Introduction

Magnesium is a cofactor in more than 300 enzyme systems that regulate diverse biochemical reactions in the body, including protein synthesis, muscle and nerve function, blood glucose control, and blood pressure regulation [1-3]. It was reported that Mg supplementation has beneficial effects on blood levels of HDL-C [4], cholesterol and/or triglycerides [4,5]. Oral intake of magnesium also has beneficial effects on lipid metabolism and efficiency of insulin in maintaining glucose homeostasis in human subjects [6,7]. Mg deficiency is known to decrease the level of GSH in erythrocytes [8,9] and even inhibit its biosynthesis [10], and in agreement with these findings, magnesium supplementation was shown to induce a significant increase in GSH in kidney of mice treated with cadmium [11]. Magnesium intake is capable of decreasing the blood concentration of vanadate in rats [12] and the cadmium level in blood, kidney, spleen, and bone marrow in rabbits [13]. In addition, both oral and intraperitoneal supplementation of magnesium acetate were effective against cadmium toxicity [14]. Other findings suggest that magnesium chenoursodeoxycholic acid (Mg-CUD) may prevent liver fibrosis induced by CCl$_4$ [15]. Moreover, magnesium has been shown to have protective effects against oxidative stress observed in experimental animals with different pathologies [16,17]. Interestingly, magnesium supplementation appears to attenuate the hepatotoxicity of CCl$_4$ [18] and prevent liver fibrosis [15]. The nephroprotective effect of magnesium has also been well documented [13,19,20] and seems to be related to its property of scavenging free radicals before the occurrence of damage to cellular macromolecules [21].

Carbon tetrachloride (CCl$_4$) is largely used as a solvent in many industries. CCl$_4$ is also frequently used to induce oxidative stress in experimental animals [22]. Although most of the published data on the toxicity of CCl$_4$ focus on liver injury, recent studies demonstrate that the liver is not the only target organ for CCl$_4$ but also other organs such as

Effects of MgCl$_2$ supplementation on blood parameters and kidney injury of rats exposed to CCl$_4$

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Abstract: The purpose of this study was to evaluate the beneficial effects of magnesium (Mg) supplementation upon carbon tetrachloride (CCl$_4$) toxicity. Our study was carried out on 24 Wistar male rats divided into 4 batches. During a 6 week period, one group served as a control, two groups received Mg (after 4 weeks one of these groups was then treated with CCl$_4$) and a final group was treated with CCl$_4$ only. Under our experimental conditions, CCl$_4$ poisoning resulted in oxidative stress indicated by a significant increase in lipid peroxidation level in renal tissues. The blood levels of creatinine and urea increased while the blood level of uric acid and proteins decreased. CCl$_4$ also induced an increase in superoxide dismutase (SOD) and glutathione peroxidase (GPX) activity in kidneys, in the number of red blood cells (RBC), and in hemoglobin content (Hb) and mean cell hemoglobin concentration (MCHC). However, white blood cell count (WBC), platelet count (Pl) and catalase activity (CAT) all decreased significantly. Treatment with Mg was found to alleviate most of CCl$_4$-induced damage by decreasing lipid peroxidation and by correcting changed hematological parameters, and catalase, glutathione peroxidase and superoxide-dismutase activities. The results provide strong evidence that Mg supplementation is beneficial in protecting the kidneys from CCl$_4$ toxicity.

Keywords: CCl$_4$; Magnesium; Kidney; Hematology; Oxidative stress
kidneys [23], lungs [23,24], heart [25], testes [26], and blood [27] are affected. Among these tissues, there is increasing interest in the adverse effects of CCl₄ on the kidney. Even though the mechanism of CCl₄ toxicity in the kidney is almost the same as in the liver [28], the kidney has a higher affinity to CCl₄ than liver [29] due to the predominance of cytochrome p-450 in the renal cortex [30]. Indeed, it has been shown that CCl₄ produces renal disease in humans [31]. In addition, many studies in vitro and in vivo demonstrated that CCl₄ can decrease the ratio of renal reduced/oxidized glutathione, microsomes and mitochondria while inducing an increase in lipid peroxidation in kidney [28,31].

The present study was designed to assess the preventive effects of Mg supplementation upon CCl₄-induced toxicity by investigating haematological parameters (WBC, RBC, Hb, MCHC and Pl), serum markers of kidney damage (levels of urea, creatinine, uric acid and proteins) and oxidative stress parameters in the kidneys (lipid peroxidation level and SOD, GPX, CAT activities).

2 Materials and methods

2.1 Animals and chemicals

24 Wistar male rats (3 months old), about 160 g body weight, purchased from the Pasteur Institute (Tunisia), were maintained for a two-week adaptation period under the same conditions of temperature (22 ± 2°C), relative humidity (70 ± 4%), and a 12 h light/dark cycle. Animals were fed with 15% protein food pellets (SICO, Sfax, Tunisia) and had tap water ad libitum and were kept according to the Tunisian code of practice for the Care and Use of Animals for Scientific Purposes. All the chemicals were of analytical grade and were purchased from E-Merck (Germany), Sigma Aldrich, Sharlau, NORMAPUR, BIOTECH, Panreac, CHIMICA PLUS, etc.

2.2 Experimental procedure

After the adaptation period, the animals were divided into 4 groups, with six rats in each group. Treatment was then carried out as follows:

- Group 1 (C), which served as the control group, received saline solution (NaCl 0.9%) (intraperitoneally) and olive oil (intragastrically).
- Group 2 (CCl₄) was kept on normal diet for 4 weeks. To induce the maximum of toxicity of CCl₄ without killing the treated rats, they received the first dose (i.e. 5 ml/kg b.w, 50% CCl₄ in olive oil) on the first day of the fifth week, then were kept intact for a week under surveillance. The same protocol was repeated during the sixth week and by the end of that week the CCl₄-treated rats were deemed unable to survive a third dose. All the groups were sacrificed by the end of the sixth week.
- Group 3 (Mg) received MgCl₂ dissolved in saline solution (NaCl 0.9%) (i.p.) one injection a day for 6 weeks (0.2 Mg²⁺ g/kg b.w.) [32].
- Group 4 (CCl₄+Mg) received MgCl₂ dissolved in saline solution (NaCl 0.9%) (i.p.) one injection a day for 6 weeks (0.2 Mg²⁺ g/kg b.w), and CCl₄ suspension as described in group 2.

After 6 weeks from the beginning of the treatment, animals from each group were rapidly sacrificed by decapitation in order to minimize handling stress. Blood serum was obtained by centrifugation (1500 x g, 15 min, 4°C), total blood was immediately used for analysis of hematological parameters and kidneys were removed, cleaned of fat and stored at -80°C until analysis.

2.3 Preparation of the kidney homogenate

Kidney homogenate was prepared by cutting 1g in small pieces and was homogenized in 2 ml of tris buffer solution (TBS) (pH 7.4) using a crusher (homogenizing Ultra-Turax), then the homogenate was centrifuged with 9000 x g during 15 min at 4°C. The supernatants were gathered and stored at -80°C until use.

2.4 Biochemical assays

The level of lipid peroxidation was measured as thiobarbituric acid reactive substances (TBARS) according to Yagi [33]. For the assay, 125 μl of supernatant (S1 of the kidney) was mixed with 175 μl of 20% trichloroacetic acid (TCA) containing 1% butyl-hydroxytoluene (BHT) and centrifuged (1000 x g, 10 min, 4°C). Then 200 μl of supernatant (S2) was mixed with 40 μl of chlorhydric acid (HCl) (0.6 M) and 160 μl of thiobarbituric acid (TBA) (0.72 mM) and the mixture was heated at 80°C for 10 min. Absorbance was measured at 530 nm and the amount of TBARS was calculated using an extinction coefficient of 156 mM⁻¹ cm⁻¹ and expressed in nmoles/mg protein. The total (Cu-Zn and Mn) superoxide-dismutase (SOD) activity was determined by measuring its ability to inhibit the photoreduction of nitroblue tetrazolium (NBT) [34,35]. One unit of SOD represents the amount that inhibits the
photoreduction of NBT by 50%. The activity was expressed as UI/mg protein, at 25°C.

Glutathione-peroxidase (GPX) activity was assayed according to the method of Flohe and Gunzler [36]. The activity at 25°C was expressed as μmoles of GSH oxidized/min/g protein.

Catalase (CAT) activity was measured according to Aebi [37]. The reaction mixture (1 ml) contained 100 mM phosphate buffer solution (PBS) (pH = 7), 100 mM \( \text{H}_2\text{O}_2 \) and 20 μl (about 1.5 mg of protein) of the kidney. Hydrogen peroxide (\( \text{H}_2\text{O}_2 \)) decomposition was followed by measuring the decrease in absorbance at 240 nm for 1 min (25°C). Enzyme activity was calculated using the extinction coefficient of 0.043 mM\(^{-1}\) cm\(^{-1}\) and was expressed in international units (UI), i.e., in μmoles \( \text{H}_2\text{O}_2 \) destroyed/min/mg protein.

Protein content in tissue extracts was determined according to Lowry’s method [38] using bovine serum albumin as standard.

Levels of serum parameters were determined by kit methods (Spinreact) and hematological parameters by automatic hematology analyzer (Mindray BC-5800).

### 2.5 Histopathology

Kidney portions were fixed in 10% formalin, processed through a graded ethanol series and finally toluene, and embedded in paraffin. Six-micrometer-thick tissue sections were prepared and stained with hematoxylin-eosin (HE).

### 2.6 Statistical analysis

All data were expressed as means ± standard deviation (SD). Statistical significance was carried out using one-way ANOVA followed by a Tukey post hoc test. \( p < 0.05 \) was considered statistically significant.

### 3 Results

#### 3.1 Hematological parameters

Table 1 shows that the number of leukocytes and platelets decreased significantly by 36.2% and 39.07% respectively. Increases were seen in erythrocyte count (19.55%), hemoglobin concentration (33.19%) and mean corpuscular hemoglobin concentration (20.89%), while there is no change in mean cell hemoglobin concentration and mean corpuscular volume in \( \text{CCl}_4 \)-treated rats. However, the supplementation of \( \text{CCl}_4 \)-treated rats with magnesium for 6 weeks protected against the alteration of blood parameters (WBC, RBC, Hb, MCHC and Pl). Treatment of rats with magnesium alone did not cause a significant alteration in hematological parameters except for WBC count, which was significantly lower when compared with the control group.

<table>
<thead>
<tr>
<th>Parameters and treatment</th>
<th>C</th>
<th>( \text{CCl}_4 )</th>
<th>Mg</th>
<th>( \text{CCl}_4 ) + Mg</th>
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<tbody>
<tr>
<td>WBC (x10(^3)/μl)</td>
<td>23.2 ± 1.57( ^b,c,d )</td>
<td>14.8 ± 1.38( ^b,c,d )</td>
<td>19.85 ± 2.75( ^a )</td>
<td>18 ± 1.44( ^a,b )</td>
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<tr>
<td>RBC (x10(^6)/μl)</td>
<td>7.57 ± 0.04( ^b )</td>
<td>9.05 ± 0.26( ^a,d )</td>
<td>8.72 ± 0.14( ^d )</td>
<td>6.18 ± 0.92( ^b )</td>
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<tr>
<td>Hb (g/dl)</td>
<td>11.75 ± 0.21( ^a,d )</td>
<td>15.65 ± 0.63( ^a,c,d )</td>
<td>12.3 ± 0.42( ^d )</td>
<td>8.35 ± 0.35( ^a,b )</td>
</tr>
<tr>
<td>MCHC (g/dl)</td>
<td>30.15 ± 0.07( ^b )</td>
<td>36.45 ± 0.63( ^a,c,d )</td>
<td>30.1 ± 0.7( ^b )</td>
<td>28.05 ± 2.47( ^b )</td>
</tr>
<tr>
<td>MCH (Pg)</td>
<td>15.55 ± 0.35( ^b,d )</td>
<td>14.4 ± 0.7</td>
<td>14.1 ± 0.7</td>
<td>11.8 ± 1.13( ^a )</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>48.75 ± 0.49( ^d )</td>
<td>47.95 ± 0.91( ^d )</td>
<td>46.4 ± 1.97</td>
<td>42.95 ± 0.91( ^a,b )</td>
</tr>
<tr>
<td>Pl (10(^3)/mm(^3))</td>
<td>1057.5 ± 3.53( ^a,b )</td>
<td>743.5 ± 51.61( ^a-c,d )</td>
<td>970.5 ± 41.71( ^a )</td>
<td>1034 ± 42.42( ^a,b )</td>
</tr>
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</table>

Values are the mean of 6 measurements ± SD; \( ^a \) \( p \leq 0.05 \) vs. control group (C); \( ^b \) \( p \leq 0.05 \) vs. \( \text{CCl}_4 \)-treated group (\( \text{CCl}_4 \)); \( ^c \) \( p \leq 0.05 \) vs. Magnesium-treated group (Mg); \( ^d \) \( p \leq 0.05 \) vs. \( \text{CCl}_4 \) and magnesium-treated group (\( \text{CCl}_4 \) + Mg).

#### 3.2 Serum markers of kidney damage

\( \text{CCl}_4 \) treatment induced severe kidney damage indicated by a significant increase in serum creatinine (by 39.87%) and urea (by 68.51%), and a significant decrease in uric acid and proteins by 24.01% and 18.75% respectively (Table 2). When \( \text{CCl}_4 \)-treated rats were supplemented with magnesium, all these biomarkers were restored to normal values. However, a significant decrease in creatinine and proteins (by 32.09% and 13.19% respectively), and a significant increase in uric acid (13.07%) were observed with administration of Mg only as compared with the control group.
3.3 Oxidative damage

TBARS levels in renal tissues were increased by 172.09% in CCl4 treated rats as compared to controls (Fig. 1). The administration of magnesium significantly reduced the TBARS level to control values in CCl4+Mg group. In rats treated with Mg only, no significant changes were observed when compared to the control group.

3.4 Antioxidant enzyme activity

Antioxidant enzyme activity, i.e., SOD, GPX and CAT were found to be respectively increased by 179.89% and 1097.79%, and reduced by 69.26% in the kidneys of CCl4 treated rats, as compared to controls (Fig. 1). These changes were significantly corrected in animals co-treated with magnesium. Nonsignificant changes were found in

![Figure 1](image)
the group treated with Mg only as compared with the control group.

### 3.5 Histopathology

Histopathological photos are represented in figure 2. The microscopic observation of kidney sections revealed a normal morphology figured by normal distal and proximal tubules with clear borders and prominent epithelial cells and intact glomeruli in control (Fig. 2A) and magnesium (Fig. 2C) groups. When compared to control kidney sections, the histology of the kidneys of rats treated with carbon tetrachloride (CCl4) shows degenerative changes in distal and proximal tubules indicated by tubular dilatation and a detachment of tubular epithelial cells. Administration of CCl4 caused dilatation of Bowman’s space with glomerular atrophy or total destruction of glomeruli (Fig. 2B). These alterations were attenuated in the case of the co-treatment with magnesium in the group (CCl4+Mg) and the kidney sections showed intact glomeruli and normal tubular structure (Fig. 2D) when compared with control rats (Fig. 2A).

### 4 Discussion

The present study was designed to assess the preventive effects of Mg supplementation upon CCl4-induced toxicity by investigating hematological parameters (WBC, RBC, Hb, MCHC and PI), serum markers of kidney damage (levels of urea, creatinine, uric acid and proteins) and oxidative stress parameters in the kidneys (lipid peroxidation level and SOD, GPX, CAT activities).

Our results are consistent with earlier works that reported that the administration of CCl4 may gravely alter blood composition [39-41]. It has been reported that renal failure is associated with abnormalities affecting hematological parameters such as erythropoiesis, platelet function, thrombopoiesis, and immune function [42]. In this study, CCl4-treated animals showed a significant elevation in the number of RBC [43] and this may be attributed to the reactivation of the erythropoiesis mechanism which is controlled by the circulating glycoprotein hormone erythropoietin, which is secreted primarily by the kidney and liver [44]. It may be also explained by erythrocytosis with increased hematocrit levels in normotensive animals treated with CCl4 [43]. The increase in the number of erythrocytes in our results may

![Figure 2](image-url)  
**Figure 2** Microscopic observations of rat kidney sections (H&E, a, b, c and d: 10×); (A): control group showing normal glomeruli (a) and renal tubules (distal and proximal) architecture (b); (B): CCl4-treated group (50% CCl4, in olive oil) showing glomerular atrophy (a) and a severe tubular destruction (b) or dilatation (c); (C): Magnesium treated rats (200 mg/Kg b.w) have normal structure of glomeruli (a) and renal tubules (distal and proximal) (b). (D): Mg + CCl4 showing marked improvement in the histological sections with normal glomeruli (a) and tubules (distal and proximal) (b).
be at the origin of the elevation of Hb and MCHC levels. Indeed, it was shown clearly that any substance which significantly affects the values of red blood cells and associated parameters would have effects on the bone marrow, kidney and hemoglobin metabolism [45]. Unlike our results, many works have shown that poisoning with CCl4 induced a significant decrease in hemoglobin content [39,41] and MCH level [41]. This attenuation is related to the decrease in RBC count [39,41] and this may be due to the adverse effect of CCl4 on hematological parameters [39].

Our results show that the administration of carbon tetrachloride induced a highly significant reduction in the number of white blood cells [39,46]. A decrease in platelet count or thrombocytopenia was also reported following the same treatment. This could be explained by damages affecting hematology function and the immune system. Platelet dysfunction is also thought to be caused by the action of uremic toxins following renal failure [47]. In chronic liver disease or cirrhosis, this could be due to a reduction in platelet production by the bone marrow or by excessive storage of platelets [48] and WBC [49] by the spleen. In rats treated with magnesium, we did not notice any differences in damaged parameters when compared with control group.

Magnesium has demonstrated beneficial effects on hematological parameters in the present study and other work through its powerful antioxidant properties [50]. Indeed, magnesium reduces the load of free radicals and has potency in inhibiting platelet aggregation [51] which gives this oligo-element a powerful protective effect against the blood toxicity of CCl4. Magnesium also has the power to protect blood from vanadate toxicity [12] and stabilize damaged red blood cell membranes [50]. In mouse, oral magnesium supplementation was found to increase hemoglobin levels and to reduce erythrocyte dehydration [52]. Consistent with previous studies, the administration of CCl4 induced a renal failure indicated by elevation of serum creatinine and urea [53-55] and a decrease in total protein concentration [55,56] and uric acid [53,57] in serum. The elevated serum levels of these parameters are possible indicators of kidney poisoning induced by CCl4 [58]. These pathological changes can also be attributed to damage to the structural integrity of nephrons [24] which is consistent with reports confirming that the level of serum creatinine increases only if at least half of the kidney nephrons are already damaged [59]. In addition, the decrease in plasma total proteins might be explained by intense leakage due to the hypercellularity of glomeruli and tubules following CCl4 renal toxicity [31]. All indices of kidney damages (creatinine, urea, uric acid and proteins in serum) were restored to almost normal values by early supplementation with magnesium chloride.

In the present study, intoxication of rats with carbon tetrachloride created a state of oxidative stress indicated by an increase in lipid peroxidation level and a weakening of antioxidative status in kidney tissue. In agreement with other work, the administration of CCl4 induced significant decrease in CAT activity [24,53,56], and significant increase in SOD [24,60] and GPX activities [23]. It is known that the activities of SOD and GPX behave in two different ways when faced with oxidative stress; an overexpression of the enzymes in the initial stage and then their inhibition if the stress is permanent. We suggest here that the increase of the activities of these two enzymes is a marker of the first response of kidney against oxidative stress. It was found that CCl4 metabolized by cytochrome p-450 induces an excessive generation of free radicals [61] which may explain the severe alteration in antioxidant enzyme status in the kidney [60]. Lipid peroxidation induced by free radicals may also be the origin of disruption of antioxidant enzyme activity [62]. It has been proved that the intoxication with CCl4 is the origin of enhanced lipid peroxidation witnessed by an elevated level of MDA in kidneys [26]. Increased lipid peroxidation in renal tissues following CCl4 poisoning has been well documented [23,28,55]. This may be due to the reduction in free radical scavenging [53,57] as a result of the weakening of the antioxidative status [23]. Lipid peroxidation is assumed to be initiated by trichloromethyl radical (CCl3 -) which is the metabolite of CCl4 by cytochrome p-450 [28]. Mg injections were able to decrease malondialdehyde (MDA) levels in diabetic rats [16]. Mg supplementation is also capable of preventing lipid peroxidation whether in vitro [63] or in vivo [64] and is known to inhibit excessive production of oxygen free radicals [17]. In the current study, magnesium injections were also able to decrease the activities of antioxidant enzymes to normal levels. However, there are some results suggesting that dietary Mg can increase SOD activity in diabetic rats [16] and its deficiency is responsible for the lower GPX activity [65]. This could be explained by the positive effect of dietary magnesium on the status of zinc and copper which are the cofactors of SOD. Indeed, the magnesium administration has a protective effect on urinary Zn and Cu elimination, keeping it within the range of normal levels [13].

The microscopic observation of the kidney of control rats revealed a very normal and well-structured glomeruli and tubules in the cortical area. However, the carbon
tetrachloride induced structural changes in the cortical area were manifested by tubular destruction or dilatation and glomeruli atrophy. Similarly to our findings, there were glomerular necrosis and vacuolization, atrophy and detachment of the tubular epithelial cells which indicate tubular necrosis in rats kidney after the exposure to CCl4 [60]. CCl4 treatment can also cause prominent damage in the kidney witnessed by interstitial mononuclear cell infiltration and fibrosis, and vascular congestion in the peritubular blood vessels [58]. In the kidney of mice, the administration of CCl4 induced severe changes, especially to glomeruli, which look small, atrophied and loosely arranged in Bowman’s capsule [66]. These changes are probably due to products of lipid peroxidation and destruction of membrane structure [67]. It is also believed that CCl4 toxicity is the origin of a vasoconstriction that may produce an ischemic local environment, to finally lead to cellular damage such as deterioration in cell membrane integrity [53]. With magnesium supplementation, kidney structure seems to be almost normal. Magnesium supplementation was reported to prevent the increase in glomerular damage index and renal hypertrophy [68] induced by Cyclosporin A. Indeed, it has been also proved that a high-magnesium diet was more effective than potassium against damage to renal arterioles and glomeruli in spontaneously hypertensive rats [69] and against Cyclosporin A-induced stripped fibrosis, mesangial cell thickening, arteriolar wall medianecrosis, and diffuse tubular atrophy [70]. In earlier studies, it was suggested that MgSO4 treatment can protect diabetic subjects from renal failure by maintaining normal oxidative stress status and regular glucose level in the blood [71]. Magnesium deficiency is known to enhance the production of free radicals and an alteration in antioxidant defenses [72]. So it is suggested that the histological alterations in the renal tissues may be due to damage of mesangial cells caused by oxidative stress and magnesium could reduce this damage by decreasing MDA production [73]. Furthermore, it was found that the supplementation of magnesium (0.06%) tended to prevent the development of kidney disease by reducing serum creatinine, as well as the degree of attenuation of tubular damage, tubulo-interstitial fibrosis, and thickening of the glomerular membrane basement after just 28 days. This protective effect of magnesium is may be due to magnesium supplementation which maintains normal activity of NOS (Nitric oxide synthase) by reducing the damage induced by free radicals and superoxide oxygen [74].

5 Conclusions

From our study, we can conclude firstly that CCl4 is a very aggressive xenobiotic acting largely on kidney by promoting an oxidative stress and peroxidation of cell lipids, and secondly that early supplementation of magnesium significantly alleviates the damage to this organ as revealed by the restoration of blood and tissue markers of toxicity to almost normal values.

Conflict of interest: The authors of this manuscript declare that there is no conflict of interest.

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