RESEARCH ARTICLE

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Geliş Tarihi / *Received* **:** October 17, 2025
Kabul Tarihi / *Accepted* **:** January 06, 2026

Bu makalede yapılacak atıf
Cite this article as
Kipel S, Nakkas H, Bilginoglu Topcu A.
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Akd Med J 2026;12: 1-8

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A portion of this study was presented as a poster presentation at the 2. International Congress of Histology and Embryology held on 26-28 September 2024 in Turkey.

Impact of Metabolic Syndrome on SVIP and p97/VCP Expression in Renal Tissue

Metabolik Sendromun Böbrek Dokusunda SVIP ve p97/VCP Ekspresyonu Üzerindeki Etkisi

ABSTRACT

Objective

Metabolic syndrome (MetS) is a clinical condition in which a series of metabolic disorders occur together, increasing the risk of cardiovascular diseases and type 2 diabetes. p97/VCP is a member of the AAA+ ATPase protein family, which functions in various intracellular mechanisms. It plays a critical role, particularly in maintaining proteostasis and ERAD. SVIP is an adaptor protein found on the endoplasmic reticulum membrane. It can bind to p97/VCP and suppress its role in processes such as ERAD. MetS affects renal tissue through multifaceted mechanisms, increasing the risk of developing chronic kidney disease. This situation plays a key role in the development of diabetic nephropathy and hypertensive nephropathy in particular. Very little is known about the role of p97/VCP and SVIP in the MetS kidney. So, it is important to study p97/ VCP and SVIP in MetS kidney tissue.

Material and Methods

Hematoxylin Eosin and Azan Trichrome stainings were used to examine the histomorphology of rat kidney tissue. The expression of p97/VCP and SVIP in tissue was investigated using immunohistochemistry.

Results

Both the control and MetS kidney tissue showed signs of p97/VCP and SVIP expression. Comparing the two experimental groups, the MetS group showed higher SVIP expression and lower p97/VCP expression than the control group.

Conclusion

Demonstrating the morphological alterations of the kidney in the control and MetS groups is crucial and histologically significant. Furthermore, SVIP and p97/VCP expressions in metabolic syndrome are significant for chronic renal disease. These results represent a significant advancement in our knowledge of the causes and consequences of metabolic syndrome.

Key Words

Metabolic syndrome, Kidney, p97/VCP, SVIP

DOI: 10.53394/akd.1805762

ÖZ

Amaç

Metabolik sendrom (MetS), bir dizi metabolik bozukluğun bir arada ortaya çıktığı ve kardiyovasküler hastalıklar ile tip 2 diyabet riskini artırdığı klinik bir durumdur. p97/VCP, çeşitli hücre içi mekanizmalarda görev yapan AAA+ ATPaz protein ailesinin bir üyesidir. Özellikle proteostaz ve ERAD'ın sürdürülmesinde kritik bir rol oynar. SVIP, endoplazmik retikulum membranında bulunan bir adaptör proteindir. p97/VCP'ye bağlanarak ERAD gibi süreçlerdeki rolünü baskılayabilir. MetS, böbrek dokusunu çok yönlü mekanizmalarla etkileyerek kronik böbrek hastalığı geliştirme riskini artırır. Bu durum, özellikle diyabetik nefropati ve hipertansif nefropati gelişiminde kilit rol oynar. MetS böbreğinde p97/VCP ve SVIP'nin rolü hakkında çok az şey bilinmektedir. Bu nedenle, MetS böbrek dokusunda p97/VCP ve SVIP'nin incelenmesi önemlidir.

Gereç ve Yöntemler

Sıçan böbrek dokusunun histomorfolojisini incelemek için Hematoksilen Eozin ve Azan Trikrom boyamaları kullanıldı. Dokudaki p97/VCP ve SVIP ekspresyonları immünohistokimya yaklaşımı kullanılarak araştırıldı.

Bulgular

Hem kontrol hem de MetS böbrek dokusunda p97/VCP ve SVIP ekspresyonuna dair bulgular görüldü. İki deney grubu karşılaştırıldığında, MetS grubunun kontrol grubuna göre daha yüksek SVIP ekspresyonuna ve daha düşük p97/VCP ekspresyonuna sahip olduğu bulundu.

Sonuç

Kontrol ve MetS gruplarında böbreğin morfolojik değişikliklerinin gösterilmesi çok önemli ve histolojik olarak anlamlıdır. Ayrıca, metabolik sendromdaki SVIP ve p97/VCP ekspresyonları kronik böbrek hastalığı açısından önemlidir. Bu sonuçlar, metabolik sendromun nedenleri ve sonuçları hakkındaki bilgimizde önemli bir ilerlemeyi temsil etmektedir.

Anahtar Kelimeler

Metabolik sendrom, Böbrek, p97/VCP, SVIP

INTRODUCTION

Metabolic syndrome (MetS) represents a cluster of interrelated metabolic disorders such as insulin resistance, obesity, hyperglycemia, dyslipidemia, and hypertension (1). This syndrome has many significant and harmful effects on renal tissue. MetS causes glomerular hyperfiltration and glomerular hypertension. In the long term, this leads to thickening of the glomerular basement membrane and glomerulosclerosis (2). As a result, the risk of proteinuria and chronic kidney disease increases. Hyperglycemia triggers oxidative stress and inflammation. Advanced Glycation End-products (AGEs) accumulate in glomerular and tubular cells, which increases tissue damage. Insulin resistance causes endothelial dysfunction, which impairs renal perfusion. Dyslipidemia, characterized by elevated triglyceride levels and low HDL levels, causes lipid accumulation in kidney tissue. This condition is known as "lipotoxicity" and causes cell damage in both glomerular and tubular cells (3).

Systemic hypertension, which is frequently seen in metabolic syndrome, accelerates glomerular damage by increasing glomerular capillary pressure. Interstitial fibrosis and nephrosclerosis develop in the long term. Chronic low-grade inflammation is seen in metabolic syndrome. This inflammation increases pro-inflammatory cytokines (TNF-α, IL-6) and pro-fibrotic factors (TGF-β). Interstitial fibrosis and tubular atrophy develop in the kidney tissue (3).

p97/ VCP (Valosin Containing Protein) is a potent enzyme from the AAA+ ATPase family and is widely distributed throughout the body, including the kidney. In the kidney, it is highly expressed in both glomerular and tubular cells (4). According to Human Protein Atlas data, p97/VCP is expressed at high protein and RNA levels in both glomerular and tubular epithelial cells in the kidney. This suggests the presence of an active protein quality control mechanism in the kidney.

p97/VCP plays a critical role in the ER-associated degradation (ERAD) system. It pulls ubiquitinated proteins from the ER membrane and transports them to the cytoplasm. It is tasked with transporting them to the proteasome. Given the high protein synthesis and metabolic activity of renal tubule cells, this relationship with the ERAD system is critical (5).

p97/VCP regulates critical cellular processes, including mitochondrial structure regulation and mitophagy. It also interacts with the autophagosome-lysosomal system to regulate autophagosome maturation and lysosomal degradation. Because the tubular epithelium is under a significant energy load, these mechanisms are essential for the clearance of damaged organelles and energy balance (6). p97/VCP promotes DNA replication, damage repair, and the cell cycle by attracting ubiquitinated proteins to chromatin. This function may be critical for cell health, as the

response to DNA damage is important in kidney cells (5). p97/VCP is a critical molecule for quality control, energy balance, and DNA maintenance in kidney cells. Its deficiencies can impair kidney function in various ways and predispose to pathology.

SVIP (Small VCP Interacting Protein) is a small protein of ~76 amino acids that binds to the N-terminus (ND1 region) of p97/VCP and regulates some of its functions. It attaches to the microsomal/ER membrane through myristoylation and palmitoylation, forming complexes with components of the ERAD (ER-associated protein degradation) machinery, such as p97, Derlin1, and gp78, or inhibits the formation of these complexes (7). SVIP is a critical regulator of p97/VCP. While direct data on renal tissue are limited, its general molecular functions can have important implications for kidney cells. These functions become critical under conditions where protein loading, oxidative stress, and organelle regeneration in renal tubule cells are crucial.

Furthermore, SVIP may indirectly influence these processes through its role as a cofactor in p97/VCP functions, including DNA repair and mitochondrial quality control. Autophagy and lysosomal pathways are critical mechanisms in the kidney for the removal of damaged organelles, and SVIP plays a central role at these processes (8). Cellular energy, DNA damage repair, and stress responses are also driven by the SVIP-VCP axis. SVIP is a key molecule in kidney cells that regulates essential protein and organelle quality control pathways, such as p97/VCP mediated ERAD and autophagy. Because these pathways are critical for healthy function, SVIP dysregulation may contribute to renal cell injury and potential fibrosis and atrophy.

Because direct kidney-specific studies on p97/SVIP expression in renal tissue with metabolic syndrome are limited, our study is important as a fundamental study. Studying p97/VCP and SVIP proteins in kidney tissue from metabolic syndrome and control groups is crucial due to their roles in vital processes such as intracellular protein quality control, stress response, and autophagy. The levels and distribution of these proteins may change during pathological processes such as cell damage, inflammation, and stress caused by metabolic syndrome. Furthermore, kidney tissue is one of the primary target organs of metabolic syndrome, particularly in the development of diabetic nephropathy and hypertensive nephropathy. Metabolic disorders can lead to consequences such as oxidative stress, protein accumulation, and fibrosis in kidney cells. Therefore, the status of systems responsible for protein quality control, such as p97 and SVIP, helps to understand the mechanisms of renal dysfunction.

MATERIAL and METHODS

Animals and Experimental Design

Three-month-old male Wistar Albino rats were provided by the Ankara Medical Faculty Animal Center. All animal experiments were approved by the Ankara University Animal Experimentation Ethics Committee (2025-18-192). The principles of the Guide for the Care and Use of Laboratory Animals were followed for all animals used in the study.

The animals were divided into two groups: the control group (n=8) and the metabolic syndrome model (MetS, n=8). The control rats were fed standard food and water. MetS rats were given drinking water and 32% sucrose for 20 weeks. To validate the model of metabolic syndrome, body weight (g), blood glucose level (mg/dl), insulin (ng/ml), triglyceride (mg/dl), Homeostatic model assessment-insulin resistance (HOMA-IR), and HOMA-β scores were evaluated in each group, as previously documented in our work (9).

Tissue Processing

In order to create paraffin blocks, kidney tissues were preserved in 10% formalin (Merck) throughout the fixation procedure. Following two to three hours of washing under running water, the tissue samples used for fixation were dehydrated by passing them through 75%, 96%, and 100% ethyl alcohol (Merck) concentrations. Xylole (Sigma-Aldrich) was used for the transparency process. Using a Leica microtome, slices of tissue samples fixed in paraffin (Merck) were cut to a thichness of 4 µm.

Histological Analyses

Hemotoxylin and Eosin

Hematoxylin and eosin (HE) staining was performed to visualize the kidney slices under a light microscope. First, the tissue slices on the slide were placed in an oven set to 60°C overnight. They were then immersed in distilled water after being exposed to xylene for 30 minutes and to 100%, 96%, and 75% ethyl alcohol for 2 minutes each. They were stained for five minutes with Hematoxylin (Sigma-Aldrich) and for one minute with Eosin (Sigma-Aldrich). The slides were cleaned with water, then run through a series of increasing alcohol concentrations before being stored in xylene and covered with Entellan.

Azan Trichrome (AT)

This staining technique is used to identify collagen fibers, which appear blue upon staining. This facilitates the diagnosis of conditions such as fibrosis, scar tissue, or stromal changes. The tissue sections taken on the slide were first kept in a 60 °C oven for 1 night. 10 drops of reagent A (PatoLab) were added to the sections and after waiting for 30 minutes, they were rinsed in water. 10 drops of reagent B were added, and the mixture was incubated for 10 minutes. 10 drops of reagent C were added to the sections and incubated for 10 minutes. Then, 10 drops of reagent

D were added and incubated for 30 minutes. At the end of the period, 10 drops of reagent E were added to the sections, and the sections were left for 30 minutes. It was quickly rinsed in distilled water (2-3 seconds) and passed quickly through the series of increasing alcohol concentrations and the procedure was terminated with the closing process by waiting in xylene.

Immunohistochemical Analysis

For one night, the sections were held in the oven. After that, they spent fifteen minutes each in three distinct xylene series. For five minutes each, they went through a variety of decreasing alcohol levels: 100%, 90%, 80%, and 70%. They were cleaned with distilled water, then microwaved for 4 minutes at 560 degrees in citric acid. H2O2 was added to the slides after they had cooled and been washed with PBS. Twenty minutes later, PBS was used to wash them once more. After being thrown onto the slides, the super block was left for fifteen minutes. After that, primary antibodies SVIP (1:100, HPA39807, Sigma) and p97/VCP (1:100, ab11433, Abcam) were added then incubated at +4 for the entire night. The slides were cleaned with PBS the following day, and then biotinylated antipolyvolent (PatoLab) was applied and left to stand for half an hour. Following washing, streptavidin peroxidases (PatoLab) were dropped and permitted to react for half an hour. Following the washing procedure, the AEC kit (PatoLab) was used. Once the response was visible under a microscope, PBS was used for washing. Mayer's hematoxylin was used to stain it in the final step. H-SCORE analyses were used to assess the p97/VCP and SVIP intensities in accordance with a previously established methodology (10).

Statistical Analysis

The data were assessed using H-Score analysis. Before selecting the statistical test, the distribution of the data was evaluated using the Shapiro–Wilk normality test together with visual inspection of Q–Q plots. As the variables demonstrated normal distribution, immunohistochemistry scores were compared using the unpaired Student's t-test, and values of $p < 0.05$ were considered statistically significant. All statistical analyses were performed using GraphPad Prism 10, and data were presented as mean ± standard error.

RESULTS

Histological Analyses Results

The kidney was damaged as an end organ by MetS; more substantial effects included decreased glomerular size, thickened glomerular basal membrane, increased fibrosis, increased interstitial area, and degraded tubules. When compared to control kidney tissues, it was demonstrated that MetS produced unique cellular and structural changes in the kidney tissue. HE staining results showed that the normal membrane appearances of both glomerulus and Bowman's capsule, and the normal proximal and distal tubulus which were presenting the main observations in the control group (Figure 1-A1 and A2). Marked degenerated corpuscule, fibrosis and increased connective tissue around the blood vessels were detected in the sections from the MetS group. Additionally, irregularities in both proximal and distal tubules, cell and cytoplasmic losses, tubular atrophy as well as irregular dilatations in the tubular lümen, have been observed at MetsS group (Figure 1-B1 and B2).

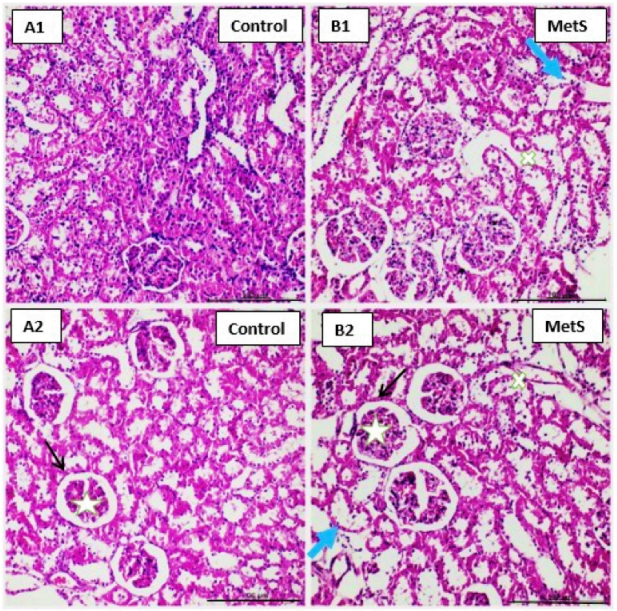

Figure 1: Histomorphological pictures of the rat kidney tissue sections with HE (A1 and A2 control group, B1 and B2 MetS group. Bar: 100 µm, Star: Glomerulus, Black Arrow: Bowmann capsule, Multiplication sign: Degradation and irregularities in both proximal and distal tubule. Blue Arrow: Tubular atrophy.

In azan trichrome (AT) staining, connective tissue stains blue, and in our study, a significant increase in connective tissue was observed in the renal tissue of the MetS group. Compared to the control group, thickening of the Bowman's membrane and increased fibrosis around the tubules were observed. Furthermore, tubular cell loss, luminal irregularities, and brush border degeneration in proximal tubules were among the observed (Figure 2).

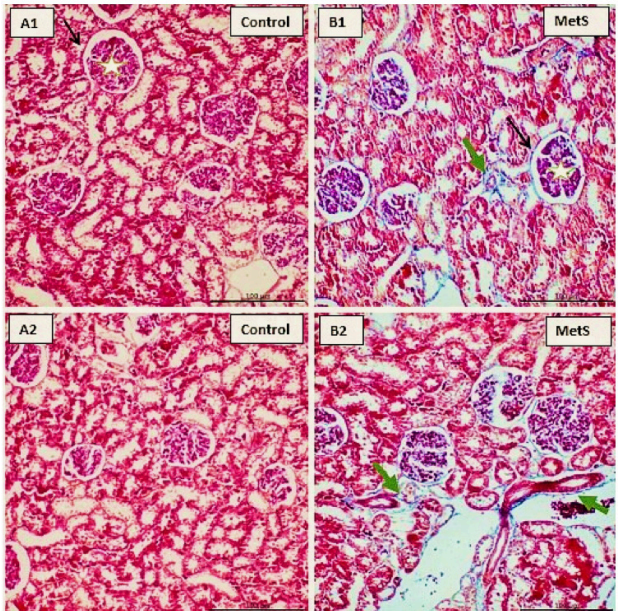

Figure 2: Histomorphological pictures of the rat kidney tissue sections with AT (A1 and A2 control group, B1 and B2 MetS group. Bar: 100 µm, Star: Glomerulus, Black Arrow: Bowmann capsule, Green Arrow: Thickened glomerular basal membrane and increasing interstitial area.

Immunohistochemistry Results

Immunohistochemical analysis demonstrated that p97/VCP was mainly localized both nuclear and cytoplasmic regions in control kidney tissue (Figure 3-A1 and A2). The decreased immunostaining of p97/VCP was detected in the same localizations at Mets group (Figure 3- B1 and B2).

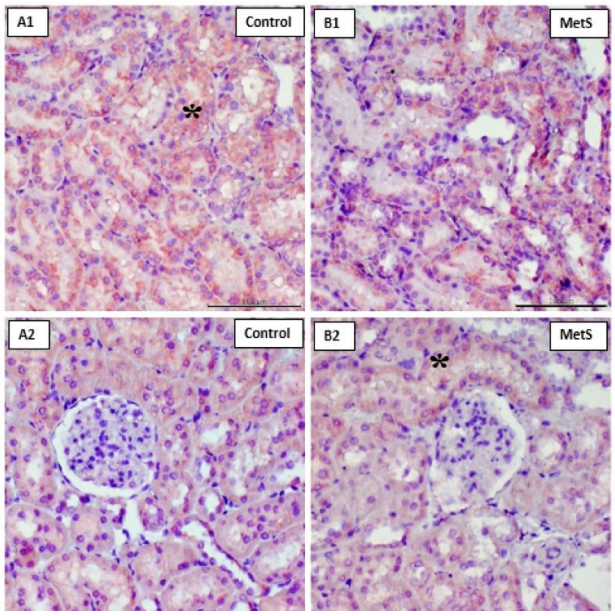

Figure 3: Localization of p97/VCP in the rat control and metabolic syndrome kidney (A1 and A2 control group, B1 and B2 MetS group. Bar: 100 µm, Asterisk *: Shows an immunopositive area).

We observed SVIP expression in the control group (Figure 4-A1 and A2). There was an increased SVIP expression in the MetS group (Figure 4-B1 and B2) compared to the control groups.

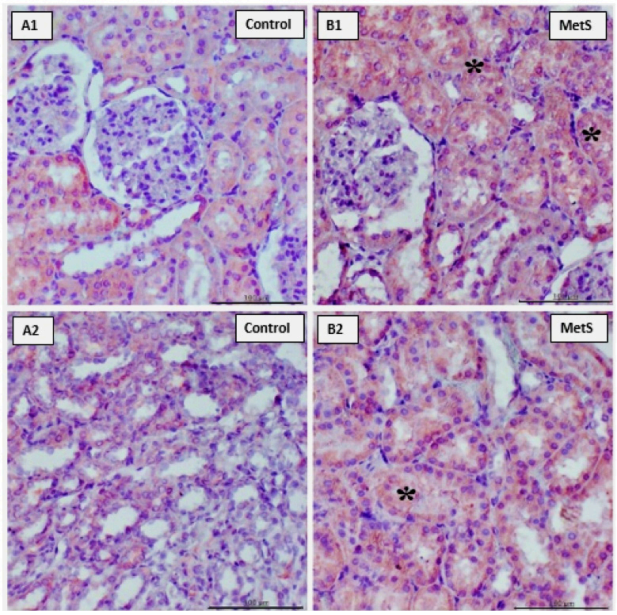

Figure 4: Localization of SVIP in the rat control and metabolic syndrome kidney (A1 and A2 control group, B1 and B2 MetS group. Bar: 100 µm, Asterisk *: Shows an immunopositive area).

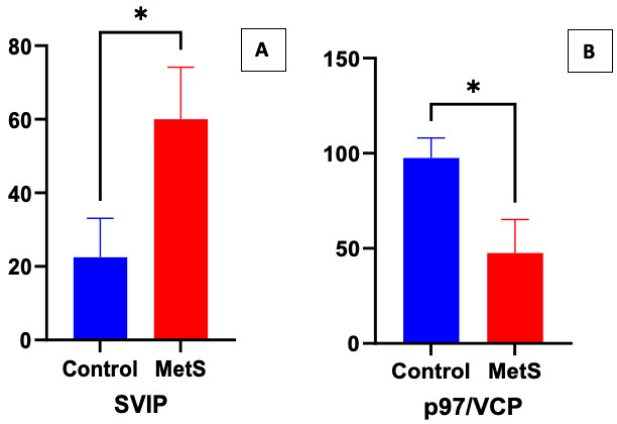

Figure 5: H-Score analysis of immunohistochemistry demonstrated significant differences in p97/VCP expression between control and Mets groups (A, p=0.038) and differences for SVIP expression between control and Mets groups (B, p=0.048).

DISCUSSION

The metabolic syndrome (MetS) has long been thought of as a single integrated disease entity that includes a number of metabolic disorders, such as insulin resistance, diabetes, abdominal obesity, hyperlipidemia, and hypertension. As MetS has become more common, our knowledge of its etiology and pathophysiology has grown. There is significant overlap between metabolic, cardiovascular, and renal problems, according to recent observational and clinical research (11).

Cardiovascular-Kidney and Metabolic (CKM) Syndrome is a combined disease condition that was recently proposed by the American Heart Association (AHA). Diabetes affects the cardiovascular and renal systems through a variety of pathways, and the pathophysiology of CKM syndrome is complicated. It is thought that CKM works

by activating the sympathetic and renin-angiotensin-aldosterone systems, as well as by causing hyperglycemia, insulin resistance and lipotoxicity, vascular stiffening, imbalances in signaling by, among other things, nitric oxide, prostaglandins, or endothelins, as well as elevated oxidative stress and inflammation (12).

The evolutionarily conserved ATPase p97/VCP is linked to a number of cellular processes, many of which are associated with proteostasis, or protein homeostasis. In general, p97/VCP is an ATP-dependent segregase that targets client proteins for ubiquitin-proteasome system degradation after removing them from macromolecular complexes or membranes. The two ATPase domains that make up p97's structure are D1 and D2. The energy needed for client protein unfolding and dislocation is provided by ATP hydrolysis in the D2 domain (13).

In the literature searches on p97/VCP protein with metabolic syndrome (MetS), no study focusing directly on p97/VCP expression in renal tissue has yet been found. Studies in the literature have shown that p9/VCP is closely associated with cell metabolism and proteostasis, and that changes in both mRNA and protein expression can be observed, particularly under nutrient-limited conditions. This suggests that VCP is an important regulator under metabolic stress (14). In another study, decreased p97/VCP expression in rat pancreatic tissue provides indirect evidence that MetS may affect p97/VCP regulation at the tissue level (15). Although not a metabolic syndrome model, proteomic analysis in mice with Meckel syndrome reported decreased expression of the ATPase p97/VCP in kidney tissue. Meckel syndrome (MCS) is a rare autosomal recessive genetic disease that affects tissues such as kidney, brain, and liver. Some of the effects of Meckel syndrome and metabolic syndrome on the kidney are histologically similar. For example, parenchymal loss and interstitial fibrosis are observed in both conditions as a result of damage. Underdeveloped or cystic glomeruli are observed in MCS, while glomerulosclerosis is observed in MetS. Although through different mechanisms, glomerular function can be impaired in both conditions. MCS presents with developmental tubular dysplasia, while MetS presents with tubular atrophy and degeneration. Tubular function is reduced in both. In MCS, tissue destruction following the genetic defect may involve limited inflammation, while in MetS, systemic inflammation plays a prominent role. In both conditions, apoptosis, oxidative stress, and mitochondrial dysfunction can be triggered in kidney cells (16, 17).

Our study demonstrated that p97/VCP expression was significantly reduced in kidney tissues with a metabolic syndrome model. This finding demonstrates that p97/VCP plays critical roles in both metabolic stress and kidney cell function. p97/VCP is a key component of the ERAD mechanism, which is responsible for the removal of misfolded proteins from the endoplasmic reticulum. It also plays active roles in various cellular processes, such as autophagy, proteasomal protein degradation, mitochondrial quality control, and the DNA damage response. In this respect, p97/VCP plays a central role in maintaining intracellular homeostasis (18, 19). In metabolic syndrome, oxidative stress and ER stress pathways are activated, particularly by high glucose, free fatty acids, and chronic inflammatory signals (20). Protein quality control elements such as p97/VCP are normally involved in controlling these stress responses. However, the decrease in p97/VCP expression seen in this study suggests that cells have limited capacity to cope with this stress. This may exacerbate chronic kidney injury in the long term by activating damage mechanisms, including protein aggregation, mitochondrial dysfunction, and tubular cell death (21, 22). Similarly, the literature has shown that decreased p97 expression has negative effects on podocyte integrity and accelerates the development of proteinuria (23). In this context, suppression of p97/VCP in metabolic syndrome conditions may also contribute to the weakening of the glomerular filtration barrier. In light of these findings, decreased p97/VCP expression may be an early marker or an enabling factor in the effects of metabolic syndrome on kidney damage. This is important for the future evaluation of p97/VCP as both a diagnostic and therapeutic target. For example, alleviating ER stress or enhancing the autophagic response with p97/VCP activity-enhancing p97 activity may prevent kidney tissue damage. However, because overactivation of p97 can lead to cellular side effects, such therapeutic strategies must be balanced.

SVIP modulates the ERAD system by interacting with the p97/VCP protein. In ERAD pathways, it regulates the function of p97/VCP to remove misfolded proteins via the proteasome. It may prevent p97/VCP from competitively binding to the ER membrane, suggesting that SVIP may act as an ERAD suppressor (7). According to Human Protein Atlas data, SVIP shows high protein expression in the kidney glomeruli and tubules; similarly, at the RNA level, it shows significant expression in both glomerular and tubular epithelial cells. This demonstrates a generally important role for SVIP in kidney function and indicates high basal expression. While the effects of MetS on the kidney have been extensively investigated in the literature, the role of SVIP in these processes has not yet been elucidated.

This study demonstrated that SVIP protein expression was significantly increased in tissues modeled with metabolic syndrome compared to healthy kidney tissues. SVIP is a protein located in the endoplasmic reticulum and involved in proteostasis. It is also known to interact with p97/VCP to modulate cellular processes such as the ER stress response and autophagy. Metabolic syndrome is characterized by factors such as hyperinsulinemia, hyperglycemia, dyslipidemia, and chronic inflammation, and these factors have been shown to induce oxidative stress and ER stress in kidney tissue. In this context, the increase in SVIP ex-

pression may be considered a compensatory mechanism in response to cellular stress induced by metabolic syndrome. Furthermore, increased SVIP expression can be interpreted as a response to reduce proteotoxic stress and maintain cellular homeostasis. However, since SVIP has also been shown to suppress autophagy in some cases, whether this increase contributes to degenerative processes in kidney cells in the long term should be evaluated in future studies. Our findings contribute to a better understanding of the molecular mechanisms of kidney damage in metabolic syndrome and suggest that SVIP may be a potential biomarker or therapeutic target in this process.

CONCLUSION

In conclusion, this study demonstrated decreased p97/VCP expression in kidney tissue in a metabolic syndrome model, while increased SVIP expression in the same tissue. These findings suggest that metabolic syndrome may affect the proteostasis balance in kidney cells and lead to significant changes in cellular stress responses through the SVIP-p97/VCP interaction. While the decrease in p97/VCP may disrupt systems that control protein quality and compromise cellular functions, the increase in SVIP may be an adaptive or pathological response to this process. In this context, the regulatory role of SVIP on p97/VCP has become an important focus in elucidating the molecular mechanisms of renal injury caused by metabolic syndrome. Our findings suggest that the combined evaluation of SVIP and p97/VCP may contribute to the understanding of renal dysfunction associated with metabolic syndrome and that these proteins may be considered potential diagnostic or therapeutic targets in the future.

Ethics Committee Approval

This research complies with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Decleration, and has been approved by the Ankara University Animal Experimentation Ethics Committee (approval number 2025-18-192).

Informed Consent

Not applicable. This study involved animal subjects only. All procedures were carried out in accordance with institutional and national guidelines for the care and use of laboratory animals. Ethical committee approval details are provided.

Author Contribution

Concept-Ş.K.; Design- Ş.K.; Supervision- Ş.K., H.N., A.B.T.; Materials- Ş.K.; Data collection- Ş.K.; Analysis and interpretation- Ş.K., H.N., A.B.T.; Literature Search-Ş.K; Writing Manuscript- Ş.K; Critical review- Ş.K., H.N., A.B.T.;

Conflıct of Interest

The authors have no conflict of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Declaration of AI and AI-assited technologies in the writng process: ChatGPT (OpenAI) was used only for literature search and language improvement during the preparation of the manuscript. All generated outputs were critically reviewed and verified by the authors, who take full responsibility for the final content of the manuscript.

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