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Vitamin D Ameliorates Oxidative and Inflammatory Effects of Hepatorenal Injury of Acute Paracetamol Toxicity: An experimental study

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ABSTRACT

Introduction and aim: An accidental or intentional paracetamol overdosage is a common condition, with hepatic injury as a common complication. Kidney could be injured in association with hepatic injury. Prevention and/or proper treatment is markedly important. The current study aimed to investigate the role of vitamin D (VD) in acute paracetamol-induced hepatorenal damage.

Methodology: Fourty male Wister rats were divided into 4 equal groups. The negative control (NC), the positive control (PC) (received paracetamol 1200mg/kg), prophylactic group (received VD (1000 IU/Kg/day) before induction of toxicity and treatment continued after induction); and the treatment group with VD (2000 IU/Kg/day) for five successive days after induction of toxicity, for three successive cycles. VD levels, serum liver enzymes, total protein, albumin, serum urea and creatinine were estimated. The concentrations of interferon-γ (IFN- γ), interleukins (IL1β, IL4, IL10, and IL-17) in the tissue lysate were determined. The oxidative stress indicators and antioxidant enzymes (glutathione peroxidase (GPx), catalase (CAT), superoxide dismutase (SOD), glutathione (GSH) and Malonaldehyde (MDA)) were also measured.

Results: Liver enzymes, serum urea and creatinine were increased in PC than NC groups, and were significantly reduced in prophylactic and treatment groups. But not return normal values, and prophylactic group is better. Total proteins and albumin significantly reduced by paracetamol toxicity and returned to near normal with VD supplementation. Vitamin-D levels were significantly reduced in PC than NC groups. However, it was significantly increased in prophylactic and treatment groups than NC and PC groups. IFN- γ, IL-1β, IL-17, and MDA were significantly increased, while IL-10, GPx, CAT, and GSH were significantly reduced in PC than NC groups. Prophylactic and treatment groups improved the values. However, SOD significantly reduced in PC than NC group. Vitamin D was significantly and inversely correlated with ALT, AST, ALP, albumin, creatinine, liver and kidney IFN-γ, IL-1β, IL-17 and MDA. But, it was proportionately and significantly correlated with liver and kidney IL-10.

Conclusion: Acute paracetamol toxicity alters hepatic and renal VD homeostasis through oxidative stress and pro-inflammation. Vitamin D supplementation had an ameliorative action on hepatorenal injury, and the long duration of VD supplementation had better outcome.

Keywords: Vitamin D; Paracetamol; Hepatorenal; Oxidative Stress; Inflammation.

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INTRODUCTION

Paracetamol is an analgesic and antipyretic drug. It is commonly obtained over the counter. It is safe at the recommended doses (4 gm for adults and 50-75 mg/kg/day for children). However, paracetamol overdose (accidental or intentional) is a frequent condition and hepatic injury is a common complication. Acute paracetamol toxicity is considered a leading cause of acute liver cell failure in many countries. However, renal affection is less frequent and could be associated with liver injury or developed independently [1,2]. Paracetamol is completely metabolized in the liver as 90.0% converted to non-toxic metabolites by glucuronidation and sulfation. These non-toxic products are then excreted via the kidney [3,4]. The residual 10.0% are converted to hepatotoxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) by an oxidation process through the cytochrome P450 enzymes [5].

Under standard conditions, the harmful effect of NAPQI are prevented by glutathione (GSH)[6]. However, with overdoses and production of higher amounts of NAPQI due to acute paracetamol overdoses consumes the hepatic stores of GSH, with subsequent accumulation of reactive oxygen species (ROS) leading to an oxidative stress, fragmentation of DNA, and necrosis of hepatic cells [7-10]. In addition, the oxidative stress stimulates inflammatory changes with production of interleukin (IL) (1β, 6, 10, 17A and 22) in the affected tissues [11-13].

Vitamin D is a fat-soluble hormone, manufactured by direct skin contact with ultraviolet sunlight rays. Others sources include Vitamin-D rich dietary sources. It is activated by successive hydroxylation in the hepatic and renal tissues to the active form calcitriol [14]. Its main primary action is the promotion of process of skeletal mineralization. It is now well- known that, Vitamin-D incorporated in pro-apoptotic, anti-angiogenic, anti-proliferative, anti-invasive, and anti-metastatic processes [15-17]. Additionally, vitamin D suggested to have some antioxidant properties [18].

Oxidative stress has a marked role in the activation of different signaling pathways, with consequent tissue damage and inflammatory processes. The tissue injury due to inflammation is a result of an interaction between innate and adaptive immunity. It is marked by persistent stimuli and release of inflammatory indicators (e.g., cytokines, biochemical mediators like reactive oxygen species (ROS) [19]. However, there is an array of antioxidant mechanism defending against oxidative stress and scavenges ROS products [20,21]. Antioxidants include superoxide dismutase (SOD) and glutathione-related enzymes. Oxidative stress is due to an imbalance in ROS production compared with antioxidant defense mechanism. Oxidative stress is a key pathogenic indicator of chronic and degenerative diseases [22, 23].

Furthermore, other trials and experimental studies, have linked vitamin D insufficiency to oxidative stress and inflammatory indicators. It could play a role in amelioration or prevention of chronic disease conditions (e.g., diabetes mellitus, hepatic ischemia, and hepatorenal damage) [24, 25]. In addition, the effect of acute paracetamol toxicity on the vitamin D is not well addressed. Thus, we hypothesized that vitamin D supplementation could prevent acute paracetamol induced hepatic oxidative stress injury and improve inflammation.

The current study aimed to study the role of vitamin D in acute paracetamol-induced hepatorenal damage.

MATERIALS AND METHODS

Study setting: Damietta Faculty of Medicine, Al-Azhar University, Damietta, Egypt. The study completed between June and December 2019. The study protocol was revised and accepted by the local ethics committee of DFM, Al-Azhar University (DFM IRB 00012367-19-05-004).

Drugs: Paracetamol (99.99% purity) was obtained from Sigma-Aldrich Corporation, MO, USA. However, Vitamin D ampoules (100,000 IU/mL) was obtained from Memphis Company for Pharmaceutical and chemical Industries (Cairo, Egypt).

Animals: Male Wister Rats were obtained from and housed in the faculty of Veterinary Medicine (Cairo University). Fourty, 14 weeks of age and 160 – 200 gm of body weight were housed in clean and sterile polyvinyl cages (5 rats/cage) under standard conditions (temperature (22–24 °C) and 12 h dark/light cycles), with free access to water ad libitum with a standard diet. The rats were equally divided into four groups (n=10 rats): 1) The negative control (NC) group included rats on normal diet without any drugs or supplementation; 2) Positive control (PC) group, with administration of a single oral doses of paracetamol (1200mg/kg); 3) The Vitamin-D prophylactic group received vitamin D (1000 IU/Kg/day) for five days before Paracetamol administration as in the positive control group followed by the same dose and regimen after administration of paracetamol. Three cycles were completed till the end of the study. 4) the Vitamin-D treatment group received (2000 IU/kg/day) for five consecutive days after paracetamol administration, for three consecutive cycles. Thus, the total dose of vitamin D was equal for each animal in prophylactic and treatment groups.

Blood sampling: At the end of the experiment, animals were sedated by diethyl ether and about 2 ml from periorbital plexus in a plain sterile tube. Samples were directly centrifuged and serum was obtained, kept at – 20° till the time of assessment. Rats were weighted after the end of the study, then decapitated, the liver and kidneys were collected. About 0.5 gm of each organ was placed in to ml of RIPA lysis buffer for total protein extraction and determination by the Pierce™ Rapid Gold BCA Protein Assay Kit (Thermo Fisher Scientific kits; MA, USA) in the resultant supernatants. The samples were then diluted with deionized water for a final concentration of 1000 µg/mL for ELISA.

Biochemical parameters: The serum levels of the liver enzymes (AST: aspartate aminotransferase), (ALT: alanine amino transferase), alkaline phosphatase (ALP), total protein, bilirubin, albumin serum urea and creatinine were determined using an automated chemistry analyzer, according to the manufacturers guidelines. The serum levels of vitamin D were measured Cobas e411 (Roche Diagnostics, Mannheim, Germany).

Inflammatory markers and oxidative stress indicators: The concentrations of interferon-γ (IFN- γ), interleukins (IL1β, IL4, IL10, and IL-17) in the tissue lysate were determined by a specific rat ELISA kits in line with manufacturers guidelines (Cloud-Clone Corp.; TX, USA). The antioxidative enzymes and oxidative stress markers (glutathione peroxidase (GPx), catalase (CAT), superoxide dismutase (SOD), glutathione (GSH) and Malonaldehyde (MDA)) were also measured in the hepatic tissues using ELISA (Abcam

Chemical Co., Cambridge, UK). The analysis was completely automated using an ELISA processor (Biobase IndiaMart Ltd. Co. Delhi, India).

Statistical analysis: The statistical package for social science (SPSS) version 16 (SPSS Inc., Chicago, USA) was used for statistical analysis. Data were examined for normal distribution by Kolmogorov and Smirnov's test. One-way analysis of variance (ANOVA) followed by either post-hoc least significant difference tests were used to compare between the study groups. Pearson correlation coefficient was calculated and p value < 0.05 was considered significant.

RESULTS

Animal study groups showed non-significant differences regarding initial body weight. After the end of the experiment, the total body weight in the positive control (PC) group was significantly reduced than the negative control (NC) group. However, the weight of prophylactic and treatment groups was not different than negative control group. Liver enzymes (ALT, AST, and ALP) were significantly higher in positive than negative control groups. Enzymes were significantly reduced in both prophylactic and treatment. But not return normal values, and prophylactic group had favorable results than treatment group. Results for protein and albumin showed similar results, but, there was no significant difference between prophylactic and treatment groups. Serum creatinine and urea significantly increased in PC than NC groups. However, it was significantly reduced in prophylactic and treatment groups than positive control group. values of serum creatinine returned to nearly normal levels, but urea is still high in treatment group. Vitamin-D levels were significantly reduced in PC than NC groups. However, it was significantly increased in prophylactic and treatment groups than NC and PC groups. Calcium levels were significantly reduced in PC, prophylactic and treatment groups than NC group and in treatment than prophylactic group (Table 1). Interferon-gamma, interleukin-1β, IL-17, and MDA were significantly increased, while IL-10, glutathione peroxidase (GPx), catalase, and glutathione were significantly reduced in PC than NC groups. Prophylactic and treatment groups improved the values, but did not reach the normal values. Prophylactic group was better than treatment group. However, superoxide dismutase (SOD) significantly reduced in PC than NC group, but the difference was not significantly different in prophylactic and treatment group than NC and PC groups (Table 2). Vitamin D was significantly and inversely correlated with each of ALT, AST, ALP, albumin, creatinine, liver and kidney IFN-γ, IL-1β, IL-17 and MDA. But, it was proportionately and significantly correlated with liver and kidney IL-10 (Table 3).

Table (1): Comparison between Study groups regarding laboratory data

	NC	PC	Prophylactic group	Treatment group	P value
Initial body weight (g)	171.50±7.83	168.80±6.23	172.60±7.26	169.60±6.55	0.61
Final body weight (g)	283.60±16.09	236.70±14.61 [a]	280.50±16.29	277.60±16.89	<0.001*
ALT (IU/L)	56.60±9.75	139.50±11.64[a]	76.40±7.88 [a b]	91.30±8.46 [a b c]	<0.001*
AST(IU/L)	46.20±8.66	165.50±11.97 [a]	77.70±8.87 [a b]	94.90±10.76 [a b c]	<0.001*
ALP (IU/L)	109.30±14.69	355.30±17.99 [a]	179.50±10.50 [a b]	228.20±16.86 [a b c]	<0.001*
Protein (g/dl)	5.95±0.55	5.00±0.51 [a]	5.53±0.50 [a b]	5.35±0.33 [a b]	0.001*
Albumin (g/dl)	3.66±0.38	3.56±0.46	3.32±0.30 [a b]	3.14±0.30 [a b]	0.014*
Creatinine (mg/dl)	0.41±0.06	0.87±0.19 [a]	0.49±0.07 [b]	0.51±0.07 [b]	<0.001*
Urea (mg/dl)	40.60±6.36	52.90±9.15 [a]	45.40±5.68 [b]	48.80±5.67 [a b]	0.003*
Vitamin-D (ng/dl)	40.20±5.96	29.90±5.82 [a]	49.20±3.65 [a b]	53.10±3.96 [a b]	0.001*
Ca (mg/dl)	10.60±0.67	9.24±0.71 [a]	9.43±0.34 [a b]	9.31±0.34 [a b c]	0.001*

a: significant difference when compared to NC group. b: significant difference when compared to PC group. c: significant difference when compared to prophylactic group

Table (2): Comparison between study groups regarding inflammatory and oxidative stress indicators of the liver and kidney

		NC	PC	Prophylactic	Treatment	P value
Liver	IFN-γ (pg/ml)	191.80±20.12	548.50±24.42 [a]	213.00±9.55 [a b]	377.10±26.42 [a b c]	<0.001*
	IL1β (pg/ml)	97.40±4.09	373.70±15.49 [a]	143.80±8.40	180.00±7.92 [a b c]	<0.001*
	IL-10 (pg/ml)	101.30±9.88	39.90±3.78 [a]	81.50±4.06 [a b]	64.10±3.67 [a b c]	<0.001*
	IL-17 (pg/ml)	586.00±268.93	1405.00±128.26 [a]	795.40±10.30 [a b]	896.40±9.05 [a b c]	<0.001*
	GPx (ug/g)	6.65±0.92	2.42±0.67 [a]	5.27±0.60 [a b]	4.13±0.55 [a b c]	<0.001*
	CAT (U/g)	496.60±8.80	198.70±6.63 [a]	304.60±9.61 [a b]	272.50±9.79 [a b c]	<0.001*
	SOD (U/g)	193.70±30.50	162.40±17.24 [a]	173.10±39.38	171.00±36.15	0.179
	GSH (mg/g)	73.00±5.50	32.40±2.63 [a]	61.70±3.33 [a b]	41.00±2.45 [a b c]	<0.001*
	MDA (mmol/g)	54.20±3.39	109.60±4.70 [a]	74.20±4.05 [a b]	81.40±4.35 [a b c]	<0.001*
Kidney	IFN-γ (pg/ml)	102.70±3.92	303.70±8.12 [a]	203.50±12.19 [a b]	281.50±16.02 [a b c]	<0.001*
	IL1β (pg/ml)	50.90±2.23	205.80±9.76 [a]	99.60±4.97 [a b]	130.80±4.83 [a b c]	<0.001*
	IL-10 (pg/ml)	65.90±3.70	24.10±3.54 [a]	40.30±2.41 [a b]	38.60±2.91 [a b]	<0.001*
	IL-17 (pg/ml)	276.00±181.07	790.00±16.55 [a]	489.60±11.51 [a b]	604.20±7.07 [a b c]	<0.001*
	GPx (ug/g)	4.80±0.58	1.76±0.31 [a]	2.94±0.14 [a b]	2.75±0.20 [a b c]	<0.001*
	CAT (U/g)	287.40±10.51	116.30±11.29 [a]	212.90±9.22 [a b]	182.70±7.80 [a b c]	<0.001*
	SOD (U/g)	100.70±5.96	95.80±5.09 [a]	100.10±5.38	99.40±4.72	0.181
	GSH (mg/g)	50.40±3.60	20.50±1.65 [a]	36.20±1.87 [a b]	31.30±2.75 [a b c]	<0.001*
	MDA (mmol/g)	37.90±1.97	76.00±2.49 [a]	57.40±1.90 [a b]	63.60±2.80 [a b c]	<0.001*

Table (3): Correlation between vitamin D and liver and kidney function test

		Vitamin-D	
		r	P value
Liver and kidney function tests	ALT (IU/L)	***-0.442***	***0.004***
	AST(IU/L)	***-0.482-***	***0.002***
	ALP (IU/L)	***-0.460***	***0.003***
	Protein (g/dl)	0.113	0.487
	Albumin (g/dl)	***-0.412***	***0.008***
	Creatinine (mg/dl)	***-0.564***	***0.001***
	Urea (mg/dl)	-0.153	0.345
Liver inflammatory and oxidative stress markers	IFN-γ (pg/ml)	***-0.446***	***0.004***
	IL1β (pg/ml)	***-0.594***	***<0.001***
	IL-10 (pg/ml)	***0.354***	***0.025***
	IL-17 (pg/ml)	***-0.515-***	***0.001***
	GPx (ug/g)	***0.315***	***0.048***
	CAT (U/g)	0.119	0.464
	SOD (U/g)	0.109	0.504
	GSH (mg/g)	0.209	0.195
	MDA (mmol/g)	***-0.407***	***0.009***
Kidney inflammatory and oxidative stress markers	IFN-γ (pg/ml)	-0.094	0.565
	IL1β (pg/ml)	***-0.409***	***0.009***
	IL-10 (pg/ml)	0.215	0.182
	IL-17 (pg/ml)	-0.268-	0.094
	GPx (ug/g)	0.210	0.193
	CAT (U/g)	0.282	0.078
	SOD (U/g)	0.263	0.101
	GSH (mg/g)	0.274	0.087
	MDA (mmol/g)	-0.239	0.138

DISCUSSION

Acute paracetamol toxicity and impact of two protocol of vitamin D supplementation were addressed in the current work. The first include administration of vitamin D before induction of acute toxicity and completed after induction as the usual treatment protocol. The second included only the treatment protocol after induction of acute paracetamol toxicity. Results revealed that, acute paracetamol toxicity is associated with harmful effects on the liver and the kidney as reflected by abnormal values of liver enzymes, liver proteins and kidney function tests (serum urea and creatinine).

These effects could be exerted through and oxidative and inflammatory processes (confirmed by abnormal values of inflammatory and oxidative stress indicators; increased lipid peroxidation marker (MDA), with concomitant reduction of GSH and the antioxidant enzymes glutathione peroxidase and catalase. In addition, there was concomitant elevations of IL-1β, IL-17 and INF-γ, with significant reductions of IL-10). Both prophylactic and treatment protocols were able to ameliorate the acute toxic effects of paracetamol. But not prevent it completely. The prophylactic regimen was better than treatment protocol.

Wang *et al.* [9] and Guo *et al.* [10] reported that, acute paracetamol toxicity lead to hepatic and probable renal pathogenic effects, particularly through an oxidative stress process and pro-inflammatory immune responses.

Under normal physiologic functions, liver produces NAPQI, a toxic metabolite subsequently detoxified by the hepatic glutathione (GSH) before urinary excretion [26].

NAPQI stimulates oxidative stress after acute toxicity by exhaustion of the cellular antioxidants (e.g., GSH, CAT and GPx). In addition, NAPQI interacts with protein residues with formation of stable protein structures with marked damage of cellular proteins [27, 28]. Concurrently, the immune response plays a significant role in the pathogenesis of the hepatorenal harmful effects due to acute paracetamol overdosage, and many cytokines (e.g., IL-1β, IL6, and IFN-γ) [29,30].

IL-10, the anti-inflammatory cytokines are associated with hepato-protective actions against acute paracetamol toxicity [31].

The results of the current study are in line with the previous reports. However, the interaction between oxidative stress and inflammation from one side and mechanism of acute paracetamol toxicity is multidimensional and each of them (oxidative stress and hepatorenal injury) could be considered as an initiator or outcome [26].

Previous animal studies showed that the use of different anti-oxidants ameliorated acute hepatorenal paracetamol toxicity and modulated several cytokines. In addition, the current clinical treatment of acute paracetamol toxicity by N-acetyl cysteine is based on the reduction of oxidative stress. However, this antidote has an inadequate efficacy at the late stages of acute toxicity. On the other side, animal experimental with the use of exogenous anti-inflammatory cytokines and inhibition of pro-inflammatory cytokines (e.g., IL1β) ameliorated hepatic cell injury induced by oxidative stress. The

use of immunomodulation therapy, especially for late stages of acute toxicity had been suggested by several studies. However, more researches are required to determine the molecular changes responsible for hepatorenal cellular damage induced by acute paracetamol toxicity [26,32,33].

Vitamin-D homeostasis is maintained by different organs. The liver and the kidney play crucial roles in the Vitamin-D homeostasis through several members of the Cyp_{450} family enzymes. In addition, both organs are major targets of actions of the active Vitamin-D. These could explain the marked reduction of Vitamin-D in acute paracetamol toxicity, due to pathological enzymatic alteration [34,35].

In addition, abnormal alterations of hepatorenal molecular enzymes controlling Vitamin-D metabolism could play a role in pathogenesis of acute paracetamol toxicity or at least aggravating the oxidative stress and inflammatory pathways associated with hepatic cellular damage of acute toxicity. VD is an anti-inflammatory and anti-oxidative compound that efficiently mitigate the effects of the acute paracetamol hepatic and renal cellular injury [36-38]. However, the available evidence on the direct interactions between paracetamol and VD is limited, only concentrated on VD binding protein (VDBP) and results showed significant increases in the VDBP circulatory concentrations after acute paracetamol toxicity [39-41].

Other trials investigated the effects of acute paracetamol hepatorenal Cyp450 enzymes, that included in Vitamin-D metabolism despite the marked roles of these enzymes in acute paracetamol metabolism and effects acute toxicity [42-43].

These studies and ours confirmed that, the acute paracetamol toxicity induce the hepatorenal injury, affect Vitamin-D metabolism, and paradoxically upregulating the catalyzing enzymes and VDBP. The abnormalities in the hepato-renal VD homeostasis could consequently lead to the oxidative stress and cytokine abnormalities in the acute paracetamol toxicity. Vitamin-D is also associated with protective effects achieved by anti-inflammatory and antioxidative mechanisms [44, 45]. An experimental study has showed that VD-stimulated the anti-inflammatory cytokines and reduced liver cellular damage [46]. Vitamin-D also ameliorated the hepatorenal cellular injuries induced by monosodium glutamate in an animal study by reduction of the MDA levels, improved the anti-oxidant capacity and inhibit cell apoptosis [47,48]. At the same time, Vitamin-D supplementation reduced the hepatic injuries by the reduction of several cytokines in advanced liver fibrosis and cirrhosis [38]. VD deficiency was also linked to the reduced GSH and the VD- supplementation restored the GSH levels and decreased inflammation [49,50].

Otherwise, VD supplementation enhanced the anti-inflammatory endogenous mechanisms in the kidney in different diseases [51,52].

Our results are in line with previous reports, that showed significant reduction in MDA levels, as well as the proinflammatory cytokines IL1β, IL6, IFN-γ and IL17A in paracetamol group. The hepatic and renal tissue proteins of the GPx enzymes in addition to the anti-inflammatory cytokine IL10 [38,51].

Moreover, Vitamin-D correlated significantly and positively with the antioxidative indicators and anti-inflammatory cytokines, whereas inverse significant correlations were observed with the pro-oxidant and pro-inflammatory molecules. The prophylactic administration of Vitamin-D appeared more protective than the treatment protocol since it resulted in better ameliorative effects. An experimental study has shown that prophylactic Vitamin-D was associated with enhanced anti-inflammatory activities with better outcomes than the treatment protocol [47].

The outcome differences between the prophylactic and the treatment groups in the current study despite using equal doses of VD may be explained by the longer intervention duration in the prophylactic group, that could permit the hepatorenal tissues to raise enough anti-oxidants and anti-inflammatory protective mechanism against toxic effects induced by the acute paracetamol toxicity [10,53].

Finally, and in line with the current work, Hassan *et al.* [54] concluded that, the vitamin D_3 supplementation alleviates the hepatic injury induced by high fructose diet. The possible mechanisms included anti-oxidative actions.

In short, this study confirmed the dysregulation of hepatic and renal Vitamin-D homeostasis by acute paracetamol toxicity. It potentiates the oxidative stress and pro-inflammatory pathogenic mechanism induced by acute paracetamol hepatorenal injury. This confirmed by Vitamin-D supplementation. The prophylactic (long duration of supplementation is better than short treatment protocol after acute toxicity. However, future studies to explore molecular mechanism of acute paracetamol toxicity and interactions with vitamin D homeostatic mechanism.

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Authors contribution: Authors contributed equally in this work

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