]. 8-OHdG serves as a responsive biomarker of ROS-induced genomic damage *in vivo*. Elevated blood levels of 8-OHdG have been assessed in various physical and neuropsychiatric diseases, including Parkinson's disease, diabetes, and alcohol dependence [18]. Methamphetamine-dependent patients also had significantly lower BMI, which is consistent with previous literature. Furthermore, several studies suggest that methamphetamine contributes to a lower BMI. This can be explained by several factors: First, methamphetamine-dependent individuals often experience cognitive deficits and irregular metabolic activity, which negatively impact their nutritional status. Additionally, methamphetamine use leads to significant deterioration in oral health, resulting in difficulties with chewing and poor digestion [12, 19].

Based on the findings of the present study, elevated levels of 8-OHdG have been linked to increased BMI. This finding aligns with the growing body of literature demonstrating that obesity, increased oxidative stress, and the accumulation of oxidative DNA lesions, such as 8-OHdG, are interconnected [20-22]. The increased concentration of 8-OHdG detected in individuals with higher BMI may be a mechanism by which obesity elevates the risk of certain diseases, including cancer, that are driven by oxidative stress and DNA damage [23]. An excess of adipose tissue, particularly visceral fat, contributes significantly to the production of proinflammatory cytokines and adipokines. As a result of these inflammatory mediators, ROS can be produced by various cellular sources, including mitochondria, peroxisomes, and NADPH oxidases [24]. Furthermore, additional fat accumulation disturbs the typical functioning of the mitochondria, resulting in increased production of ROS [25]. The positive correlation between patient age and increased biomarkers of DNA oxidation detected in the present study is consistent with the findings of previous studies [26, 27]. The increase in 8-oxoG with age results from an imbalance between the generation of ROS and the cellular repair mechanisms' ability to remove these oxidative DNA lesions. According to previous studies, cells have displayed deficient DNA repair abilities, leading to amplified rates of genomic instability [27].

Induction of elevated levels of 8-OHdG in patients reflects genomic damage. Additionally, the increased frequency of MN in buccal cells indicates persistent mutations at the chromosomal level. Methamphetamine is a widely abused psychomotor stimulant. While numerous research have tested the neurotoxicity of Methamphetamine, the studies involving the estimation of genotoxic effects of methamphetamine are very scarce. In 2003 Li, et al [28] detected the genotoxicity of Methamphetamine in Methamphetamine abusers and in vitro his study demonstrated that Methamphetamine increased the frequency of sister chromatid exchange (SCE) and micronuclei, in CHO-K1 cells (Chinese hamster ovary K1 cells). Moreover, he concluded that the genotoxic effects of Methamphetamine were reduced in the submitted of rat liver S9, demonstrating that the metabolites of Methamphetamine were not

genotoxic and genotoxic effect result from Methamphetamine. Furthermore, utilized antioxidant material that attracted reactive oxygen species (ROS) repressed formation micronuclei in CHO-K1 cells. Additional study with long-term Methamphetamine abusers revealed that the percentages of SCE and micronucleus in cultured lymphocytes were associated with Methamphetamine exposure. He concluded that Methamphetamine is a genotoxic agent and the ROS have essential role in Methamphetamine-induced genotoxicity.

The findings of the current study are consistent with previous studies that demonstrate that Methamphetamine induces genomic damage in buccal cells and human-derived liver cells, including micronuclei formation, DNA single-strand breaks, and apurinic sites [12]. A significant increase in binucleated cells in the control group suggests that these individuals possess a proficient genomic repair system, which inhibits the proliferation of cells containing abnormal chromosomal numbers. Cytokinetic represents the final stage of cell division, and defects in this process are believed to contribute to carcinogenesis by leading to tetraploidy. Aneuploid cells can arise from unbalanced tetraploid intermediates. Cells exhibit multiple mechanisms to inhibit the survival and proliferation of those with extensive chromosomal changes. For example, cytokinetic is suppressed in cells with abnormal chromosomal numbers by the Aurora B-controlled checkpoint, which prevents furrow regression [29, 30].

CONCLUSIONS

The current study offers original findings on the effect of methamphetamine abuse on genomic instability, as demonstrated in an Iraqi cohort. Significant variances were detected between patients' group, involving methamphetamine users, and control group in some marker of genomic instability including micronuclei in exfoliated buccal mucosa using the BMCyt assay.

Additionally, urinary levels of 8-OHdG were measured as a biomarker of DNA oxidative damage. This directs a higher frequency of chromosomal abnormalities mitotic distraction among methamphetamine users, supporting the link between methamphetamine abuse and elevated genomic instability which is an identified risk factor for the development of cancer.

PROSPECTS FOR FUTURE RESEARCH

Further research is warranted to elucidate the mechanistic pathways linking addiction, genomic damage, oxidative stress, and the accumulation of 8-OHdG, as well as to explore how genetic and epigenetic factors may influence an individual's susceptibility to the combined effects of addiction and oxidative stress.

AUTHOR CONTRIBUTIONS

FS and HG: sample collection and analysis, data collection, statistical analysis, and manuscript writing. LR and NJ: conceptualization of the research, research design, and manuscript proofreading.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ETHICAL STATEMENT

Ethical approval was obtained from Ethics Committee at College of Science, Mustansiriyah University (No. BCSMU/0124/0057Z, dated June 15, 2024).

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