Original Article:
Malathion-increased Hepatotoxicity in Diabetic Rats

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ABSTRACT

Background: Malathion (MT), an organophosphorus pesticide, induces hepatotoxicity and is associated with hyperglycemia and the development of diabetes mellitus.

Objectives: This study was aimed to evaluate the effects of sub-acute exposure to sub-lethal dose of MT in the liver of diabetic rats.

Methods: Non-diabetic and streptozotocin-induced diabetic rats received MT at a dose of 150 mg/kg/day orally. After 28 days, fasting blood glucose, Glucose Tolerance Test (GTT), serum aminotransferases, and liver histopathology and antioxidant status were examined.

Results: MT impaired GTT, caused alteration in histopathology of histopathology and antioxidant status of liver in non-diabetic rats. Impairment in GTT did not observe in diabetic rats exposed to MT, but histopathology changes and antioxidant status alteration was more severe.

Conclusion: Repeated sub-lethal dose of MT exacerbated hepatotoxicity in diabetes condition through further impairment in the antioxidant defense system.

Introduction

Agricultural application of pesticides has been linked to a wide range of human health hazards through occupational, accidental, and intentional exposure [1]. Among all pesticides, Organophosphorus (OP) pesticides are more toxic to vertebrates with low mammalian toxicity [2]. The primary mechanism of OP pesticides is the inhibition of acetylcholinesterase (AChE), which leads to the accumulation of acetylcholine in cholinergic synapses [2]. However, OP pesticides exert their in vivo and in vitro toxicities through AChE-independent mechanisms [3]. They can influence body glucose homeostasis by alteration in carbohydrate metabolism and induction of oxidative and nitrosative stress [4]. The long-term effects of OP pesticides on carbohydrate, lipid, and protein metabolism, as well as their association with increased risk of diabetes, have been addressed [5]. Studies also have suggested that hyperglycemia-induced oxidative stress and lack of antioxidant defense systems play an essential role in beta-cell and liver tissue damages [6].

Malathion (MT), one of the most popular OP pesticides, damages the liver by the production of toxic in-

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termediates, such as free radicals, Reactive Oxygen Species (ROS), and inflammatory cytokines [7]. Due to the increasing global use of OP pesticides in agriculture [1] and the high prevalence of diabetes worldwide [8], as well as the potential of OP pesticides in inducing diabetes and oxidative stress [4], the present study aimed at evaluating the impact of repeated sub-lethal dose of MT on blood glucose level, liver histopathology parameters, and antioxidant capacity in diabetic rats.

Materials and Methods

Chemicals

Technical-grade MT (>96%) was obtained from the Shimi-Keshavarz Pesticide Production Company (Tehran, Iran). Other used materials with high purity were purchased from the Sigma-Aldrich (St. Louis, MO).

Animals

Male rats weighing 190-210 g were kept under a 12/12 h light/dark cycle at 25±2°C temperature and 25%-30% humidity. Standard laboratory diet and water were applied ad libitum. The Ethics Committee of Kerman Neuroscience Research Center approved all the animal experiments (Code: IR.79.KMU.REC.1395-79).

Pilot study

A pilot test was designed to determine the sub-lethal dose of MT, which can inhibit 30% of the plasma AChE activity [9]. The treated groups received MT doses of 75, 100, 150, and 300 mg/kg/d for five weeks. Blood samples were taken at the end of each week, and plasma activity of AChE enzyme was measured using the Elman colorimetric method [10].

Experimental design

Diabetes was induced by intraperitoneal injection of a single dose of Streptozotocin (STZ) (35 mg/kg) solubilized in 0.1 M trisodium citrate buffer (pH=4.5) after 3 days [11, 12]. Forty rats were randomly assigned to four groups of ten rats each (two diabetic groups and two non-diabetic groups) and treated for 28 days. The control group (non-diabetic rats) received corn oil orally every day; MT group (non-diabetic rats) received MT dissolved in corn oil at the dose of 150 mg/kg/d; DM group (diabetic rats) received corn oil orally every day, and DM+MT group were diabetic rats that received MT dissolved in corn oil at a dose of 150 mg/kg/d. At the end of the experiment, all rats were sacrificed, and blood samples were taken and immediately centrifuged for the separation of plasma and serum. Small pieces of the liver tissue were fixed in 10% formalin for histological analysis, and the remaining liver was collected for the evaluation of oxidative stress biomarkers.

Measurement of serum alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) activities

The activities of AST and ALT were measured in serum by enzymatic methods using the diagnostic kit of Pars Azmoon Company (Tehran, Iran). The results were expressed as U/L.

Measurement of fasting blood glucose (FBG) and glucose tolerance test (GTT)

Blood glucose was measured using blood samples obtained by a small cut on the tip of rat's tail immediately after overnight fasting using the commercial glucose diagnostic kit of Pars Azmoon Company (Tehran, Iran). For GGT, glucose (2% w/v) was dissolved in distilled water and administered by gavage, and the blood glucose was determined every 30 min. The results were analyzed by calculating the area under the curve (AUC) for plasma glucose during the test using the trapezoidal method [13].

Measurement of liver catalase (CAT) activity

The CAT activity was assayed by measuring the decomposition rate of H_2O_2 at 240 nm. The concentration of H_2O_2 was calculated using the following expression: H_2O_2 (mM)=(absorbance×1000)/molar extinction coefficient (43.6 M^{-1} cm^{-1}). One unit of CAT was estimated as the amount of enzyme necessary for the decomposition of 1 µM of H_2O_2 in 1 min under standard conditions. Finally, the CAT activity was expressed as U/mg protein [14].

Measurement of liver Superoxide Dismutase (SOD) activity

The SOD activity was measured based on pyrogallol autoxidation rate at 420 nm according to the method developed by Li [15] with minor adjustments and expressed as U/mg protein. One unit of SOD activity was defined as the amount of SOD needed for 50% inhibition of pyrogallol oxidation.

Measurement of liver Glutathione (GSH)

GSH was measured according to the Elman method [16], which is based on the measurement of the absorbance of

the yellow derivative of 5'-thio-2-nitrobenzoic acid (TNB) at 412 nm. TNB forms through the oxidation of GSH by 5,5′-dithio-bis (2-nitrobenzoic acid) (DTNB). GSH content was expressed as nmol/mg protein using the molar extinction coefficient of DTNB (13.6×10^3 M^{-1} cm^{-1}).

Liver histopathology

Formalin-fixed tissues were embedded in paraffin, sectioned into 5-µm slides, and stained with eosin and hematoxylin. Blind imaging and evaluation of the prepared slides were performed under a microscope (Olympus, magnification of 400 x) by an expert pathologist.

Statistical analysis

Data were analyzed by using commercially available SPSS software. Data was analyzed by one-way ANOVA followed by Tukey's multiple comparison test. Results were presented as Mean±SD and p values less than 0.05 were regarded as statistically significant.

Results

AChE activity

MT at the dose of 150 mg/kg inhibited 30% of the AChE activity compared with the control group with no toxic physiological effect on rats (Table 1).

FBG and GTT

Three days after the intraperitoneal injection of STZ, the rats showed diabetic symptoms, such as polyuria, polydipsia, and weight loss with hyperglycemia (FBG of more than 300 mg/dL). As shown in Figure 1, an increase in FBG was observed in diabetic and MT-treated diabetic rats.

GTT was impaired in both diabetic groups compared with the control group. GTT in the MT-treated diabetic rats had no significant difference with the diabetic group (P=0.09). MT in non-diabetic rats impaired GTT and increased the AUC0-120 minute of GTT significantly (P=0.03) (Figure 2A and 2B).

Serum AST activity

ALT and AST levels in all groups were higher than the control group. ALT in the diabetic group treated with MT was also significantly (P=0.01) higher than the non-treated-diabetic group. However, there was no significant difference (P=0.06) in AST between the diabetic rats and the diabetic rat received MT (Table 2).

Liver CAT and SOD activity

MT significantly (P=0.02) decreased CAT activity in the liver tissue of diabetic rats; however, no significant differences were found among other groups. SOD activity decreased significantly in all groups except for the diabetic group compared with the control group (Table 3).

Liver GSH content

GSH content of the liver decreased in all groups in comparison with the control group. Moreover, exposure to MT significantly (P=0.001) reduced GSH content in diabetic rats (Table 3).

Histopathology of liver

The microscopic observation of the liver tissue in the control group showed normal hepatocytes, healthy portal spaces, and normal bile duct (Figure 3A). In the diabetic rats, moderate degeneration and vacuolated cytoplasm were observed in hepatocytes, especially in

Table 1. Plasma cholinesterase activity as a percentage of inhibition (%) after 28 days of daily administration of multiple doses of malathion

Time of blood sampling	Malathion (mg/kg)				
	0	75	100	150	200
Day 7	98.4±4.3	93.2±1.8	86.6±2.1***	76.4±5.7***	63.8±3.3***
Day 14	101.4±9.1	93.3±1.4*	86.4±2.2***	77.3±5.5***	63.0±2.6***
Day 21	99.5±5.8	91.4±1.8*	85.2±3.2***	71.0±4.2***	59.1±6.6***
Day 28	100.6±7.5	84.5±1.6***	80.8±1.9***	66.7±2.9***	54.9±4.8***

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Values are expressed as Mean±SD; n=10; *P<0.05 and ***P<0.001 significantly different from the control group (two-way ANOVA followed by Tukey's multiple comparison test).

Table 2. AST and ALT activities after 28 days in the control group, diabetic group (DM), MT-treated non-diabetic group (150 mg/kg/d) (MT), and MT-treated diabetic group (150 mg/kg/d) (DM+MT)

Aminotransferases	Control	DM	MT	DM+MT
ALT (U/L)	55.9±9.7	115.4±15.2**	104.3±7.9**	128.4±13.4***
AST (U/L)	217.1±13.1	314.5±15.3***	293.7±18.4**	335.5±7.4 ***

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Values are expressed as Mean±SD and compared with the control group (one-way ANOVA followed by Tukey's multiple comparison test); n=10; **P<0.01; ***P<0.001.

Table 3. SOD activities and GSH content of the liver tissue after 28 days in the control group, diabetic group (DM), MT-treated non-diabetic group (150 mg/kg/d) (MT), and MT-treated diabetic group (150 mg/kg/d) (DM+MT)

Antioxidants	Control	DM	MT	DM+MT
Catalase (U/mg pro)	8.3±1.9	7.1±0.5	6.7±0.5	6.3±1.1*
SOD (U/mg pro)	2.8±0.3	2.4±0.2**	1.9±0.05**	1.0±0.1**
GSH (nMol/mg pro)	47.7±0.6	37.9±2.5***	26.1±0.9**	21.5±5.5**

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Values are expressed as Mean±SEM and compared with the control group (one-way ANOVA followed by Tukey's multiple comparison test);

n=10;

*P<0.05; **P<0.001; ***P<0.01

the centrilobular part (Figure 3B). The non-diabetic rats received MT (150 mg/kg/d) for 28 days showed drastic degenerative changes in hepatocytes. The inflammation of hepatocytes was severe in the pre-portal area, and the cytoplasm of hepatocytes was highly vacuolated (Figure 3C and 3D). In the diabetic rats received MT, similar to the MT group, severe degenerative disorders were observed in liver tissue. In this group, the infiltration of mononuclear inflammatory cells was observed, especially in the portal area and around the bile duct. Besides, in some sections, hyperplasia in bile duct epithelium was seen (Figure 3E and 3F). These alterations were similar to those of the MT group; however, they were more server than the histopathological changes in the diabetic group (Figure 3G).

Discussion

In this study, the sub-acute exposure to MT resulted in impairment in GTT, liver tissue, and antioxidant status in non-diabetic rats. MT also worsened tissue damages

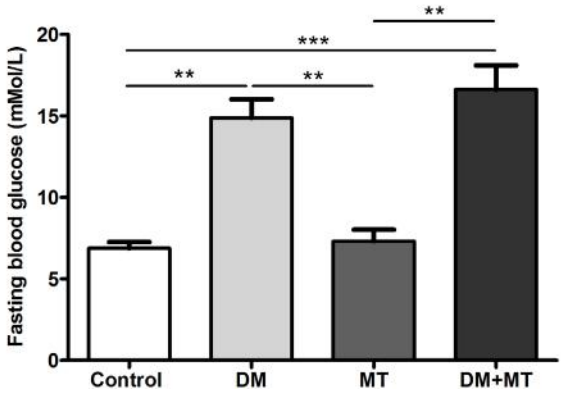

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Figure 1. Fasting blood glucose in the control group, diabetic group (DM), MT-treated non-diabetic group (150 mg/kg/d) (MT), and MT-treated diabetic group (150 mg/kg/d) (DM+MT) after 28 days (n=10).

Values are presented as Mean±SD.

P<0.05 was considered significant.

**P<0.01; ***P<0.001

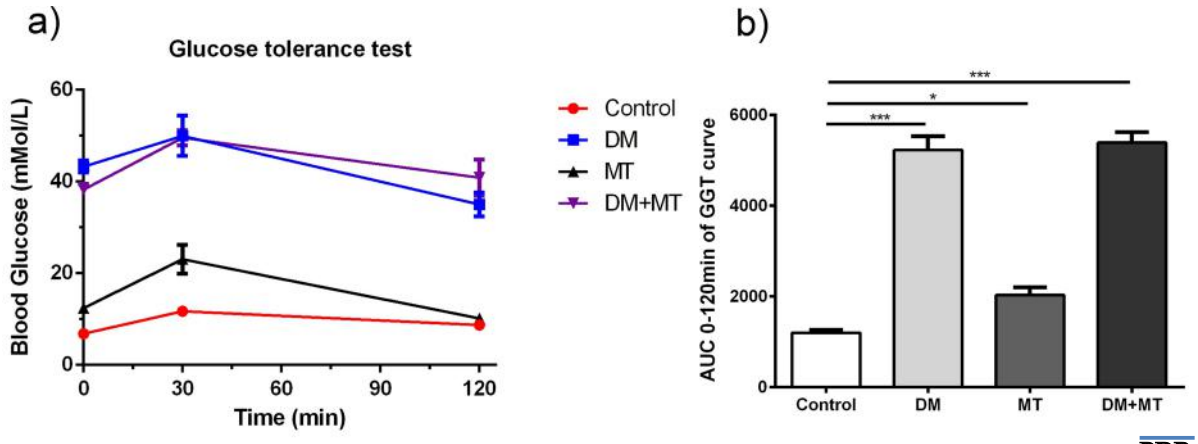

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Figure 2. A. Glucose Tolerance Test (GTT); and B. Area Under the Curve (AUC) of GTT in the control group, diabetic group (DM), MT-treated non-diabetic group (150 mg/kg/d) (MT), and MT-treated diabetic group (150 mg/kg/d) (DM+MT) after 28 days (n=10).

Values are presented as Mean±SEM. P<0.05 was considered significant.

*P<0.05; ***P<0.001

and decreased GSH content and enzymatic antioxidants defense system in the liver tissue of diabetic rats.

The exact mechanism of alteration in glucose metabolism by OP pesticides has not been revealed yet. Several studies have mentioned possible pathways related to the disruption of glucose hemostasis by OP pesticides, such as oxidative stress and disruption of liver glycogenolysis and gluconeogenesis [5]. Consistent with our findings, monocrotophos exposure in diabetic rats depleted liver glycogen content, and increased gluconeogenesis enzymatic activities, which disrupted glucose homeostasis [17]. Exposure to diazinon also impaired GTT in diabetic rats [18].

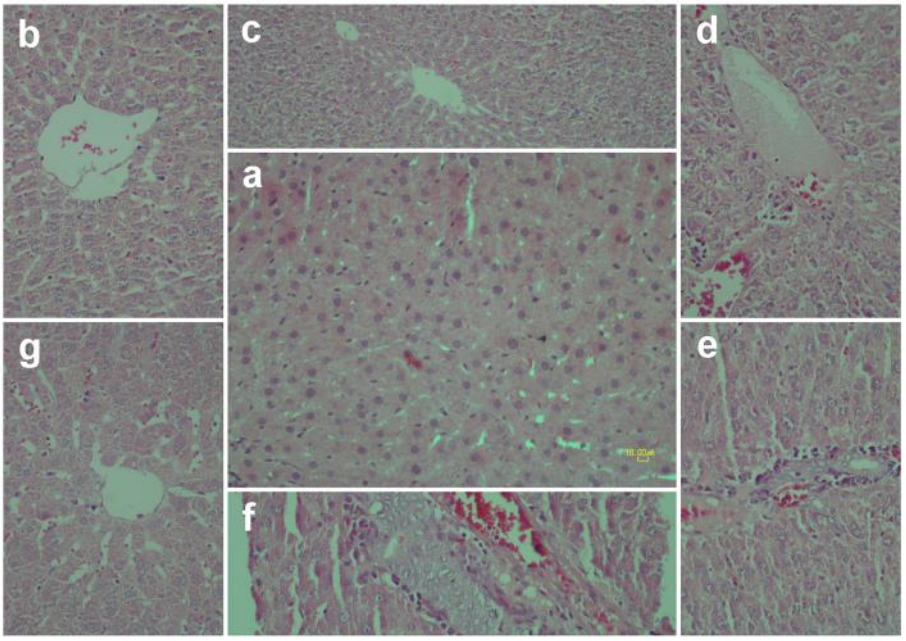

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Figure 3. Optical photomicrograph of the liver tissues stained with hematoxylin and eosin (magnification×10)

A. Normal liver tissue: The control group; B. Moderate degenerative disorders of hepatocytes in the centrilobular area: Diabetic group; C. Severe degenerative disorders of hepatocytes in the pre-portal area: MT-treated non-diabetic group (150 mg/kg/d); D. Moderate degenerative disorders of hepatocytes in the centrilobular area: MT-treated diabetic group (150 mg/kg/d); E. Hyperplasia of the bile duct epithelium; F. Degenerative disorders and mononuclear inflammatory cells around the bile duct; and G. Fairly high degenerative disorders of hepatocytes in the centrilobular area after 28 days.

Exposure to multiple sub-lethal doses of MT exacerbates histopathological damages of the liver in diabetic rats. It has been shown that both MT exposure and the diabetic condition cause histopathological disorders in liver tissue as the primary site of carbohydrate metabolism [5, 19]. Hypertrophy of hepatocytes increases the number of mitochondria, and a distinct reduction of glycogen granules was also identified in diabetic rats [20]. Miyamoto et al. reported that the production of ROS by STZ probably causes mitochondrial dysfunction and consequent hepatic toxicity in STZ-induced diabetic rats [21]. MT also increases the activities of serum liver aminotransferases, including ALT and AST, as biomarkers mainly used to assess liver damage in diabetic rats. The elevation of these enzymes in serum is due to the leakage of hepatocyte cytoplasmic content into the bloodstream [22, 23].

In the current study, a reduction in the liver GSH content and the activity of CAT and SOD were higher than MT-treated diabetic rats, which indicates augmentation of oxidative damages in the liver of the diabetic rats exposed to MT. Both diabetes condition and exposure to OP pesticides can disrupt the metabolic functions of the liver and induce oxidative stress. Oxidative stress, in turn, boosts the generation of free radicals, which disables the antioxidant system and, consequently, exerts destructive effects on the liver [4, 24]. Reduction in the activity of antioxidant enzymes, SOD, and CAT, has been reported after exposure to OP pesticides [25, 26]. Proteins with sulfhydryl groups are an essential defense system against free radicals and can mitigate the generation of free radicals. A reduction in total thiol content of the tissue can lead to oxidative and nitrosative stress [27]. Reduced liver GSH content has been reported in MT-treated rats [25] and other OP pesticides [4]. Induction of oxidative stress through the elevation in lipid peroxidation and alteration in antioxidant enzymes has also been reported in kidney and liver tissues of monocrotophos-exposed diabetic rats [17]. Vismaya et al. also demonstrated that monocrotophos in diabetic rats decreases GSH content in the intestinal brush border [26].

Conclusion

Widespread use of OP pesticides in agriculture induces toxic effects through the inhibition of AChE and AChE-independent mechanisms. The results of this study indicate that MT exacerbates hepatotoxicity in diabetic rats, verified by histopathological examination. One mechanism of such alteration is the induction of oxidative stress through impairment in the antioxidant defense system. Histopathological disorders in the liver, as the primary site of glucose metabolism, affect the metabolism of carbohydrates, and leads to disruption in GTT. Therefore, based on the high prevalence of type 2 diabetes, it is recommended to evaluate hepatotoxicity and impairment in GTT in diabetic patients occupationally exposed to OP pesticides. Moreover, further consideration is required to restrain the use of OP pesticides, especially MT, which is widely used in developing countries.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by Kerman University of Medial Sciences, Deputy of Research.

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Authors' contributions

All authors contributed in designing, running, and writing all parts of the research.

Conflict of interest

The authors declared no conflict of interest.

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