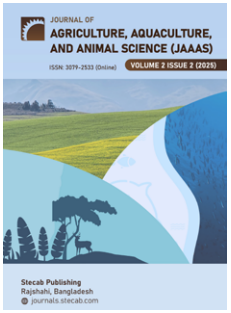

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Review Article

Physiological and Immunological Evaluation of Hepato-Renal Disturbances Due to Low and High Doses of Carbimazole in Rats

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About Article

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ABSTRACT

Carbimazole is a widely utilized thionamide antithyroid drug that also functions as a prodrug for methimazole, It is normally administered to treat hyperthyroidism, but a large number of patients have recorded a number of side effects. Investigation the effects of low and high doses of carbimazole on liver and kidney functions and to assess immune-related responses through the measurement of various serum biochemical markers. Thirty adult female rats were purchased, acclimated and equally divided into three groups; NCG (Normal Control Group): rats does not receive carbimazole, LCG (Low-Dose Carbimazole Group): rats treated with 80mg/Kg body weight, HCG (High-Dose Carbimazole Group): rats treated with160mg/Kg body weight. After the experimental peroid, blood samples were collected directly from the heart and centrifuged to obtain serum, and after that the serum samples were analyzed for hepato-renal biomarkers [alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), cystatin C (Cys-C), gamma-glutamyl transferase (GGT), urea (BUN), furthermore liver fatty acid binding protein (L-FABP)] and immunological [kidney injury molecule-1 (KIM-1), Netrin-1 (Ntn-1), and neutrophil gelatinase-associated lipocalin (NGAL)] serum markers by using the quantitative ELISA. Compared with the control group (NCG), both treated groups (LCG and HCG) exhibited significant increases ($p<0.05$) in AST (0.88 ± 0.07 vs. 2.01 ± 0.19 ng/ml, respectively), BUN (1466.3 ± 2.02 vs. 2316 ± 129.58 nmol/ml, respectively), GGT (49.52 ± 3.79 vs. 79.42 ± 6.08 ng/L, respectively), L-FABP (300.1 ± 44.02 vs. 746.6 ± 48.12 pg/ml, respectively), NGAL (1393.8 ± 72.66 vs. 1601.1 ± 52.33 pg/ml, respectively), and Ntn-1 (48.86 ± 5.72 vs. 99.7 ± 7.64 pg/ml, respectively). Furthermore, ALP (9.87 ± 0.75 ng/ml), ALT (662.5 ± 34.27 pg/ml), Cr (35.25 ± 4.087 nmol/ml), Cys-C (48.6 ± 4.26 ng/ml), and KIM-1 (449.2 ± 74.02 pg/ml) were significantly elevated ($p<0.05$) only in rats of HCG group .Notably, AST, GGT, BUN, L-FABP, NGAL, and Ntn-1 levels were marked higher in the HCG group compared with the LCG group. Carbimazole administration can cause variable degrees of hepatic and renal disturbances that following the received dose highlighting the importance of thorough patient selection, diligent monitoring, as well as, personalized therapeutic strategies to maximize the benefits and minimize the risks associated with carbimazole treatment.

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1. INTRODUCTION

In the early 1940, antithyroid drugs have been evolved and immediately recognized as a revolutionary new therapy for the treating hyperthyroidism (Sawin & Cooper, 2023). Post 10 years later, carbimazole was utilized clinically as an antithyroid agent of thionamide derivative functions by inhibiting thyroid peroxidase, thereby blocking the organification of iodide and also the coupling of iodotyrosines, which are essential steps in thyroid hormone synthesis (de Oliveira *et al.*, 2021; Anandabaskar, 2021). In vivo, furthermore carbimazole undergoes rapid conversion to its active metabolite, methimazole, which is responsible for its therapeutic effects (Michałowski *et al.*, 2025). Besides, this mechanism directly addresses the elevated thyroid hormone levels, making it as an effective first-line drug that also used widely in treatment of various conditions such as Graves' disease (autoimmune cause of hyperthyroidism), toxic multinodular goiter, and solitary toxic adenoma (Dharmalingam & Kaduskar, 2017; Almutairi *et al.*, 2024). Beyond primary mechanism, carbimazole has often immunomodulatory effects include alterations in antigen presentation and also inhibition of thyroid autoantibody production, furthermore maintaining of biological activity (Viola *et al.*, 2025). Despite its broad applicability, the efficacy of carbimazole can vary, with some studies indicating a reduced treatment success rate particularly in patients co-administered with radioiodine therapy (Costa *et al.*, 2024). Worldwide, there are several studies have been demonstrated potential adverse events in a substantial proportion of individuals which can range from minor, self-limiting skin rashes and gastrointestinal disturbances to severe life-threatening conditions such as agranulocytosis and hepatotoxicity in addition to renal dysfunction as well as tissue necrosis and degeneration (Mohan *et al.*, 2015; Abdelmoneim, 2020; Naser & Aziz, 2022). Moreover, carbimazole can significantly impact adrenal gland and other organs with a glycemic side effect for patient with co-morbidities like type-2 diabetes mellitus and increased the obesity (Chakrabarti *et al.*, 2017; Marumudi *et al.*, 2017; Mishra *et al.*, 2018). These potential interactions suggest that a complex pharmacological interplay that warrants careful consideration in therapeutic protocol (Sharfalddin & Hussien, 2021; Şorodoc *et al.*, 2024).

2. LITERATURE REVIEW

In Iraq, though a number of experimental studies have been conducted to identify the effects of carbimazole on reproductive system of male rats (Mahmood *et al.*, 2013), hepatic tissues of female rats (Abdullah *et al.*, 2021), liver and kidney parameters of male rats (Kadhim *et al.*, 2018; Naser & Aziz, 2022), renal histopathological parameters in female rats (Al-Seray *et al.*, 2022), and sex hormones of female rats (Al-Seray *et al.*, 2025); data that provided by these studies remain limited and need to be supported. Therefore, the present study was conducted to investigate the effect of low and high doses of carbimazole on the liver and kidney functions with estimation the level of the immunity through measurement of various serum biochemical markers using the quantitative ELISA.

3. METHODOLOGY

3.1. Ethical approval

This work obtains the license from the Scientific Committees in the College of Veterinary Medicine and also the College of Science (University of Wasit).

3.2. Animals

A total of 30 adult female Wister rats weighted 229-248 grams of 12 weeks age old were purchased from the local animal house, furthermore transported to the Animal House Unit in the College of Veterinary Medicine (University of Wasit) and acclimated for one weak to be prepped for this study. During this preparation period, study rats were kept under controlled conditions of 12/12 hours light/dark at room temperature (22-26°C), besides fed the ready to pellets and received the tap-water.

3.3. Study design

After the ending of acclimation period, the study rats were divided equally and randomly into three groups using the plastic cages as following:

1. NCG (Negative control group): Rats were not received carbimazole, and fed /drunk normally and also considered as a healthy group.
2. LCG (Low-carbimazole group): Rats were received a single-daily oral dose of carbimazole (20mg / Amdipharm, UK) at 1.35mg/Kg. BW for 30 days and was considered as the first experimental group (Mahmood *et al.*, 2013).
3. HCG (High-carbimazole group): Rats were received two-daily oral doses of the carbimazole (20mg / Amdipharm, UK) at 1.35mg/Kg. BW for each dose (totally 2.7 mg/Kg each day) for 30 days and also considered as the second experimental group.

3.4. Dose justification

Based on to the recent reproductive toxicity study (2013) dose justification was done using honey-bee venom doses of 1.35 and 2.7 mg/kg/day. The lower dose was considered sub-toxic and was supposed to have minimal systemic impact, on the other hand the higher dose was considered to be near to the hepato-renal change threshold, without being fatal. In addition, these doses were used to indicate the exposure levels of low and high as used in the experimental determination of liver and renal damage. Even though the human equivalent dose is lower, higher doses are often used in animal models to compensate the differences in metabolic rate and learn early pathophysiological responses within a shorter period.

3.5. Samples

After one day of last dose of carbimazole, all study rats were anesthetized with chloform, and the blood samples were drained directly from the heart using a disposable syringe (5ml) after that transferred into a labeled glass gel-tubes that centrifuged at 5000rpm for 5 minutes (Al-Gharban & Al-Taee, 2016). The obtained serum of each sample was transferred into labeled 1.5 Eppendorf tube and kept frozen within dark plastic container until be tested using the quantitative ELISA.

3.6. Serological analysis

Following the manufacturer instructions of the quantitative ELISAs' kits (Sunlong Biotech, China), eleven of hepato-renal (ALP, ALT, AST, Cr, Cys-C, GGT, BUN, and L-FABP) and immunological (KIM-1, Ntn-1, and NGAL) serum markers were calculated. Briefly, the serum samples furthermore to contents of each ELISA's kit were prepared at room temperature, processed step-by-step, and the absorbance of Standards and sera were measured at an optical density (OD) of 450nm automatically using the ELISA Reader System. After that, the OD values of sera in addition to OD values and the concentration of Standard were plotted on the X and Y scales of Standard Curve to obtain the concentration of each marker in the serum samples.

3.7. Statistical analysis

One-Way ANOVA in the GraphPad Prism Software was be applied to detect significant differences in each markers between the values (mean ± standard error) of study groups (NCG, LCG, and HCG) at a probability level of $p<0.05$ in addition confidence interval at 95% (95%CI), (Ajaj *et al.*, 2021).

4. RESULTS AND DISCUSSION

4.1. Hepato-renal markers

Significant elevation ($p<0.0009$; 95%CI: 18.13 to 35.83) in the values of ALP was shown among the study rats of HCG (9.87 ± 0.75 ng/ml) when compared to the values of NCG (2.50 ± 0.24 ng/ml) and LCG (2.66 ± 0.17 ng/ml). Also, there was no significant alteration ($p>0.05$) was seen in the values of LCG when compared to those of NCG (Figure 1).

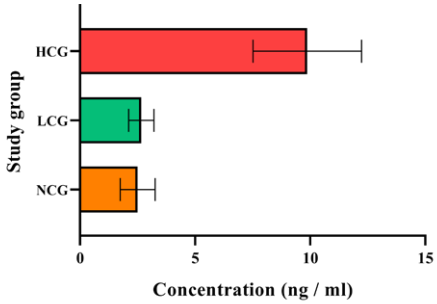

Figure 1. Comparative analysis for values of ALP among three study groups

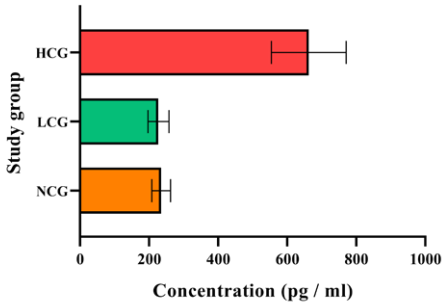

Figure 2. Comparative analysis for values of ALT among three study groups

For ALT, there was a marked elevation ($p<0.0001$; 95%CI: 244.0 to 993.7) in the values of HCG (662.5 ± 34.27 pg/ml) in comparison with those of NCG (235.1 ±8.48 pg/ml) and LCG (227 ± 9.58 pg/ml). Morever, insignificant variation ($p>0.05$) was observed between the values of NCG and LCG (Figure 2). Significant higher values of AST ($p<0.0001$; 95%CI: 0.7815 to 3.061) were also reported among the study rats of both experimentally groups; LCG (0.88 ± 0.07 ng/ml) and HCG (2.01 ± 0.19 ng/ml) than those of NCG (0.53 ± 0.04 ng/ml). As well as, the findings of HCG were significantly ($p<0.05$) higher than those of LCG (Figure 3).

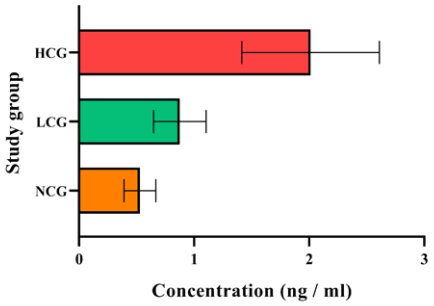

Figure 3. Comparative analysis for values of AST among three study groups

Values of Cr were increased significantly ($p<0.0434$; 95%CI: 4.090 to 49.64) in the study rats of HCG (35.25 ± 4.087 nmol/ml) but not ($p>0.05$) in values of LCG (17.07 ± 1.66 nmol/ml) when compared to those of NCG (16.01 ± 0.85 nmol/ml), (Figure 4).

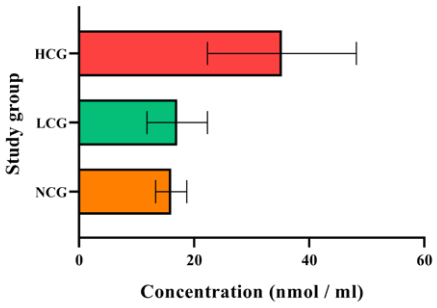

Figure 4. Comparative analysis for values of Cr among three study groups

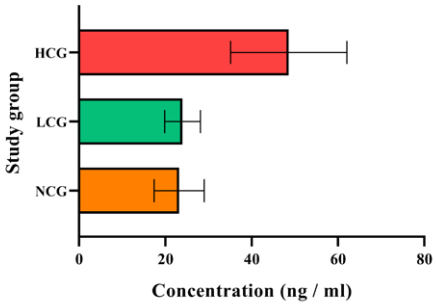

Figure 5. Comparative analysis for values of Cys-C among three study groups

Regarding Cys-C, the findings of HCG (48.6 ± 4.26 ng/ml) were also elevated significantly (p<0.0119; 95%CI: 3.924 to 67.80) when compared to the values of LCG (23.99 ± 1.3 ng/ml) and NCG (23.22 ± 1.83 ng/ml); Although, no significant variation (p>0.05) was observed between the values of LCG and NCG (Figure 5).

Significantly, higher values of GGT (p<0.0042; 95%CI: 3.852 to 112.1) were also reported in both experimentally groups; HCG (79.42 ± 6.08 ng/L) and LCG (49.52 ± 3.79 ng/L) than NCG (33.43 ± 3.02 ng/L). Besides, the findings of HCG were significantly higher (p<0.05) than those of LCG (Figure 6).

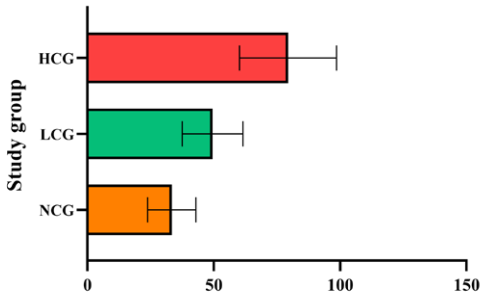

Figure 6. Comparative analysis for values of GGT among three study groups

Relation to BUN, significant elevation (p<0.0001; 95%CI: 643.4 to 3691) in the values of both experimentally study groups; HCG (2316 ± 129.58 nmol/ml) and LCG (1466.3 ± 72.02 nmol/ml) when compared to those values of NCG (588.8 ± 29.18 nmol/ml). In addition, the findings of HCG were significantly higher (p<0.05) than values of LCG (Figure 7).

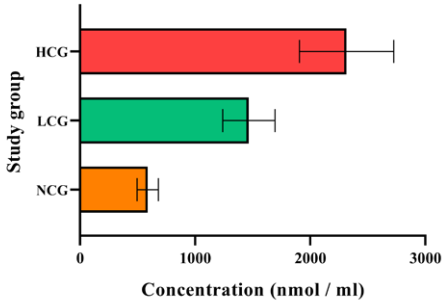

Figure 7. Comparative analysis for values of BUN among three study groups

Concerning the findings of L-FABP, there was a significant elevation (p<0.0012; 95%CI: 257.8 to 1116) in the values of HCG (746.6 ± 48.12 pg/ml) and LCG (300.1 ± 44.02 pg/ml) in comparison with the results of NCG (240.7 ± 19.69 pg/ml). Furthermore, the findings of HCG were significantly higher t(p<0.05) than those of LCG (Figure 8).

4.2. Immunological markers

The findings of the KIM-1 were shown a significant increase (p<0.0016; 95%CI: 228.9 to 698.9) in the values of HCG (449.2 ± 74.02 pg/ml) when compared to values of LCG (149.7 ± 10.11 pg/ml) and NCG (106.2 ± 10.43 pg/ml). Morever, no significant variation (p>0.05) was seen between the values of LCG and NCG (Figure 9).

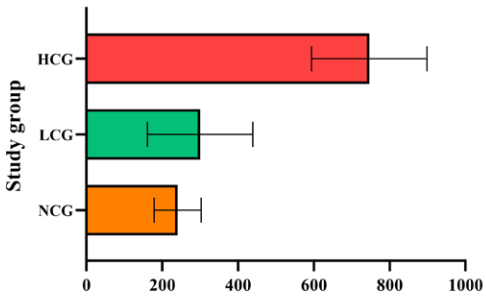

Figure 8. Comparative analysis for values of GGT among three study groups

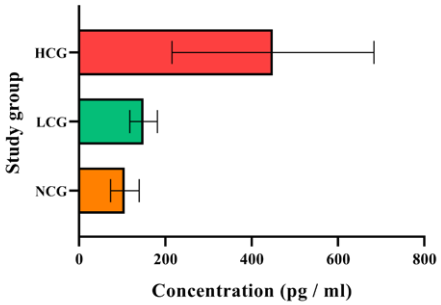

Figure 9. Comparative analysis for values of KIM-1 among three study groups

In comparison to the values of NCG (24.26 ± 2.16 pg/ml), the findings of Ntn-1 were elevated significantly (p<0.0012; 95%CI: 37.97 to 153.2) in both experimentally groups; HCG (99.7 ± 7.64 pg/ml) and LCG (48.86 ± 5.72 pg/ml). Beides, the findings of HCG were significantly higher (p<0.05) than values of LCG (Figure 10).

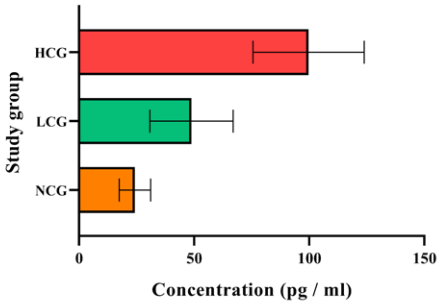

Figure 10. Comparative analysis for values of Ntn-1 among three study groups

The findings of NGAL were also reported a significant elevation (p<0.0001; 95%CI: 9.900 to 2447) in the values of both experimentally study groups; HCG (1601.1 ± 52.33 pg/ml) and

LCG (1393.8 ± 72.66 pg/ml) when compared to the values of NCG (660.1 ± 56.14 pg/ml). Morever, the findings of HCG were significantly higher ($p<0.05$) than those values of LCG (Figure 11).

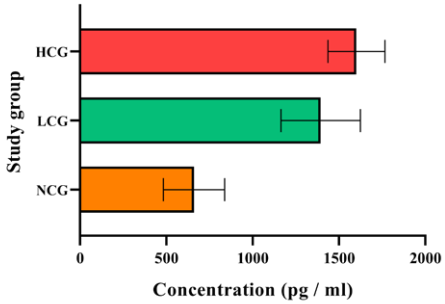

Figure 7. Comparative analysis for values of NGAL among three study groups

4.3. Discussion

Locally and globally, there were several previous and recent in vivo studies have been demonstrated the role of carbimazole in the direct or indirect induction of the different systemic disorders such as jaundice (Lunzer *et al.*, 1975), intrahepatic cholestasis (Blom *et al.*, 1985), immune hemolytic anemia (Salama *et al.*, 1988), testicular damage (Sakr *et al.*, 2011), abnormal structure and also, function of prostate (Sakr *et al.*, 2012), lupus (Haq *et al.*, 2013), reproductive system disorder (Mahmood *et al.*, 2013), the agranulocytosis (Mohan *et al.*, 2015), exudative pleural effusions (Attard *et al.*, 2016), disturbances in sex hormones (Al-Seray *et al.*, 2025), and the cardiotoxicity (Liu *et al.*, 2025). Furthermore, in the present study, the findings of hepato-renal markers including AST, BUN, GGT, and L-FABP were elevated significantly in the rats of both LCG and HCG groups; as well as, the results of ALP, ALT, Cr, and Cys-C were increased significantly in rats of the HCG group only. In addition, the findings of AST, GGT, BUN, and L-FABP were higher markedly in the rats of HCG group than those values of LCG group. Also, our findings were in agreement with that recorded by the other studies that confirmed the role of a carbimazol in induction of the hepatic (Kadhim *et al.*, 2018; Naser & Aziz, 2022; Abdullah *et al.*, 2021; Liu *et al.*, 2025) and renal (Kadhim *et al.*, 2018; Rajesh *et al.*, 2021; Al-Seray *et al.*, 2022; Naser & Aziz, 2022) disturbances. Although, hepatic dysfunctions can also manifest as either cholestasis that typically resolve upon the drug discontinuation (Abdelmoneim, 2020; Al Hariri *et al.*, 2025), or less commonly as well as hepatocellular injury (Akmal & Kung, 2014; Karalus *et al.*, 2016; Ibrahim *et al.*, 2022). While, the researchers have shown that a carbimazole can also influence lipogenic gene expression within the liver cells of hyperthyroid patients, contributing to an abnormal lipid profile (Jasim, 2017; Bhat & Srinagar, 2021). Kimmel *et al.* (2012) demonstrated the influence of thyroid functions on different kidney function tests through the significant increasing the levels of Cys-C and also marked decreasing of Cys-C-based eGFR (estimated glomerular filtration rate. In addition, Sakr *et al.* (2015) found that the administration of carbimazol at dose of 1.35mg/kg B.W was contributed markedly in the elevation of serum ALT, AST and malondialdehyde with the depletion the activity of the antioxidant enzymes. Siddiqui *et al.* (2015) detected that the levels of ALT were reduced decreased significantly as well as AST was also increased significantly in hyperthyroidism patients received carbimazole. Besides, among the various studies, it has been suggested that the direct effects of carbimazole on the liver enzymes represent a critical clinical consideration as those effects can exacerbate pre-existing hepatic dysfunction associated with the hyperthyroidism itself (Jones & Boelaert, 2018; Piantanida *et al.*, 2020; Campos *et al.*, 2024). Also, the precise mechanisms underlying carbimazole hepatotoxicity are complex and multifaceted, often involving idiosyncratic reaction that can range from mild biochemical elevations to severe fulminate hepatic failure (Rai *et al.*, 2024; Al Hariri *et al.*, 2025). Furthermore, concerning the renal markers, emerging evidence detects that carbimazole administration can also induce adverse effects in kidney such as alterations in the renal function parameters which included increasing of Cr and total protein content, alongside histological changes like glomerular degeneration and the tubular necrosis. Thus, these renal pathologies manifest as elevated levels of certain serum enzymes and the metabolic products which refer to compromise kidney functions (Kingsley, 2018; Mosa *et al.*, 2021; Rajesh *et al.*, 2021; Foda & Nour, 2023).

In addition, our immunological findings reported that the values of NGAL and Ntn-1 were elevated significantly in rats of both LCG and HCG groups; while, values of KIM-1 were higher significantly in the rats of HCG groups only than other study groups, LCG and NCG. Furthermore, the findings of NGAL and Ntn-1 were higher markedly in rats of HCG group as the values of LCG group. In comparison with the finding of other studies, many of various researchers have evaluated the gene expression of inflammatory markers alongside anti-inflammatory cytokines and also key regulatory proteins to insight into the molecular pathways that underlying a carbimazole-induced systemic responses (Hegazy *et al.*, 2023; Hussein *et al.*, 2024; Gaber *et al.*, 2025). KIM-1 is a trans-membrane protein that present normally at low levels and upregulated in the proximal tubules of the kidney after damage where it shed in urine and bloodstream indicating the kidney injury (Krstic *et al.*, 2016; Jana *et al.*, 2023). Sağlam *et al.* (2022) reported that KIM-1 was correlated significantly with Cr levels in hypothyroid pregnant women. NGAL is protein that also act functions as both an immune marker and immunomodulator, in addition, play a roles in both the innate immune system and most of various disease states (Buonafine *et al.*, 2018; Romejko *et al.*, 2023). Worldwide, several studies indicated that the quantitative measurement of the levels of serum NGAL can provide sensitive and also early indicators of acute renal injury and chronic kidney diseases (Nguyen & Devarajan, 2008; Sinna *et al.*, 2019; Wang *et al.*, 2020). Kimmel *et al.* (2012) found that NGAL was also elevated significantly in the hyperthyroidism patients and decreased significantly after a carbimazole treatment. Furthermore, Ntn-1 is a secreted protein plays neural and non-neural roles, and is essential for development as well as in advancing of diseases, inflammations, and cancer progression (Claro & Ferro, 2020; Honeycutt, 2023). Thus, different studies have estimated that defects or mutations in

the gene fir Ntn-1 can lead to the thyroid abnormalities such as ectopic thyroid tissue and congenital defects (Opitz *et al*., 2015; Wang *et al*., 2018; Kostopoulou *et al*., 2021).

5. CONCLUSION

The use of carbimazole resulted in the hepato-renal abnormalities that manifested by the great increase in the specific indicators of damage, including liver-type fatty acid binding protein (L-FABP) and neutrophil gelatinase-associated lipocalin (NGAL). These findings indicate that L-FABP and NGAL are very sensitive markers of early hepatic and renal injury due to the exposure to carbimazole. Consequently, it is highly recommended that these biomarkers should be monitored routinely during the treatment of the disease with carbimazole in order to prevent the occurrence of the toxicity at an earlier stage and provide more appropriate clinical care.

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