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Article

Postoperative Investigation of Serum Biochemical and Immunological Markers in Nephrectomized Rabbits

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Abstract: Nephrectomy, the surgical removal of a kidney, is a significant medical intervention often necessitated by conditions such as renal cell carcinoma, severe trauma, or end-stage renal disease. This study aims experimentally to investigate physiological changes in enzymatic, hormonal and immune markers following nephrectomy in rabbits. A total of 20 adult rabbits were purchased acclimated for one week, and divided randomly into two groups including CG (5 rabbits did not operated surgically) and NG (15 rabbits subjected surgically to full removal of left kidney from each one under aseptic conditions). Sampling of venous blood was performed at different times [preoperative (0), in addition to postoperative 1st, 2nd, 3rd, and 4th weeks) as well as from rabbits of NG at the end of the study (30 days post nephrectomy). After centrifugation, the obtained sera was utilized to measurement of study markers that involved creatine kinase (CK), D-dimer (D2D), erythropoietin (EPO), intercellular adhesion molecule 2 (ICAM-2), interferon-gamma (IFN-γ), macrophage inflammatory protein-1 alpha (MIP-1α), tumor necrosis factor-alpha (TNF-α), and tumor necrosis factor-gamma (TNF-γ) quantitatively by specific rabbit ELISAs' kits. In comparison to values of NG, the findings of 0 week were shown insignificant differences ($p>0.05$) among all study markers. Concerning other times, the findings of CK, D2D, ICAM-2, IFN-γ, and MIP-1α were increased significantly ($p<0.05$) at the 1st, 2nd, 3rd, and 4th weeks. However, the findings of nephrectomy group were revealed a significant reduction ($p<0.05$) in values 4th week when compared to the 1st, 2nd and 3rd weeks. For TNF-α, though the findings of 1st, 2nd, and 3rd weeks were elevated significantly ($p<0.05$), the findings of 4th weeks were reduced significantly when compared to 0 week as well as to other weeks of nephrectomy group (1st, 2nd, and 3rd). While values of TNF-γ were differed insignificantly ($p>0.05$) at the 1st week, values of 2nd, 3rd, and 4th weeks were increased significantly ($p<0.05$). In contrast, significant reduction in values of EPO was identified among the samples of 1st, 2nd, 3rd, and 4th weeks This study indicated that marked physiological changes in enzymes, hormones and immunes markers was occurred due to nephrectomy suggesting the importance of intensive studies on the mechanism and harmful complications. However, complicated interaction between surgical intervention and different biochemical markers highlights the complexity of dealing with patients under various conditions.

Keywords: Kidney Removal, Oryctolagus Cuniculus, Quantitative ELISA, Iraq

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1. Introduction

Kidneys are a pair of retroperitoneal, bean-shaped organs which play a critical role in maintaining of systemic homeostasis through their intricate anatomical structure and diverse physiological functions [1]. Histologically, each kidney comprises millions of functional units called nephrons that are responsible various functions including the blood filtration to remove the metabolic waste products and excess fluid, regulation of blood pressure, electrolyte balance, and production of red blood cells [2], [3]. Beyond filtration, kidneys have a crucial endocrine role, synthesizing hormones such as erythropoietin and active vitamin D, which are vital for erythropoiesis and calcium homeostasis, respectively [4]. Also, this multifaceted organ performs gluconeogenesis during periods of fasting, synthesizing glucose from non-carbohydrate precursors to support metabolic demands and contribution to detoxification by eliminating various toxins and drug metabolites from the body, which further underscoring their indispensible role in sustaining life [5], [6].

However, kidney function might be compromised as seen in conditions like polycystic kidney diseases or chronic kidney diseases, accumulation of waste materials and imbalances in homeostasis [7]. Such dysfunctions can lead to severe medical complications that pose significant threats to patient morbidity and mortality, medical intervention appears necessary to managing renal condition [8]. Nephrectomy represents a surgical procedure to remove all or part of one or both kidneys, which indicated in patients with an irreversible damaged kidney owing to symptomatic chronic infection, obstruction, calculus disease or severe traumatic injury [9], [10], [11]. Nephrectomy may also be indicated to treat renovascular hypertension owing to uncorrectable renal artery disease or severe unilateral parenchymal damage from nephrocalcinosis, pyelonephritis, reflux or congenital dysplasia [12]. Nevertheless, surgical removal of a kidney, regardless of the underlying etiology, carries several risks that included immediate surgical complications like bleeding, infection, injury to nearby organs, and blood clots as well as potential long-term issues such as high blood pressure or chronic kidney disease [13], [14]. Therefore, careful postoperative assessments using laboratory tests are paramount to ensure optimal patient outcomes and identifying the extent of damage [15], [16].

In Iraq, few studies have been conducted in human to indicate the outcomes and survival rates of patients [17], as well as animals such as cats to estimate the ultrasonographic and biochemical concentrations of erythropoietin and vitamin D3 [18], and rabbits to evaluate the effect of nephrectomy on histology and biochemical markers including uric acid and creatinine [19], and the effect of nephrectomy on hematological, biochemical (uric acid, urea and creatinine), and hormonal (angiotensin-II, erythropoietin and vitamin D3) markers [20], [21]. Hence, the current study was done to investigate the effect of nephrectomy (complete removal of one kidney) on some serum biochemical and immunological markers quantitatively using ELISA.

2. Materials and Methods

Ethical approval

Scientific Committee in the College of Agriculture (University of Al-Qadisiyah) was licensed the current work.

Study animals

A total of 20 adult male New Zealand white rabbits (*Oryctolagus cuniculus*) of 6-7 months age old with 2.91-3.58 Kg weight were purchased from a private animal house in Baghdad province, transported and acclimated for one week; during which, they fed a ready to use pellets, drank tap-water, and exposed to 12hours light / 12 hours dark. Then, the study animals were divided randomly into two groups:

Control group (CG): An overall five rabbits that not operated surgically.

Nephrectomy group (NG): An overall 15 rabbits that subjected surgically for full removal of the left kidney from each one under aseptic conditions.

Nephrectomy

Following the steps described by [20], [21], rabbits of NG were anesthetized generally using a combination of ketamine hydrochloride (10%, 35mg/Kg.BW) and xylazine hydrochloride (20%, 5mg/Kg.BW) intramuscularly. Then, the ventral midline of surgical area was shaved, sterilized using tincture iodine, and incised carefully. Post clamping of left renal artery and vein, the ureter was ligated using an absorbable suture material and the left kidney was removed outside the abdominal cavity. Finally, the muscles and skin was closed routinely. Postoperative care was included injection of fluid therapy, intramuscular administration of antibiotic (penicillin-streptomycin at a dose of 20 mg/Kg.BW, twice daily) for three days.

Blood sampling

At different times including preoperative (0) in addition to postoperative 1st (1), 2nd (2), 3rd (3), and 4th (4) weeks, 2.5ml of venous blood was collected carefully from the lateral saphenous vein under aseptic conditions using a disposable syringe into a free-anticoagulant glass gel tube. Also, rabbits of NG were subjected to collection of venous blood at the end of the study (30 days post nephrectomy). At laboratory, the tubes of all blood samples were centrifuged (5000rpm for 5 min) and the obtained sera were pipetted and transferred into labeled Eppendorf tubes that kept frozen (-20°C) until be tested.

Biochemical testing

Following the manufacturer instructions of the quantitative ELISAs (SunLong Biotech, China), serum samples and the contents of each kit utilized on the present study [CK (SL0309Rb), D2D (SL0065Rb), EPO (SL0280Rb), ICAM-2 (SL0105Rb), IFN-γ (SL0108Rb), MIP-1α (SL0133Rb), TNF-α (SL0217Rb), and TNF-γ (SL0317Rb)] were prepared at room temperature, processed, and the absorbance values for the sera and Standard diluents were read at an optical density (OD) of 450nm by the Microplate reader. Then, the ODs of sera in addition to ODs and concentrations of the Standard diluents were used to determining the concentration of each marker using the standard curve in the Microsoft Excel sheet.

Statistical analysis

One-Way ANOVA in the GraphPad Prism Software was served to identify significant differences between the values study groups at $p<0.05$ (*), $p<0.01$ (**), $p<0.001$ (***), and $p<0.0001$ (****). Values were represented in this study as mean ± standard errors (M±SE), [22], [23].

3. Results

In comparison with the values of NG, the findings of NG were shown a significant differences ($p<0.05$) at various periods. For CK, the findings of 0 week (2.47±0.13ng/ml) were differed insignificantly ($p<0.0819$) when compared to values of the NG (2.04±0.15ng/ml); whereas, significant elevation ($p<0.0001$; 95%CI:3.212 to 14.64) was identified in values of the 1st (13.23±0.5ng/ml), 2nd (13.36±0.37ng/ml), 3rd (13.5±0.53ng/ml), and 4th (8.95±0.72ng/ml) weeks. However, the findings of 4th week were reduced significantly ($p<0.05$) in comparison with the values of the 1st, 2nd and 3rd weeks (Figure 1). Concerning D2D, though no significant variation ($p<0.0913$) was seen between the values of NG (203.6±23.53ng/ml) and 0 week (204±11.9ng/ml), there were significant increases ($p<0.0001$; 95%CI:206.5 to 566.0) in values of 1st (385.53±30.26ng/ml), 2nd (647±29.39ng/ml), 3rd (496±27.7ng/ml), and 4th (381.33±37.23ng/ml) weeks. However, significant highest value ($p<0.05$) was recognized at 2nd week while lowest at 4th week when compared to other weeks of nephrectomy group (Figure 2).

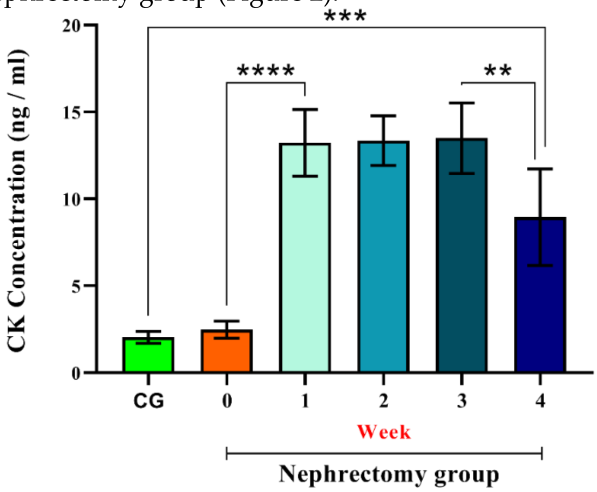

Figure 1. Concentration of CK among rabbits of control and nephrectomy groups

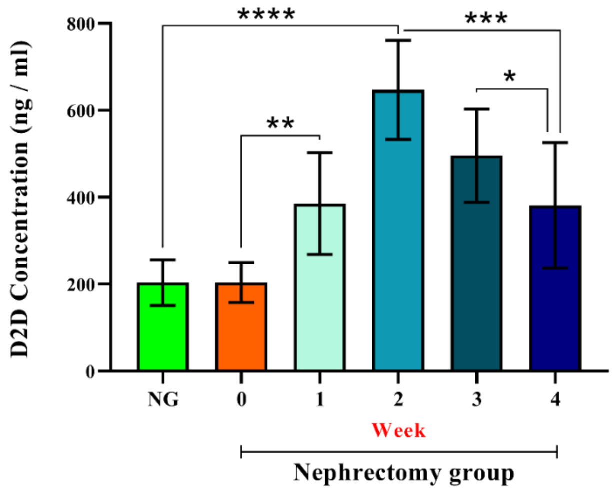

Figure 2. Concentration of D2D among rabbits of control and nephrectomy groups

Significantly, the findings of EPO were differed insignificantly (p<0.0993) in 0 week (612.47±18.85) when compared to NG (626.8±34.51pg/ml); while, significant reduction (p<0.0001; 95%CI: 218.4 to 601.6) was observed among the 1st (162.87±12.26pg/ml), 2nd (288.33±23.72pg/ml), 3rd (357.27±26.69pg/ml), and 4th (412.13±26.22pg/ml) weeks. Subsequently, value of EPO was reduced more significantly (p<0.0.0007) at 1st week, and elevated gradually at the 2nd, 3rd, and 4th weeks (Figure 3).

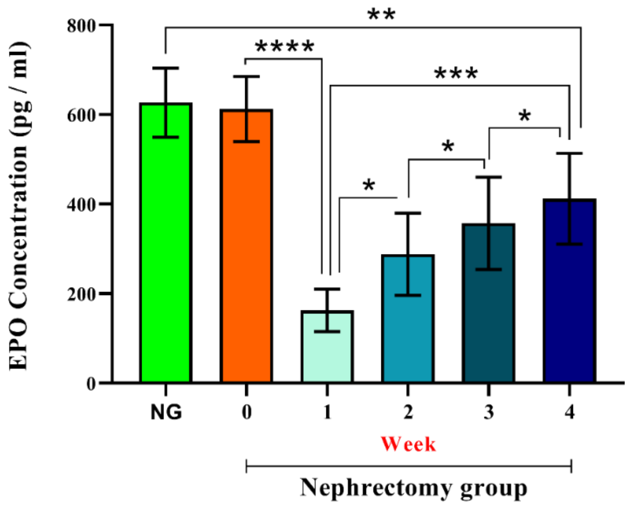

Figure 3. Concentration of EPO among rabbits of control and nephrectomy groups

Relation ICAM-2, though no significant differences (p<0.0899) were recorded in values 0 week (216.27±10.83pg/ml) when compared to NG (227.2±23.03pg/ml), significant increases (p<0.0001; 95%CI:258.5 to 1290) were detected in values of 1st (1363.6±40.99pg/ml), 2nd (1234.87±38.91pg/ml), 3rd (933.4±45.17pg/ml), and 4th (668.87±76.28pg/ml) weeks. However, higher value (p<0.0001) was reported significantly at 1st week while lower at 4th week when compared to values of the 2nd and 3rd weeks (Figure 4). Regarding the IFN-γ, the findings of the 1st (145.33±5.59pg/ml), 2nd (140.33±6.39pg/ml), 3rd (131.13±8.44pg/ml), and 4th (134.4±6.5pg/ml) weeks were significantly higher (p<0.0001; 95%CI:69.39 to 154.3) than reported in samples of 0 week (59.4±5.14pg/ml) and NG (60.6±5.61pg/ml). However, significant differences were lacked (p>0.05) between values of NG and 0 week as well as between 1st, 2nd, 3rd, and 4th weeks (Figure 5). The findings of MIP-1α were shown an insignificant variation (p<0.0842) in values of 0 week (53.8±4.87pg/ml) when compared to NG (51.2±6.52pg/ml), while significant elevation (p<0.0001;95%CI:62.56 to 170.4) was identified in other nephrectomy groups; 1st (138.93 ± 5.56 pg/ml), 2nd (166.27±7.19pg/ml), 3rd (159.87±4.18pg/ml), and 4th

(128.93±5.94pg/ml). However, the highest values were observed significantly ($p<0.0001$) in 2nd and 3rd weeks while the lowest in 1st and 4th weeks (Figure 6).

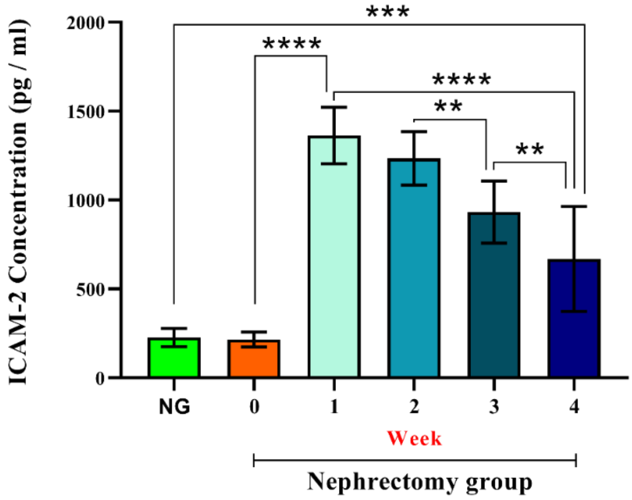

Figure 4. Concentration of ICAM-2 among rabbits of control and nephrectomy groups

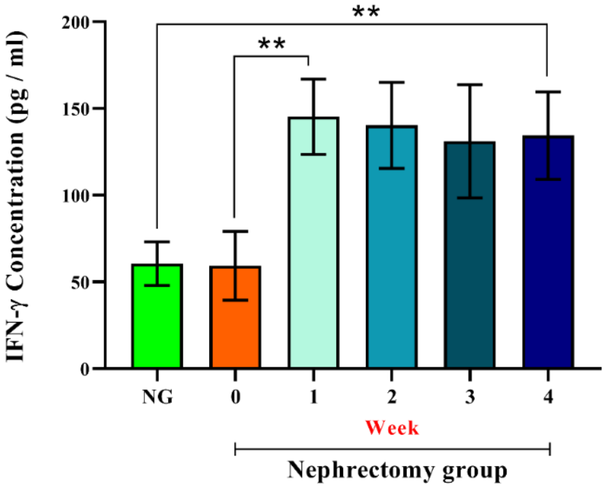

Figure 5. Concentration of IFN-γ among rabbits of control and nephrectomy groups

Although, no marked alteration ($p<0.0905$) was identified in values of 0 week (6.15 ± 0.59 pg/ml) in comparison with the those of NG (6.38±0.76 pg/ml), significant elevation ($p<0.0001$; 95%CI:5.095 to 17.67) in values of TNF-α was recorded in nephrectomy group at the 1st (16.41±0.57pg/ml), 2nd (18.39±0.66pg/ml), and 3rd (15.53±0.6pg/ml) weeks. However, values of 4th (5.43±0.47pg/ml) week were reduced significantly ($p<0.0056$) in comparison to values of NG as well as other weeks of nephrectomy group (Figure 7).

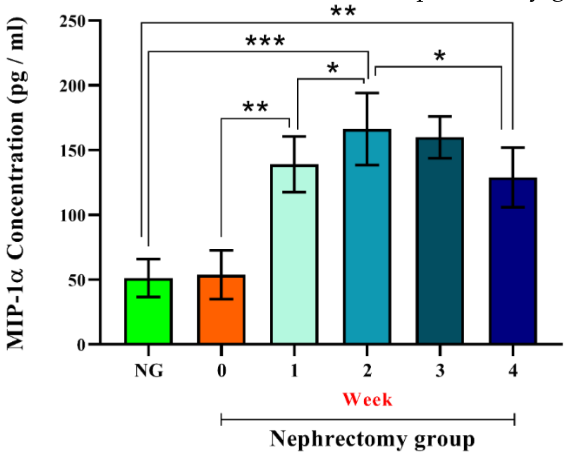

Figure 6. Concentration of MIP-1α among rabbits of control and nephrectomy groups

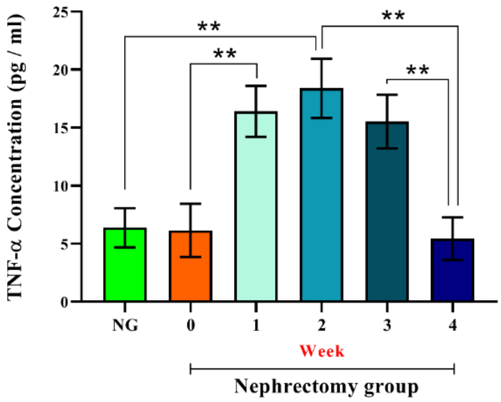

Figure 7. Concentration of TNF-α among rabbits of control and nephrectomy groups

Significant differences in values of 0 (21.37±0.69pg/ml) and 1st (24.87±2.73pg/ml) weeks were not detected (p<0.0549) when compared to values of NG (21.66±1.51pg/ml); however, significant higher values (p<0.0001; 95%CI:16.19 to 55.63) was reported in samples of 2nd (55.44±4.07pg/ml), 3rd (63.97±3.84pg/ml) and 4th (28.13±1.97pg/ml) weeks (Figure 8).

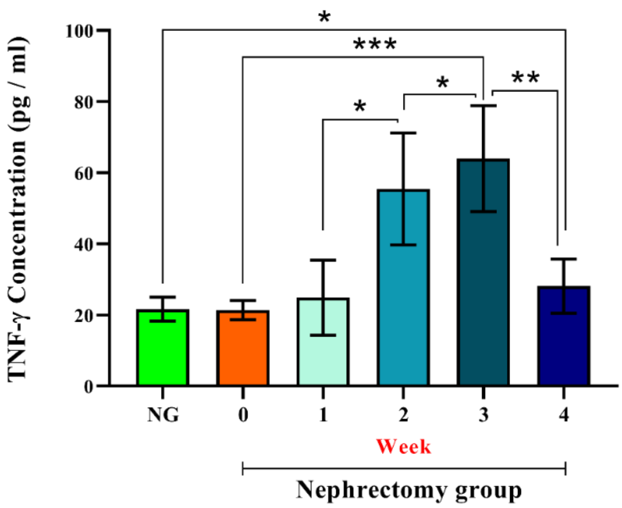

Figure 8. Concentration of TNF-γ among rabbits of control and nephrectomy groups

4. Discussion

Nephrectomy represents a foundational surgical intervention for a variety of renal pathologies; but under certain conditions, morbidity and mortality can be occurred due to temporary or permanent decrease in activity and damage to the patient's quality of life [24], [25]. In this study, the findings revealed a relative and marked elevation in values of CK and D2D at the 1st, 2nd, 3rd, and 4th weeks; however, this increase was diminished at the 4th week when compared to the 1st, 2nd and 3rd weeks. CK plays a vital role in homeostasis of cellular energy, especially in tissues with high energy requirements [26]. Therefore, high plasma CK is often used in clinical diagnostics to assessment muscle damage caused by a number of pathological conditions as well as surgical contexts especially those dealing with large amounts of tissue such as nephrectomy [27], [28]. It has been reported that the level of muscle damage based on serum CK is correlated with the level and severity of surgical dissection [29]. This may result in acute kidney disease due to myoglobin nephrotoxicity as myoglobin is released during the disorders of the muscle [30]. Hence, the dynamics of CK in setting of nephrectomy, which may be accompanied by the significant muscle disruption, is the most important to comprehend prior to the onset of complications and to act in time. Additionally, CK activity during the postoperative period is believed to be a valid parameter through which muscle injury during various surgical operations, which include spine surgeries, can be measured [31], [32]. Considering that it is high in muscle tissues, CK release in bloodstream can be a predictor of muscle cell necrosis or injury and therefore its exploitation as a diagnosis tool [33]. D2D is a key biomarker and a fibrin degradation-product which reflects the activation of coagulation and fibrinolysis systems in many pathological conditions [34]. In field, measurement of D2D has provided useful data as independent prognostic factor in overall and disease-free survival [35]. Additionally, D2D is becoming well-known in determining the extent of trauma and probability of thrombosis, especially in postoperative environment emphasizing its importance in assessing surgical patients in conditions such as nephrectomy, where coagulation status may influence the outcome of surgical operations [36], [37]. Several researchers have mentioned to the relationship between D2D level and outcomes following nephrectomy in patients with renal cell carcinoma suggesting its potential predictor of risk of such complications as acute kidney injury and prognosis in general [38], [39].

In the present study, the findings of immune markers revealed that the concentrations of ICAM-2, IFN-γ, and MIP-1α were elevated significantly at the 1st, 2nd, 3rd, and 4th weeks; whereas, the levels of TNF-α was elevated at 1st, 2nd, and 3rd weeks but reduced significantly at the 4th weeks when compared to 0 week; while TNF-γ was increased at the 2nd, 3rd, and 4th weeks. This intricate interplay between the perioperative factors such as immunological responses and inflammatory mediators such as ICAM-2 are important to understanding the patient outcomes after nephrectomy [40], [41]. ICAM-2 belongs to the immunoglobulin superfamily, represents a cell-cell adhesion and leukocyte trafficking, involved in recovery following nephrectomy [42]. This is especially relevant in light of the reported systemic inflammatory response that results after surgery and is known to affect kidney progression and biology of the renal disorders which potentially affecting the prognosis of the patient [43], [44], [45]. IFN-γ is also essential in the immune responses against different malignancies throughout its ability to control tumor microenvironment, control the invasion of immune cells, and even affect the effectiveness of therapeutic interventions [46]. Considering its proven role in immunology, it is crucial to establish the particular relationship between the activity of IFN-γ and results of nephrectomy, in particular, regarding metastatic conditions [47]. Considering the immune suppression, decrease in immune suppressions after nephrectomy can support a more vigorous IFN-γ-induced anti-tumor effect, which can potentially enhance therapeutic performance and regulation of signaling pathway [48]. In particular, the complex factors of efficacy of immune-targeted combination therapy include immune evasion, metabolic reprogramming, and tumor immune microenvironment in addition to tumor-infiltrating lymphocytes and expression. [49] demonstrated that unilateral nephrectomy can provoke systemic inflammation with an increased rate of pro-inflammatory cytokines, such as TNF-α, IL-6, and MIP-1α. Inflammatory cascades have the capacity to cause neutrophil and macrophage inflammation further contributing to the systemic response seen after nephrectomy [50]. Additionally, it has been established that MIP-1α increase after surgical procedures, which indicates a more general role of this chemokine in the acute inflammation stage after surgery [51]. Such systemic inflammatory effects may lead to greater morbidity and mortality especially in patients with underlying chronic kidney disease [52]. MIP-1α increases in the serum following nephrectomy might be as a result of a compensatory or rebound inflammatory event as opposed to a direct pathogen-dependent event and this may result in impaired end-organ performance due to the impaired supply of nutrients and increased retention of leukocytes, thus influencing the overall outcomes of surgery [53], [54]. The complex interaction of TNF-signaling and kidney pathologies, and especially models in nephrectomy, are a particularly important field of study in nephrology. The TNF-receptors one and two (TNFR1 and TNFR2) are core agents of the pathogenesis and progression of chronic kidney disease, which affect process of inflammation and tissue damage [55], [56]. In particular, TNF-α has been seen at high levels in serum and renal fluids in different experimental kidney diseases models and in human chronic kidney disease [57]. Furthermore, the higher circulating concentrations of TNF mean the higher the long-term mortality and poor renal performance of patients with chronic kidney disease [58]. On the other hand, [59] detected that the high soluble TNFR1 levels can predict the development of chronic kidney disease in elderly patients independently, and high plasma TNFR2 levels can predict the risk of mortality in patients with chronic kidney disease. However, the circulating forms of these receptors, sTNFR1 and sTNFR2, their release depends on receptor shedding, exosomal release, and alternative splicing, which are manifestations of the functions of these receptors in the regulation of TNF-γ signal transmission [60]. These soluble receptors are either neutralizing TNF-γ by binding to it or are agonists, which make them difficult to determine in renal pathophysiology [61].

Our findings showed that the values of EPO were decreased significantly at the 1st, 2nd, 3rd, and 4th weeks of nephrectomy group when compared to values of 0 week as well as NG. EPO, glycoprotein hormone, is mainly produced by kidneys and is essential to erythropoiesis [62]. Chronic kidney disease frequently causes erythropoietin deficiency, which is the main cause of anemia in the patients [63]. As the kidney disease progresses, the risk of anemia in patients is high which largely explained by the fact that the production of EPO by the damaged kidneys is weakened [63]. In addition, the EPO-coding gene, secreted by cells in the kidney as EPO, is controllable in a hypoxia-regulated manner and the renal oxygen sensing is directly connected to erythropoiesis [64]. The impairment of renal functioning with the course of chronic kidney disease causes a significant drop in EPO secretion, which causes insufficient levels to support normal erythropoiesis [65]. [66] reported that these effects underscore the kidney has a poor ability to adequately increase EPO production in response to hypoxic-stimulating conditions that is a major, compensatory mechanism in healthy individuals. Also, the poor response of EPO leads to the formation of such symptoms like fatigue and low exercise capacity [67]. It should be mentioned, though, that although the deficiency of EPO is the key pathophysiological factor, the etiology of anemia in kidney diseases is multifactorial, which requires consideration of other pathophysiological processes, including inflammation, iron deficiency, and reduced red blood cell survival [68].

5. Conclusion

This study indicated that marked physiological changes in enzymes, hormones and immunes markers was occurred due to nephrectomy suggesting the importance of intensive studies on the mechanism and harmful complications. However, complicated interaction between surgical intervention and different biochemical markers highlights the complexity of dealing with patients under various conditions.

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