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THE EFFECT OF SUBTOTAL NEPHRECTOMY PROCEDURE ON THE GLOMERULOSCLEROSIS INDEX

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Abstract

Background: Chronic kidney disease is one of the kidney disorders with a steadily increasing incidence rate.

Objective: This study aims to determine the effect of subtotal nephrectomy on the renal glomerulosclerosis in Mus musculus L. at 7, 14, and 28 days post-operation.

Methods: This true-experimental study with a randomized post-test-only control group design used 16 white mice divided into four treatment groups (SO, SN7, SN14, and SN28). Kidney specimens were stained using Hematoxylin-Eosin and imaged to assess the glomerulosclerosis index. The results were analyzed using one-way ANOVA.

Results: The findings showed that glomerulosclerosis could be observed as early as 7 days post-procedure. The highest score was found in the SN28 group (3.55 ± 0.129). A significant difference was observed between the SO and SN7, SN14, and SN28 groups ($p < 0.05$). Significant differences were also found between the SN7 and SN14 and SN28 groups ($p < 0.05$), while no significant difference was observed between the SN14 and SN28 groups.

Conclusions: These results indicate that subtotal nephrectomy can induce glomerulosclerosis as early as day seven post-operation. The highest glomerulosclerosis index was observed on day 28, although statistically, it did not differ significantly from the index on day 14.

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INTRODUCTION

The kidneys are a pair of urinary system organs that play a vital role in the human body. They function as filters that remove metabolic waste products from the blood. Chronic kidney disease (CKD) is one of the kidney disorders with a steadily increasing incidence rate (1,2). In 2017, the World Health Organization (WHO) reported a 5–10% increase in the prevalence of CKD compared to the previous year (3). A systematic review released in 2025 projected that, by 2032, the age-adjusted prevalence and mortality rates will increase to 8,773.85 and 21.26 per 100,000 individuals, respectively (4). In Indonesia, the number of CKD patients also increased by 19.3% in 2018 (5). A similar trend was observed in Bali, where the number of CKD patients rose 38.7% in 2016 compared to the previous year. That year, 21,050 individuals underwent hemodialysis for the first time, while 30,554 patients were already undergoing regular hemodialysis (6).

Several factors, including infections, disorders of renal blood supply, immunological diseases, nephrotoxins, metabolic disorders, malnutrition, hypertension, urinary tract obstructions, congenital abnormalities, and primary tubular dysfunction, primarily cause CKD (7,8). Most conditions can trigger sclerosis in the tubules, vascular interstitium, and glomeruli. When sclerosis affects the glomerulus, the condition is known as glomerulosclerosis (9,10). The disease progression occurs in several distinct stages. The initial stage is the onset of inflammation in the glomeruli. If not managed properly, this leads to the progression stage and eventually fibrosis. In CKD patients, glomerulosclerosis is most often caused by metabolic diseases such as diabetes mellitus and hypertension. Glomerular damage triggered by hypertension generally results from activation of the renin-angiotensin-aldosterone system, which causes necrosis of kidney cells. Damage to the glomeruli leads to global sclerosis, indicating permanent injury. This condition results in the death of kidney nephrons, gradually reducing glomerular filtration function (11).

Subtotal nephrectomy, commonly referred to as the remnant kidney model, is a surgical intervention that has been reported to induce renal deterioration and injury resembling that observed in CKD. Animal models are essential in helping researchers understand the pathophysiology, disease progression, and effective therapies. Subtotal nephrectomy is an animal model that can mimic human disease conditions, though it remains a challenge to refine further. The procedure involves removing 5/6 of the kidney, leaving only one-third of the kidney mass intact (12,13).

There are two methods to perform nephrectomy: surgical excision and vascular ligation. The difference between these two methods lies in the tools used during the surgery. Researchers use surgical sutures to tie off kidney parts in the ligation method, whereas in the ablation method, a scalpel removes specific kidney parts. Both procedures reduce the number of nephrons, increasing the workload on the remaining nephrons. This condition can potentially trigger injury to the glomeruli and the renal tubules (14). Previous studies have shown that two weeks after subtotal nephrectomy, renal function impairment can occur, as indicated by the presence of proteinuria and severe glomerular injury (13).

Based on the background above, it is evident that the subtotal nephrectomy procedure has been widely used as an animal model for CKD. However, there is still limited research focusing on evaluating the effect of this procedure on glomerular conditions over time. Therefore, the author finds it necessary to conduct further research to assess the state of glomerulosclerosis following subtotal nephrectomy. This study aims to determine the effect of subtotal nephrectomy on the degree of renal glomerulosclerosis in white mice (Mus musculus L.) at several time intervals: 7, 14, and 28 days post-operation.

MATERIALS AND METHODS

a. Design, Sample, and Research Ethics

This is a true-experimental research study with a randomized post-test-only control group design. The research samples were obtained from stored biological materials (paraffin blocks) from a previous study by Dr. dr. Putu Nita Cahyawati, M.Sc. in 2021, titled "The Effect of Chronic Kidney Disease on the Macroscopic and Microscopic Features as well as Organ Function of the Kidneys, Liver, and Heart in a Subtotal Nephrectomy Mouse Model." The samples in this study were divided into four treatment groups: sham operation (SO), 7-day subtotal nephrectomy (SN7), 14-day subtotal nephrectomy (SN14), and 28-day subtotal nephrectomy (SN28) (Unpublished data). The research was conducted at the Research Laboratory and Biomedical Laboratory, Faculty of Medicine and Health Sciences, Warmadewa University.

The inclusion criteria for the research samples were: Swiss strain white mice (Mus musculus L.), male, aged 3–4 months, and weighing between 30 and 40 grams. The exclusion criterion included mice that died during the acclimatization period, while the dropout criteria included those that died after the surgical procedure.

The sample size in this study was calculated using the degree of freedom (DF) method, with a sample range between 10 and 20, which is appropriate for statistical analysis using ANOVA. Based on the DF range, the minimum and maximum number of animals per group were determined using the resource equation method, as follows:

Minimum number of animals per group: Minimum $n = 10/k + 1$
Maximum number of animals per group: Maximum $n = 20/k + 1$
Where:
n = number of research subjects
k = number of study groups (4)
Minimum $n = 10/4 + 1 = 3.5$ (rounded up to 4 animals per group)
Maximum $n = 20/4 + 1 = 6$ animals per group

Based on the above sample size calculation, the minimum number of animals used in this study was 4 per group, resulting in 16 experimental animals. This study has obtained ethical approval from the Research Ethics Committee of Udayana University (Ethical clearance number: 1375/UN14.2.2.VII.14/LT/2023).

b. Subtotal Nephrectomy Procedure

The subtotal nephrectomy procedure was carried out in two surgical stages. In the first surgery, an incision was made in the right flank to remove the entire right kidney. In the second surgery, an incision was made in the left flank, followed by ablation of the upper one-third and lower portion of the left kidney. These two surgeries were performed on two consecutive days. Before surgery, the experimental animals were anesthetized intraperitoneally using a combination of ketamine (90 mg/kg body weight) and xylazine

(10 mg/kg body weight). All surgical procedures were conducted under aseptic and sterile conditions to minimize the risk of postoperative infection (15).

c. Glomerulosclerosis Assessment

Data collection in this study began with tissue sectioning and staining using the Hematoxylin-Eosin (HE) method (15,16). The staining procedure was carried out following these steps:

I. Deparaffinization:

-Immerse in xylene (three times), each for 5 minutes
-Immerse in graded alcohol: 100%, 95% I, 95% II, 70%—each for 1 minute; 100% (twice), each for 5 minutes
-Rinse with distilled water (aquadest) until clear and ready for staining

II.HE Staining:

-Immerse in hematoxylin for 5–10 minutes
-Rinse with distilled water three times, each for 1 minute
-Immerse in acid alcohol for 30 seconds
-Rinse under running water for 1 minute, then rinse again (second rinse) for 5 minutes
-Immerse in eosin stain for 1–3 minutes
-Rinse with distilled water three times for 1 minute each

III.Dehydration:

-Immerse in graded alcohol: 70%, 95% I and II, 100% I and II, each for 3 minutes
-Immerse in xylene three times, each for 3 minutes. Dry and clean the slides with tissue; once completely dry and clean, apply mounting medium (Entellan), cover with a coverslip, and press gently with forceps to remove air bubbles.
-Observe the slides under a microscope.

After the histological slides were prepared and HE-stained, images were captured using a light microscope connected to an Optilab camera (16). Each group's photos were taken from ten different fields of view at 400x magnification. The captured images were then analyzed semi-quantitatively using the Glomerulosclerosis Index (GSI). This index assesses the extent of glomerular injury based on several parameters, including synechiae, sclerosis, and capillary loop damage. The evaluation is carried out semi-quantitatively by assigning scores from 0 to 4. A score of 0 indicates a normal glomerulus; a score of 1 indicates less than 25% damage; a score of 2 indicates 25–50% damage; a score of 3 indicates 50–75% damage; and a score of 4 means more than 75% damage (12,17).

d. Data Analysis

Data analysis was performed using SPSS version 24.0. The results are presented as mean ± standard deviation (SD). Data analysis in this study employed the one-way ANOVA. One-way ANOVA is an inferential statistical technique used to compare means between two or more groups. This test aims to determine whether there are statistically significant differences in the mean values among the groups. Bonferroni post hoc testing was performed to determine specific group differences, as the variances were homogeneous.

RESULTS AND DISCUSSIONS

The Effect of Subtotal Nephrectomy Procedure on the Degree of Renal Glomerular Injury 7 Days Post-Operation

The study's results revealed that in the SN7 group, the presence of synechiae (adhesions), abnormal capillary loops, and glomerular sclerosis was observed. These findings were in contrast to the glomerular condition in the control group (SO), which still exhibited regular capillary loops, no synechiae, and routine glomerular staining (Figure 1). The glomerulosclerosis index in the SN7 group reached 25–50%. Semi-quantitative analysis showed that the degree of glomerular injury in the SO group was 0.73 ± 0.26, while in the SN7 group it was 2.20 ± 0.22 (Table 1). Statistical analysis showed a significant difference ($p < 0.05$) between the two groups.

Effect of Subtotal Nephrectomy Procedure on the Degree of Tubular Injury 14 Days Post-Operation

In the SN14 group, abnormal capillary loops, synechiae or adhesions, and glomerular sclerosis were also observed. The control group (SO) showed regular capillary loops, no synechiae, and routine glomerular staining (Figure 2). The extent of tubular injury in the SN14 group ranged from 50% to 75%. Semi-quantitative analysis revealed that the degree of injury in the SO group was 0.73 ± 0.26, while in the SN14 group it was 3.06 ± 0.46 (Table 1). Statistical analysis showed a significant difference ($p < 0.05$) between the two groups.

Effect of Subtotal Nephrectomy Procedure on the Degree of Tubular Injury 28 Days Post-Operation

In the SN28 group, abnormal capillary loops, synechiae or adhesions, and glomerular sclerosis were also identified. In contrast, the control group (SO) continued to exhibit regular capillary loops, no synechiae, and routine glomerular staining (Figure 3). Glomerular injury in the SN28 group reached over 75%. Semi-quantitative analysis showed that the injury score in the SO group was 0.76 ± 0.26, while in the SN28 group, it was 3.55 ± 0.13 (Table 1). Statistical analysis showed a significant difference ($p < 0.05$) between the two groups.

The one-way ANOVA test performed on all four treatment groups showed a significant difference among the groups with $p < 0.05$. Post hoc Bonferroni analysis revealed a significant difference in GSI between the SO, SN7, SN14, and SN28 groups ($p < 0.05$). However, no significant difference was found between the SN14 and SN28 groups ($p > 0.05$) (Table 1).

Researchers studying humans with CKD have found that biopsy results reveal glomerulosclerosis with varying degrees, ranging from 17% to 54%. The glomeruli show hypertrophy and signs of ischemia, such as shrinkage of the glomerular basement membrane and periglomerular fibrosis. Researchers also identified segmental sclerosis in a small number of samples. In most cases, they observed mild interstitial fibrosis and tubular atrophy affecting less than 25% of the cortical area. They also noted tubulitis, polymorphonuclear cells in the tubular lumen, and casts. Although they found no significant vascular abnormalities, they did observe mild intimal thickening and smooth muscle hyperplasia in the arteries. They also reported mild arteriolar hyalinosis, although most arterioles appeared normal (18,19).

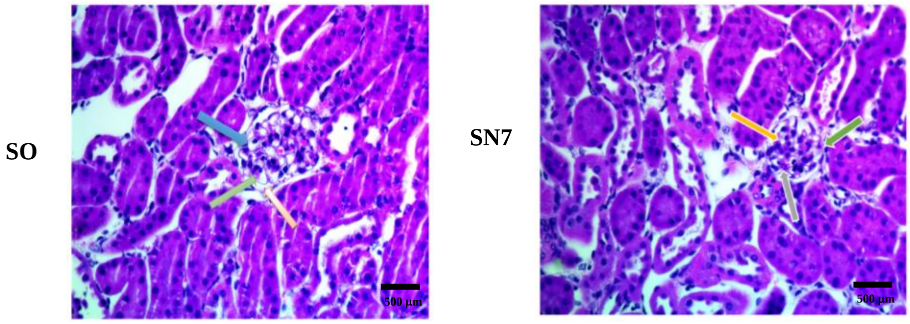

Figure 1. Kidney morphology in the SO and SN7 groups stained with Hematoxylin-Eosin (HE). SO (sham operation); SN7 (subtotal nephrectomy, 7 days post-operation); yellow arrow (abnormal capillary loop); green arrow (presence of synechiae/adhesion); grey arrow (sclerosis).

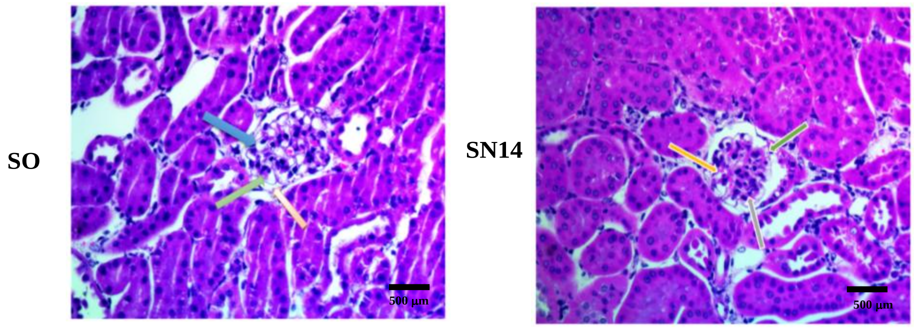

Figure 2. Kidney morphology in the SO and SN14 groups stained with Hematoxylin-Eosin (HE). SO (sham operation); SN14 (subtotal nephrectomy, 14 days post-operation); yellow arrow (abnormal capillary loop); green arrow (presence of synechiae/adhesion); grey arrow (sclerosis).

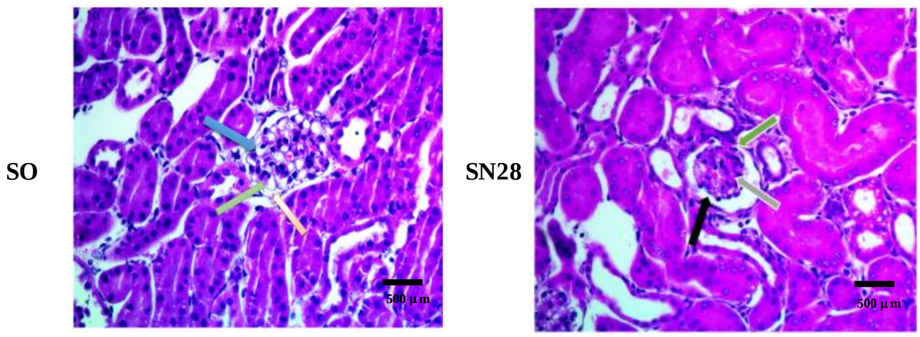

Figure 3. Kidney morphology in the SO and SN28 groups stained with Hematoxylin-Eosin (HE).
SO (sham operation); SN28 (subtotal nephrectomy, 28 days post-operation); black arrow (shrunken glomerulus); green arrow (presence of synechiae/adhesion); grey arrow (sclerosis)

Table 1. Analysis of Glomerulosclerosis Index

Group	N	Mean ± SD	p-value
SO	4	0.73 ± 0.26	< 0.05
SN7	4	2.20 ± 0.22[acd]	
SN14	4	3.03 ± 0.46[ab]	
SN28	4	3.55 ± 0.13[ab]	

One-way ANOVA, Post hoc Bonferroni. SO vs SN7 p=0,00; SO vs SN14 p=0,00; SO vs SN28 p=0,00; SN7 vs SN14 p=0,01; SN7 vs SN28 p=0,00; SN14 vs SN28 p=0,16.
a < 0,05 vs SO; b < 0,05 vs SN7; c < 0,05 vs SN14; d < 0,05 vs SN28
SO (Sham operation); SN7 (Subtotal nephrectomy, 7 days post-operation); SN14 (Subtotal nephrectomy, 14 days post-operation); SN28 (Subtotal nephrectomy, 28 days post-operation).

The findings of this study are consistent with those reported by other researchers. Renal morphological damage appears as early as one week post-surgery, and the damage's severity increases with the observation period's length. However, the time required to induce such damage varies across studies, and the extent of injury may also differ depending on the method used. Increases in serum creatinine, blood urea nitrogen, and proteinuria have occurred as early as four weeks after surgery, while other studies have noted these changes at 12 weeks post-procedure. The earliest reported increase in serum creatinine was observed two weeks post-surgery (13).

Renal damage is characterized by increased fibrosis, glomerulosclerosis, alpha-smooth muscle actin expression, and transforming growth factor-beta (TGF-β). Histopathological features include adhesion of the glomerular basement membrane to Bowman's capsule, extracellular matrix deposition, loss of glomerular capillary lumens, and the accumulation of proteinaceous material in capillaries (hyalinosis) and intracapillary foam cells (lipid-laden macrophages) (7,13,20). Renal fibrosis represents a common pathway in CKD and is marked by the extracellular matrix deposition. The interstitial matrix deposition is primarily attributed to the activity of myofibroblasts, which are considered the key effector cells in CKD progression. Several factors are implicated in the development of interstitial fibrosis, including oxidative stress and inflammation. However, the fibrotic process is primarily driven by TGF-β, angiotensin II, nuclear factor kappa B (NF-κB), and tumor necrosis factor-alpha (TNF-α), which are produced by renal tubular and interstitial cells, as well as macrophages (7).

The mechanism of kidney damage following the 5/6 nephrectomy procedure remains under investigation. Reducing renal mass after surgery leads to a decreased number of functional nephrons. The remaining nephrons must compensate by performing a heavier filtration workload. Consequently, the glomeruli undergo hypertrophy accompanied by increased intraglomerular pressure. This condition leads to glomerular hypertension, which can ultimately impair the structural integrity of filtration components inside and outside the glomerulus (13).

Mechanical stress plays a critical role in the progression of glomerulosclerosis. Hyperfiltration occurs due to damage to the filtration barrier, resulting in an elevated single-nephron glomerular filtration rate (SNGFR) and glomerular hypertrophy. Glomerular hypertrophy leads to an imbalance in the glomerulo-basement membrane and worsens podocyte injury, further exacerbating renal damage. This mechanism induces reactive oxygen species (ROS) production via the angiotensin II pathway, contributing to kidney injury and the progression of glomerulosclerosis (7).

Additionally, the upregulation of TGF-β leads to structural injury and disrupts podocyte integrity. TGF-β also induces mesangial cell proliferation and increases extracellular matrix synthesis. The development of glomerulosclerosis is further evidenced by synchiae between glomerular capillaries and Bowman's capsule. These adhesions create a path for parietal epithelial cells to migrate toward the glomerular capillaries. Consequently, the migrating parietal epithelial cells accumulate within the matrix, forming sclerotic lesions (7)

CLINICAL IMPLICATION

The results of this study indicate that the subtotal nephrectomy procedure significantly impacts the progression of glomerulosclerosis, as noted in the glomerulosclerosis index. Clinically, these findings reinforce the relevance of subtotal nephrectomy as a valid experimental model for studying the mechanisms of CKD, particularly those related to glomerular injury and fibrosis.

Understanding the pathological changes that occur following subtotal nephrectomy can assist clinicians in predicting the onset of renal function decline in patients who have lost nephron mass due to surgery, trauma, or congenital abnormalities. By identifying this critical time point, clinicians can implement effective preventive therapies to halt the progression of kidney damage. Consequently, appropriate interventions may prevent the deterioration toward end-stage renal disease.

Furthermore, this model can serve as a foundation for developing and evaluating pharmacological strategies to inhibit glomerulosclerosis, thereby enabling more targeted treatment for patients at high risk of progressive kidney damage. Thus, integrating these findings into clinical research could contribute to advances in nephroprotective therapies and more personalized patient care in nephrology.

LIMITATIONS

This study has several limitations. First, the variables examined are still limited, which restricts the scope of discussion and the ability to draw comprehensive conclusions. Second, this study utilized stored biological materials, making presenting this article's sample characteristics and biochemical parameters impossible. Third, this study employed a post-test only control group design, so the initial condition of the kidneys at the beginning of the study could not be determined with certainty.

CONCLUSIONS

Based on the results of a study on the comparative effects of vitamin A on the renal glomerular area of rats with type 2 diabetes mellitus, it can be concluded that there is a significant increase in the average glomerulus area in the positive control group compared with the negative control group. However, there was no significant effect of vitamin A in the 50mg/kg b.w, 100mg/kg b.w, and 150mg/kg b.w on the decreased rat renal glomerular area with diabetes mellitus.

CONFLICT OF INTEREST

The authors affirm that they have no conflicts of interest related to this study. There are no financial or personal interests that could have influenced the outcomes.

AUTOR CONTRIBUTIONS

I Wayan Yoga Diva Peranawa contributed to the study by performing the HE staining procedure and observing kidney morphology. Ni Putu Diah Witari guided the histological assessment of the glomerulosclerosis index. Putu Nita Cahyawati contributed by conceptualizing the research idea, supervising the research process, providing the stored biological materials used in this study, and drafting the manuscript.

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